The National University of Ireland

NUI MAYNOOTH

Ollscoil na hÉireann Má Nuad

Reconsolidation: Behavioural and Electrophysiological Sequelae of Context and Stress in Human Episodic Memory

Thesis submitted to the Department of Psychology, Faculty of Science, in fulfilment of the requirements for the degree of Doctor of Philosophy, National University of Ireland, Maynooth.

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June 2009

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Table of Contents

Chapter III

Behavioural correlates of local versus global contextual processing in episodic memory retrieval

Abstract

Chapter IV

Electrophysiological correlates of local contextual processing in episodic memory

Chapter V

Behavioural and electrophysiological differentiation of memory consolidation, reconsolidation and updating in human episodic memory

Abstract

Chapter VI

The effect of stress and context on reconsolidation of episodic hippocampally-based memory in humans

Chapter VII

General Discussion

Acknowledgements

I would like to take the opportunity to express my sincere thanks to the people who have accompanied and supported me throughout this process.

Firstly, I have been incredibly fortunate with my supervisor, Dr. Richard Roche, who always possessed an uncanny ability to complement the many stress fuelled moments encountered throughout with his chilled out unflappable demeanor. You always provided unstinting support, encouragement and guidance throughout. Without your enthusiasm for the area of cognitive neuroscience, introduction to the field of reconsolidation and belief in my ability, this incredible journey and fascinating future would not have been possible. I hope your first experience as a supervisor wasn't too harrowing!

For this research, data were essential. I collected a lot of data. Many people helped with this, for which I would like to thank them wholeheartedly. Without their generosity there would be nothing to work with. Without the friends & family who let me pilot my studies on them the data would have been far less useful- particular thanks to my sister in this regard. I would also like to thank my first and second year students who were such a pleasure to teach and who always helped in terms of data collection. Many thanks to each and every one of my participants.

Running Experiments and collecting data is invariably a trying experience. Many thanks to the following people in particular who made the experience an enjoyable one. Niamh and Jenny made running the stress Experiment an absolute joy: the huge amounts of laughing we did saved us all from going insane, I'm sure. Enormous thanks also to Caroline Rawdon, Elizabeth Kehoe, Sarah Cassidy, Lisa Melville and Orlaith Donnelly for help with Experimentation. I would like to further express sincere gratitude to Dr. Derek Doherty of the Immunology Dept in NUIM for letting me use his lab and to Andrew Hogan for teaching me how to run ELISAs. Thanks also to Dr. Matthew Hill in St. James's Hospital for his invaluable and enormous assistance with the final ELISA analysis.

There were many people who gave interesting feedback & valuable suggestions, for which I am indebted. Dr. Lynn Nadel provided invaluable assistance throughout. Many thanks also to Sinéad Conneely at NUI Galway for her enormously helpful and detailed suggestions while I was commencing the stress research without which I would have been lost. Thanks also to the Neuroscience 'crew' here in Maynooth: Páraic Scanlon, Jonathan Murphy, John Kealy, Mairéad Diviney, Jennifer Murphy, Joe Duffin, Deirdre Harvey, and Anne-Marie McGauran who continually provided unique insight and important suggestions throughout. To *Drs* Anne-Marie McGauran and Deirdre Harvey, both of whom I watched go through this process long before I did. Respect. Finally, I would like to thank Andrew who read many many drafts and provided ingenious insight to each and every one. Your intellectual support was unfailing and insightful throughout.

I would like to sincerely thank the NUIM psychology department for making my experience here a thoroughly enjoyable one from start to finish and for providing unending support throughout the years. Particular thanks to the lecturers who were responsible for inciting such a passion for the field of psychology, and in particular Dr. Seán Commins and Dr. Fiona Lyddy for directing me ultimately to the field of cognitive neuroscience. I also wish to thank the postgrads for thoroughly enjoyable lunches throughout the years: Anne-marie, Deirdre, Páraic, Jono, Christine, Stephen, Claire C, Claire K, Anne, Amanda, Sarah, Sinéad, Chris and Conor from the original crew, and John, Mairéad, Jenny, Joe, Caroline, Nigel, Claire C, Patricia, Ian, Justé, Sean, and Corinna from the new gang. I have never laughed so much. Particular thanks also to Derek Walsh for crisis support during many computer meltdowns. It is wholly attributable to Derek that none of the computers in the department ever left the building via the window! Massive thanks also to Victoria, Anne and Caroline

who were always available for my never ending questions and for putting up with me for all these years.

I have been incredibly fortunate to come across many fantastic friends, without whom Phd life would have been bleak. Special thanks go to Aisling, Steph, Deirdre and Christine in particular, and to Niamh for her ever-present support and for making me laugh hysterically throughout our *many* coffee breaks in O'Brien's. Who would have thought that one of my best students would have become one of my best friends. To Páraic and Jono for making every one of our conference experiences immensely enjoyable and memorable. To Jenny Smith for emptying the entire contents of her kitchen cabinet when I was at my most stressed and in need of a good feed! Those marshmallows were delicious.

Most importantly perhaps, Andrew distracted me completely and joyously. Discussing philosophy, Dylan lyrics or your never ending attempts to make me smile (jogging around the postgrad room, dancing around the living room, impersonations of Jason Byrne, and 'Was only asking…' being particular favourites) were always exactly what I needed after a day spent fighting with data (or the absence thereof) and grappling with complex theory. You have been a constant source of joy and inspiration. You always made sure to pick me up whenever I fell and to put a plaster on my grazed knees. You hugged me when I was down, held my hand when I was scared, saw my potential when I saw nothing, had faith in me when I lost all hope and were always there for me when nobody else was. Thank you so much for sticking by my side throughout this often arduous and seemingly never ending journey. I'm looking forward to our future together *sans* thesis.

To my family: Mum, Dad, Laura, Marie, Niall, Neil, and Andrew. Every time I fell you all caught me, picked me up and encouraged me to never give up. You are the best bunch of people a girl could hope for. Thank you. In particular, I would like to thank my mother for always instilling the importance of education, and my father for instilling the importance of perseverance. None of this would have been possible without the enormous sacrifices made by my mother, for which I am eternally indebted and immensely grateful. You have thought me all the important lessons that I will ever need to know. Dad, thank you for your unfailing enthuasiasm for all of my pursuits. To my sister for being a constant source of inspiration and the most beautiful person I know, as well as the many hugs and constant reminders that it is indeed necessary to eat! To Marie, for the many words of wisdom, various chats, and vast supplies of green tea throughout. You understand me better than most- thank you for that.

Finally, I would like to acknowledge and sincerely thank the Irish Research Council for Science, Engineering & Technology for awarding me a Postgraduate Studentship, which has supported me in innumerable respects throughout my Phd research.

Abstract

Recently, it has been shown in animals that reactivation of previously consolidated memory trace works to destabilize the trace, thereby rendering it once again labile and sensitive to disruptive treatments. While in this labile state (due to retrieval or reinstantiation of the learning context), the trace may be updated, altered, strengthened or eradicated. This effect, termed 'reconsolidation' sheds light on possible treatment options for some patient populations (e.g. PTSD and drug addiction). Many studies have demonstrated that a variety of pharmacological agents can disrupt fear memory reconsolidation if applied immediately after memory reactivation, thereby suggesting that it might be possible to identify pharmacotherapies to be used in tandem with exposure-based therapies to weaken pathogenic memories that are responsible for perpetuating the strength of traumatic or drug paired contextual cues. Investigating the behavioural and electrophysiological sequelae of context and stress in human episodic memory in terms of reconsolidation processing, the experiments reported here represent an important first step in isolating the factors which could allow for strides to be made within this therapeutic realm in humans. Firstly we demonstrated, using visual paired-associates, that episodic processing takes place behaviourally on a conscious, item-familiarity based level. Further, we found that context facilitates episodic stimulus recognition in the same way that it influences episodic word recognition and semantic object identification. Further, we isolated the neural correlates of implicit local context processing, showing that implicit local context interacted to affect learning of paired-associates at a relatively early stage in the information-processing stream and that item-context pairings were processed as a unitary percept rather than as a set of linked elements. The electrophysiological findings suggested that the association between context and stimulus

pair occurs unconsciously and somewhat separate from later processing. We ultimately contend, in line with Multiple Trace Theory, that implicit contextual processing of episodic memory remains within the remit of MTL regions, whereas explicit item-based processing no longer relies upon MTL regions at this juncture. We subsequently found that reactivation of a pre-consolidated episodic memory trace allows for the integration of new information into the trace, and that reactivation of an episodic memory trace exerts an immediate effect on memory for that trace. Finally, we attempted to induce reconsolidation-based amnesic effects on episodic memory by disrupting protein synthesis while traces were labile; data showed that stressed participants appear to lose the ability to distinguish “true” and “false” memories when stressed, possibly reflective of the role of both the hippocampal and prefrontal systems in contextual remembering, and the modulation of these systems by stress. These findings have implications for treatment of patient groups wherein stress is often a precipitating factor in terms of relapse. Overall, the results emanating from the present thesis have numerous widespread implications for the attenuation of implicit pathological memory traces through reconsolidation of consciously-mediated episodic memory.

1

Chapter I

Literature Review

Part of this chapter has been published:

Moore, J.L., & Roche, RAP (2007). Reconsolidation revisited: A review and commentary on the phenomenon. *Reviews in the Neurosciences*, 18(5), 365-382.

1.1 General Introduction

1.1.1 Rationale Underpinning the Present Thesis

"Memory" refers to the mind's ability to retain and retrieve past experiences. The human brain supports *several* different memory systems, which are in turn supported by *distinct* neural networks (Baddeley & Hitch, 1974; Squire & Zola-Morgan, 1991; Schacter & Tulving, 1994; Milner *et al*., 1998). Research distinguishes multiple types of memory, either declarative or non-declarative in nature (Squire, 1992). Declarative memories are subdivided into *explicit* consciously recalled memory for facts (i.e., semantic memory) and episodes, which are tied to specific events at a particular time and place (i.e., episodic memory; Cohen & Squire, 1980; Tulving, 1983; Schacter & Tulving, 1994; Squire & Zola, 1996). Conversely, non-declarative memory refers to *implicit* unconsciously recalled memory for skills and habits that have been previously learned.

According to Consolidation Theory, immediately after acquisition of information, the memory for the event is fragile and can be impaired through disruption such as cerebral trauma, stress, pharmacological intervention or electroconvulsive shock (ECS; for review, see Spear & Riccio, 1994). If this disruption takes place within hours of the learning experience, amnesia will typically follow (McGaugh, 2000). However, in the weeks following acquisition, as the uninterrupted memory consolidates, it gradually becomes independent of the hippocampus, with the cortex taking over as the locus of the memory trace. Once hippocampal-independent, the memory becomes stable and less sensitive to disruption (Squire & Alvarez, 1995). Consolidation research has repeatedly demonstrated that this is the case; animals that receive pharmacological agents blocking protein synthesis

immediately after learning a new task show severe amnesia for the task, when compared to saline injected controls (Nader, 2003; Nader, Schafe & Le Doux, 2000; Pryzbylslawki & Sara, 1997; Sara, 2000). However, this disruptive effect disappears after approximately two weeks, during which consolidation is believed to have fully taken place and protein synthesis blockade is ineffective. On the cellular level (i.e., cellular consolidation), protein synthesis is required for this transformation to occur (Davis & Squire, 1984; Goelet *et al*., 1986; McGaugh, 2000). The memory consolidation hypothesis is also supported by evidence which suggests that the memory impairment induced by post-training treatments is permanent (e.g., Chevalier, 1965; Luttges & McGaugh, 1967).

This concept of memory consolidation has been challenged by evidence that retention performance is also impaired by a variety of treatments affecting brain functioning if the treatments are administered shortly after a memory *retrieval test* (Nader, 2003; Nader *et al*., 2000; Przybyslawski & Sara, 1997; Sara, 2000). For example, Debiec *et al.* (2002) demonstrated that a reminder presented after complete consolidation of a hippocampal-dependent memory can *re*initiate susceptibility to hippocampal damage. Such findings have given rise to the proposition that reactivation of a consolidated memory may de-stabilize the consolidated trace and initiate a process of memory *re*consolidation (Dudai, 2004; Nader *et al*., 2000; Sara, 2000). If allowed to consolidate again over time (i.e., to "re" consolidate), the memory trace will be strengthened. However, while in this destabilized state (due to retrieval or reinstantiation of the learning context), the trace may be updated, altered, strengthened or eradicated. This is the basic tenet of reconsolidation theory.

Notably, in the *broader* context of the present thesis, the concept of reconsolidation has wider implications for patient groups. For example, the persistent retrieval and reconsolidation of traumatic memories in post-traumatic stress disorder (PTSD) patients enables such memories to persist. Thus, patients with PTSD suffer from intrusive memories

of the original traumatic event, which are often precipitated by contextual cues that have become associated with the event (Tronel & Alberini, 2007). Many recent as well as earlier studies have demonstrated that a variety of pharmacological agents can disrupt fear memory reconsolidation if applied immediately after memory reactivation, thereby suggesting that it might be possible to identify pharmacotherapies to be used in tandem with exposure-based therapies to weaken pathogenic memories that are responsible for PTSD (Przybyslawski *et al*., 1999; Debiec & LeDoux, 2004; Bustos *et al*., 2006; Tronson *et al*., 2006). More specifically, Miller and colleagues (2004) found that the β-adrenergic receptor antagonist propranolol impaired the reconsolidation of conditioned fear in humans. Brunet and colleagues (2008) recently tested the effect of propranolol given after the retrieval of memories of past traumatic events. Subjects with chronic PTSD described their traumatic event during a script preparation session and then received a one-day dose of propranolol or placebo. A week later, they engaged in script-driven mental imagery of their traumatic event while physiological measures were taken. Physiologic responses were significantly smaller in the subjects who had received post-reactivation propranolol a week earlier. It was concluded that propranolol given after reactivation of the memory of a past traumatic event reduces physiologic responding during subsequent mental imagery of the event

Furthermore, contexts and discrete cues associated with drug-taking are often responsible for relapse among addicts (Childress *et al*., 1999; O'Brien *et al*., 1998), as well as relapse to drug seeking in Experimental animals (de Wit & Stewart, 1981; Fuchs *et al*., 1998; Meil & See, 1996; Weiss *et al*., 2000). Attempts to extinguish the powerful acquired properties of such contextual cues have not generally been successful as a treatment strategy for drug addiction (Di Ciano & Everitt, 2004; Conklin & Tiffany, 2002). As a result, relapse is a constant risk, despite extended periods of abstinence (Hernandez & Kelley, 2005).

Repeated relapse induced by drug-related cues is likely to be influenced by memory reconsolidation in which a consolidated memory could theoretically return to a labile state following reactivation of the trace (e.g., Nader *et al*., 2000; Przybyslawski & Sara, 1997). Animal models have shown that *interference* with the reconsolidation of drug-cue memories can reduce seeking of drugs or drug-paired stimuli. Using drug cues as reinforcers, investigators reported that the β-adrenoreceptor antagonist propranolol, administered after reactivation of cocaine or morphine conditioned place preference (CPP), impairs drug seeking via disruption of reconsolidation (Bernardi *et al*., 2006; Robinson & Franklin, 2007). Various researchers have thus far demonstrated that it is possible to weaken drug-related memories by interfering with molecular signals in the brain's reward pathways. Lee and colleagues (2005) found that infusions of Zif268 antisense oligodeoxynucleotides into the basolateral amygdala of rats, prior to the reactivation of a well-learned memory for a conditioned stimulus (CS)-cocaine association, abolished the acquired conditioned reinforcing properties of the drug-associated stimulus and thus its impact on the learning of a new cocaine-seeking response. Furthermore, it was shown that reconsolidation of CS-fear memories also requires Zif268 in the amygdala. These results demonstrate that appetitive CS-drug memories undergo reconsolidation in a manner similar to aversive memories and that this amygdala-dependent reconsolidation can be disrupted to reduce the impact of drug cues on drug seeking. Morphine CPP is persistently disrupted when anisomycin, a protein synthesis inhibitor, is administered after a conditioning session (Milekic *et al*., 2006). When mice previously conditioned for cocaine place preference are re-exposed to cocaine in the drug-paired compartment after systemic administration of SL327, an inhibitor of ERK (extracellular signal-regulated protein kinase) activation, CPP response is abolished (Valjent *et al*., 2006). Together, drug-related memory can be inhibited or erased by interrupting its reconsolidation process.

Further, the importance of stress and stress hormones during the different stages of memory processing, *including* reconsolidation, has been implicated in the literature (Diamond *et al*., 1996; Loscertales *et al*., 1998; Newcomer *et al*., 1994, 1999; Roozendaal, 2002). Stress and glucocorticoids (GCs) both *enhance* (Loscertales *et al*., 1998; Roozendaal, 2002) as well as impair (Diamond *et al*., 1996; Newcomer *et al*., 1994, 1999) memory *consolidation*, and memory *retrieval* is typically impaired (de Quervain *et al*., 1998; Kuhlmann *et al*., 2005). To date, only a few groups have studied the effects of stress or GCs on the *reconsolidation* of memory. Maroun and Akirav (2008) provided the first evidence that stress may exert an inhibitory effect on the reconsolidation of memory. They found that, in habituated (low arousal level) and nonhabituated (high arousal level) rats, exposure to an out-of-context stressor *impaired* long-term reconsolidation of object recognition memory. In a recent study conducted by Wang and colleagues (2008), morphine CPP was blocked in rats that received a cold-water stressor or corticosterone following a single-trial reactivation by disrupting reconsolidation of morphine reward memory. It was found that stress administered *after* drug-related memory retrieval significantly decreased subsequent recall through an impaired drug-related memory reconsolidation process, a result consistent with previous studies suggesting that stress impairs the reconsolidation of recognition memory (Maroun & Akirav 2008). However, little is known regarding the effects of stress on the reconsolidation of drug-related memories in *humans*.

The concept of reconsolidation, however, remains one of the most puzzling anomalies within the realm of memory research. Whereas consolidation has, to date, been detected in every type and instance of long-term memory formation (for a review, see Dudai, 2004), reconsolidation does *not* appear to be universal. Many studies have failed to detect reconsolidation (e.g., Cammarota *et al*., 2004; see Dudai, 2004 for a review). In certain systems reconsolidation could not be detected, whereas in others, conditions have been

observed wherein the phenomenon disappears (see Dudai, 2006). This has led to the concept that there are boundary conditions underlying reconsolidation (Nader *et al*., 2005).

Further, human-based research within the area has focused, to a large extent, on *implicit* memory. For example, Walker and colleagues (2003) demonstrated reconsolidation in humans using a procedural motor-skill task that involved finger-tapping a simple sequence (e.g., 4-1-3-2). Twenty-four hours after original exposure to the sequence, participants briefly rehearsed the sequence, thereby reactivating it, and learned a second sequence (e.g., 2-3-1-4). When tested on Day 3, accuracy performance for Sequence 1 was significantly impaired relative to control subjects who did not rehearse Sequence 1 before learning Sequence 2. This shows that the reactivation of the memory for Sequence 1 on Day 2 destabilized it such that a competing motor pattern could interfere with the memory trace. Further, Galluccio (2005) and Galluccio and Rovee-Collier (2005), adopting a conditioning-based paradigm, investigated the fate of reactivated memories in infants trained to kick their foot to activate a mobile. After a delay period, infants were reminded of the event: The moving mobile was presented for a brief period during which it was no longer attached to the baby's foot. Following reactivation, one group of infants learned to move a novel mobile. One day later, infants who were exposed to the novel mobile showed a modification of the reactivated memory such that they no longer recognized the original mobile reacted only to the novel one.

These experiments however, tackled only implicit forms of memory that do not require *conscious* recollection. As such, if reconsolidation is to have any therapeutic value within both anxiety and addiction mediated psychopathologies, for which current treatment strategies have shown limited effectiveness (Di Ciano & Everitt, 2004), it is pertinent to both demonstrate and address contentious issues in *humans*, through adopting declarative-based methods. In so doing, we reasoned that episodic memory, which has been previously shown

to be susceptible to post-event information (e.g., Loftus, 2005), would enable us to achieve these aforementioned goals. Given that contextual information is a pivotal component of episodic memory, it was deemed necessary to first turn our attention to context-based processing.

1.2 Context

1.2.1 Anatomy and Connectivity of the Declarative Memory System

The Hippocampal Fomation

The hippocampal formation (HF) is a C-shaped structure (see Figures 1.1 and 1.2) located within the medial-temporal lobe of humans and non-human primates, with a characteristic laminar organization (i.e., if the hippocampus is cross-sectioned at any septo-temporal level, it is evident that the cells are packed into distinct layers). More extensively, the HF comprises three subregions; the dentate gyrus, hippocampus proper, and the subiculum (comprising the presubiculum, parasubiculum) (Amaral & Witter, 1989; 1995; see Figure 1.2). The hippocampus proper is composed of regions with tightly packed pyramidal neurons, mainly areas CA1, CA2, and CA3. This region is referred to as the 'trisynaptic circuit' or 'trisynaptic loop' of the hippocampus (Anderson, Bliss & Skrede, 1971). Surrounding the HF are the entorhinal, perirhinal, and the parahippocampal cortices (PHC or parahippocampal gyrus, PHG), which surround the rhinal sulcus on the ventromedial surface of the primate brain (Lavenex & Amaral, 2000). The hippocampus derives its name from the Greek word meaning "sea-horse" due to the resemblance between this marine creature and the grossly-dissected human hippocampus.

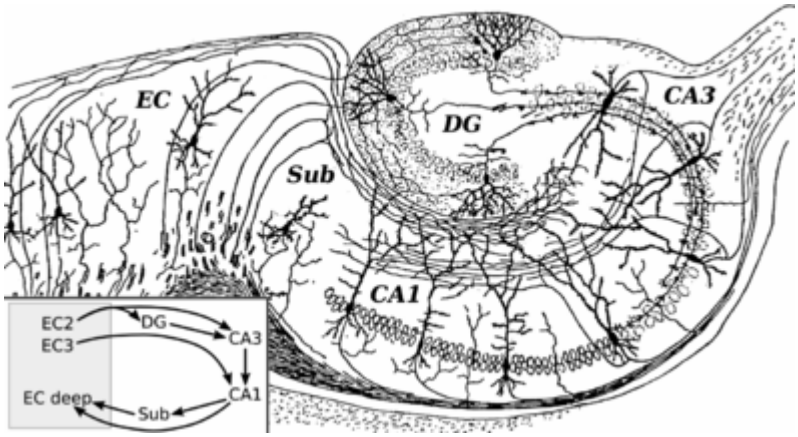


Figure 1.1: Basic circuit of the hippocampus, shown using a modified drawing by Ramon y Cajal. DG: dentate gyrus. Sub: subiculum. EC: entorhinal cortex.

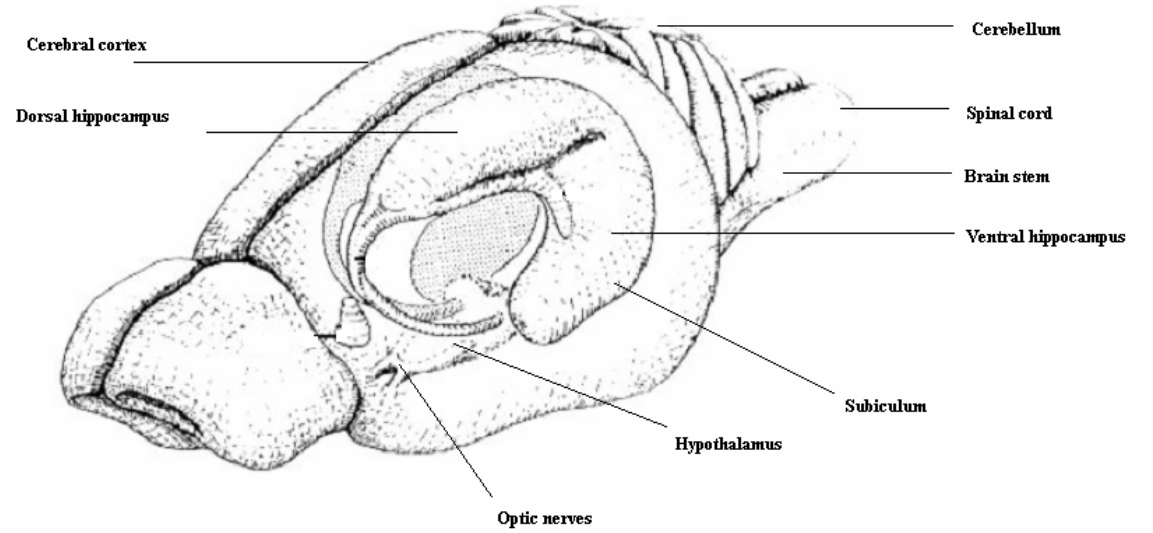


Figure 1.2: A three-dimensional representation of the septo-hippocampal system in the rat brain with the surrounding structures highlighted. The hippocampus is the C-shaped structure (Adapted from Amaral & Witter, 1995).

Information enters the trisynaptic one-way loop via the axons of the entorhinal cortex (EC; i.e., originating in layer II), known as perforant fibres (or the perforant path, given that it penetrates through the subiculum and the space that separates it from the dentate

gyrus). These axons constitute the loop's first connection, together with the granular cells of the dentate gyrus (Anderson *et al*., 2007; Amaral & Witter, 1989; see Figure 1.1). From these cells, mossy fibres in turn project to make the loop's second connection, with the dendrites of the pyramidal cells in area CA3. The axons of these cells divide into two branches. One branch forms the commissural fibres that project to the controlateral hippocampus via the corpus callosum. The other branch forms the Schaffer collateral pathways that make the third connection in the loop, with the pyramidal cells of area CA1 (Ishizuka, Weber & Amaral, 1990). The axons of the cells in CA1 then project to the neurons of the subiculum and of the EC. The *receiving* portion of the HF thus consists of the dentate gyrus, whereas the *sending* portion consists of the subiculum (see Figure 1.4). The axons of the large pyramidal neurons of the subiculum then project to the subcortical nuclei via the fimbria, a thin tract of white matter located at the inner edge of the hippocampus. Finally, the information returns to the sensory cortical areas from which it came prior to hippocampal processing. Apart from the entorhinal input, the dentate gyrus and CA cell fields receive few direct inputs from the cortex. Instead, cortical inputs merge at the subiculum and EC where they are passed to the hippocampus. Subcortically, the hippocampus receives wide-ranging direct inputs, including projections from the septal region to the dentate gyrus, CA3, subiculum and EC (Amaral & Kurz, 1985; Mosko, Lynch & Cotman, 1973; Swanson, Sawchenko & Cowan, 1981). Hypothalamic projections are also made from the dentate gyrus and CA3, and thalamic projections to the subiculum, EC and CA1 (Blackstad *et al*., 1970; Dent *et al*., 1983; Herkenham, 1978; Wyss, Swanson & Cowan, 1979).

Output from the subiculum and EC is the primary pathway by which the hippocampus influences cortical activity. The perirhinal cortex, the cortex of the temporal pole, and the caudal parahippocampal gyrus all receive projections from the subiculur complex or EC (Amaral, 1999; Amaral, Insausti & Cowan, 1984). Subcortical outputs occur

mainly via the fimbria and include projections to the septal nuclei, nucleus accumbens, thalamus, and mamilliary nuclei (Anderson *et al*., 2007). There are also extensive commissural connections between cell fields of the left and right hippocampus (Anderson *et al*., 2007). Further, there are extensive commissural connections between the left and right hippocampi (Anderson *et al*., 2007).

The Medial Temporal Lobe

On a larger scale, the medial temporal lobe (MTL) *encompasses* anatomically related structures including the the hippocampal formation and adjacent parahippocampal, perirhinal, and entorhinal cortices, which lie along the parahippocampal gyrus (collectively referred to as the parahippocampal region; see Witter *et al*., 2000). The *complex* anatomy of the MTL has led to a debate about the nature of the contributions of subregions of the MTL and whether they are associated with functionally distinct processes or act collectively as an integrated system (e.g., Eichenbaum *et al*., 2007; Squire *et al*., 2004).

Anatomically (Figure 1.3 below), the MTL extends from the anterior part of the temporal pole posteriorly to the junction of the temporal and occipital lobes, where it interfaces with the retrosplenial region of the cingulate gyrus (Duvernoy, 1988; Van Hoesen, 1995; Duvernoy, 1999). In the medio-lateral direction, the hippocampus and parahippocampal region have sometimes been viewed as the "fifth temporal gyrus" in addition to the superior, middle, and inferior temporal, and fusiform (or, occipito-temporal) gyri. The lateral boundary of the human parahippocampal region (Witter & Wouterlood, 2002) lies in the collateral sulcus located between the parahippocampal and fusiform gyri. This sulcus is deep and approximately 12–15 cm long, but it is anatomically highly variable and has separate anterior and posterior parts in some individuals (Insausti *et al*., 1998; Pruessner *et al*., 2002).

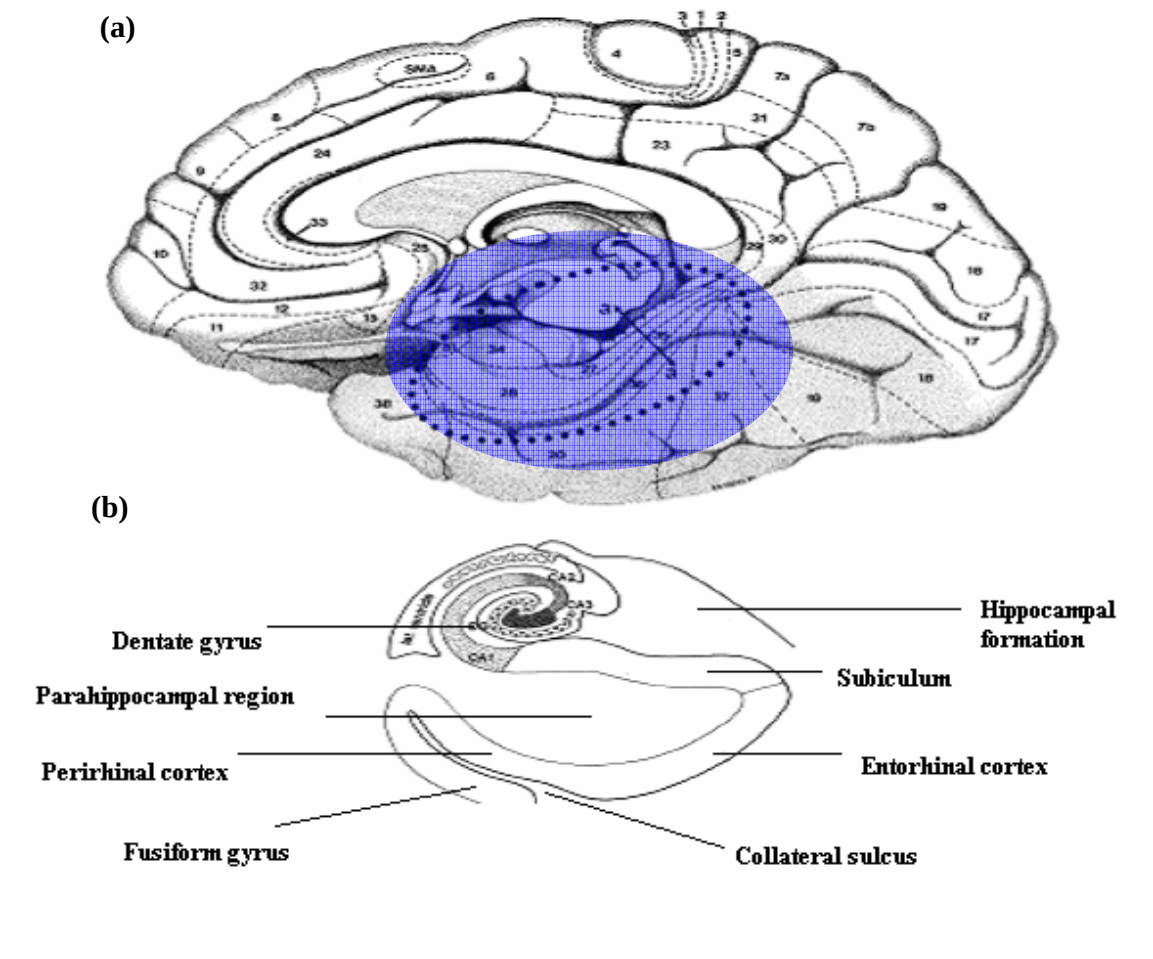


Figure 1.3: Inferomedial surface of the right hemisphere of the human brain with the cytoarchitectonic Brodmann areas (BA) and a transverse section through the medial temporal lobe (MTL), modified from Duvernoy (1999). The purple shaded region in (a) *roughly* delineates the the MTL with its neighboring areas; (b) shows a schematic transverse section through the hippocampal formation and parahippocampal region.

The importance of the MTL as a *memory system* is attributable to its connectivity with the *broader neocortex*. Multiple uni- and polymodal cortical regions project to the parahippocampal and perirhinal cortices (Burwell & Amaral, 1998; Schmahmann & Pandya, 2006; Suzuki & Amaral, 1994a). These cortical projections encompass two parallel pathways. The parahippocampal cortex receives inputs from visual association areas, retrosplenial cortex, the dorsal bank of the superior temporal sulcus, and the parietal lobe, among other regions. The perirhinal cortex receives inputs including from visual areas in the

ventral temporal cortex and the ventral and dorsal banks of the superior temporal sulcus (Lavenex & Amaral, 2000; Suzuki & Amaral, 1994a,b).

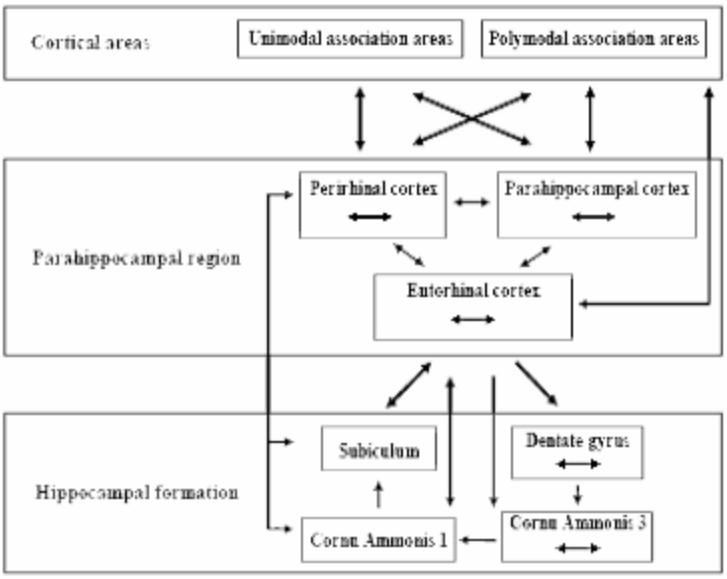


Figure 1.4: Schematic of cortical and intrinsic connections of the MTL in the monkey. Adapted from Lavenex and Amaral (2000).

The neocortical connections of parahippocampal and perirhinal cortices are complementary (Burwell & Amaral, 1998; Suzuki & Amaral, 1994a; see Figure 1.4). Both the parahippocampal and perirhinal cortices feed information into the entorhinal cortex. The parahippocampal cortex mainly projects to the medial entorhinal area, whereas the perirhinal mainly projects to the lateral entorhinal area. The entorhinal cortex, in turn, projects to the HF. These parallel pathways, however, are interconnected with a substantial projection from parahippocampal cortex to perirhinal cortex, in addition to connections between the lateral and medial areas of the entorhinal cortex. Thus the anatomy of the cortico-parahippocampal-hippocampal system is best described as including *both* parallel and hierarchical components, positioning it well to integrate diverse informational sources important to memory (Burwell, 2000; Furtak *et al*., 2007; Lavenex & Amaral 2000; Witter *et al*., 2000). These two pathways

have been heuristically related to spatial and nonspatial aspects of sensory input due to their preferential connections to parietal areas (i.e., the parahippocampal pathway) and inferior temporal areas (i.e., the perirhinal pathway), respectively.

The cortical connections of the parahippocampal region have *functional* implications. The perirhinal cortex is uniquely situated to fulfill its hypothesized role in high-level visual processing, such as object identification (Murray & Richmond, 2001), whereas associational inputs to the parahippocampal cortex suggest a role in visual and visuospatial cognition (Bohbot *et al*., 2000). Since the perirhinal cortex does not have connections with parietal or retrosplenial cortices, it is not thought to have a significant role in visuospatial processing. The perirhinal and parahippocampal cortices are at the same hierarchical level, *i.e*. the first stage on the neocortical-hippocampal system for memory consolidation (see Figure 1.4). These cortical structures appear, however, to differ in terms of reciprocity of their cortical connections, although the functional significance of these differences is thus far unknown. The final stage of the neocortical-hippocampal loop is the HF. Connections within the parahippocampal, perirhinal, and entorhinal cortices allow for a significant integration of information that eventually reaches the hippocampus (Suzuki & Amaral, 1994b; Witter *et al*., 2000). The strongest projection to the hippocampus, the perforant pathway, arises from layer II of the entorhinal cortex (Witter *et al*., 1989b, Lopes da Silva *et al*., 1990). Furthermore, the perirhinal and parahippocampal cortices have direct connections to the CA1 and subicular subfields of the HF (Insausti & Munoz, 2001). In terms of its unique input of information, the HF may contribute to the formation of new associations between novel stimuli and their spatial contexts thereby forming new events, or associating facts with their semantic contexts thus forming new semantic concepts (Eichenbaum, 2001; Manns *et al*., 2003b).

1.2.2 The Hippocampus, Context and Episodic Memory

As previously outlined, the HF of the medial temporal lobes receives input from cortical areas specialized for processing sensory information in *all* modalities, thereby rendering HF a likely candidate for a role in both the instantiation and *re*instantiation of context. Indeed, an extensive literature involving brain lesions has implicated the hippocampus in *context processing* (for review, see Myers & Gluck, 1994; Anagnostaras *et al*., 2001; Maren, 2001). For example, hippocampal lesions impair conditioned fear responses to contextual stimuli (Kim & Fanselow, 1992; Phillips & LeDoux, 1992), and lesions of the hippocampus or entorhinal cortex render subjects insensitive to changes in the context (Penick & Solomon, 1991). Also, subjects with fornix lesions have been shown to be severely impaired in learning two different discrimination tasks that were trained in different contexts (Smith *et al*., 2004). In the same subjects, context-specific neuronal firing patterns were degraded in structures receiving hippocampal input via the fornix (i.e., anterior thalamus and cingulate cortex). Such findings infer that the hippocampus generates a unique context code that modulates processing in downstream structures.

Furthermore, the hippocampus has been widely implicated in *episodic* memory (e.g., Tulving & Markowitsch, 1998; Aggleton & Brown, 1999; Eichenbaum & Cohen, 2001). Hippocampal neurons respond preferentially to conjunctions of stimuli, such as the concurrence of a conditional stimulus and a place (Wood *et al*., 1999; Moita *et al*., 2003), and spatial firing can be contingent on past or future actions (Frank *et al*., 2000; Wood *et al*., 2000; Ferbinteanu & Shapiro, 2003). Findings such as these suggest that hippocampal neurons encode the relations among stimuli in the interest of episodic memory. Smith and Mizumori (2006) recently suggested that the hippocampus contributes contextual information to a wider circuitry for the formation of episodic memories. Therefore, episodic memory may be mediated by extended circuitry that includes, but is not limited to, the hippocampus.

Several authors have suggested that hippocampal memory functions are mediated by circuitry involving the entorhinal cortex, anterior thalamus, prefrontal cortex, and retrosplenial cortex (Aggleton & Brown, 1999; Eichenbaum, 2000; Suzuki & Eichenbaum, 2000; Smith *et al*., 2004; Wiltgen *et al*., 2004; Siapas *et al*., 2005). Thus, it would appear that the HF, as suggested by Mesulum (1998), organises the various distributed representations that together form an episodic memory, without itself becoming their physical repository, thereby ensuring the remembrance of the original trace and enabling access to the entire engram via partial cues from different sensory modalities.

Although there is general consensus stipulating that the hippocampus plays a role in context effects (e.g., see Smith & Mizumori, 2006; Rudy *et al*., 2004; Gerwitz *et al*., 2000), a lack of cohesion arises concerning the nature of context itself, in particular the fact that there are multiple forms, and hence representations, of context, only one of which depends upon the hippocampus. Nadel and Willner (1980) have argued that context representations formed in the hippocampus are essentially configural, being based on relations among the environmental features that comprise the physical lay-out of space. The authors further argued that because of this configural nature, learning about spatial context diverges in important respects from learning about isolated cues, or elements, within an environmental context. The authors further asserted that hippocampal damage would manifest as a lack of context-specificity, in the respect that learning should theoretically be inappropriately generalized to novel contexts. Indeed, in humans, the contribution of contextual factors has been well established and it has been repeatedly shown that returning a participant to the original context in which information was initially learned results in facilitation for recall of that information, while altering context can impair recall (Tulving, 1974; Tulving & Thomson, 1973). Further, adopting conditioned fear paradigms in animals (e.g., Anagnostras *et al*., 1999, 2001; Fanselow, 1999, 2000), it has been found that; the hippocampus seems to

be necessary for the acquisition of context fear, and for the retrieval of such fear for days (or weeks) following initial training, but *not* for retrieval 28 days after training; and the acquisition of context fear itself depends upon the animal having had some previous exposure to the context prior to fear training. In the absence of such experience, context fear does not develop.

Squire (1992) proposed the *Classic Consolidation Theory* which postulates that the hippocampus stores memories as a result of encoding, but the memories are then consolidated over time to more stable cortical areas. Evidence for this theory derives primarily from the phenomenon of retrograde amnesia (an inability to recall past memories occurring along a temporal gradient). Patients demonstrating such memory loss appear to have CA1 damage along with more extensive damage to the dentate gyrus and entorhinal cortex (Rempel-Clower *et al*., 1996). This suggests that, as the damaged area extends further from the hippocampus, patients suffer retrograde amnesia. However, Nadel and Moscovitch (e.g., Nadel & Moscovitch, 1997, 1998; Moscovitch *et al*., 2006), have argued that this standard model of memory consolidation is misguided in assuming that memories "transfer" from the hippocampus to the neocortex over a period of time. According to these authors, the major problem with this concept, which is succinctly evident in conditioned fear memory research, resides in its assumption that the content of the memory remains constant as the neural systems responsible for it shifts across the aforementioned 28 days. Instead, Nadel and Moscovitch (1997) have proposed the *Multiple Trace Theory* according to which the hippocampus is involved in episodic and spatial memories for as long as they exist with only a time-limited contribution to other forms of memory (i.e., semantic) which are stored elsewhere in the brain. Thus, memories can lose their "context" dependence, becoming less "episodic" and more "semantic" in nature. As such, the "context" representation that supports

conditioned fear after several weeks is a representation based on *elements* present in the test situation rather than a configural representation of the whole.

Such an explanation mirrors findings pertaining to the 'pre-exposure' effect. In this case, when an animal is given fear training without some exposure to the training context prior to the introduction of the unconditioned stimulus, it fails to learn to associate shock with the "context" understood as the configuration of elements (and their spatial relations) in the chamber. This happens, according to Nadel, because exposure to the shock chamber is essential for the animal to acquire a configural representation of the context in the first place – what is termed a 'cognitive map' (O'Keefe & Nadel, 1978), or a contextual representation (Nadel & Willner, 1980). According to Nadel, such a finding parallels what happens over time within the realm of consolidation. Initial training (with pre-exposure) leads the animal to associate fear with the configurally-represented context. As such, the behavior depends upon the hippocampus as well as the amygdala. Over time, and as a direct consequence of what has been termed consolidation, the contextual binding weakens, leaving behind only linkages between elements of the chamber and the shock.

These considerations make it much easier to understand the existing literature concerning context and hippocampal lesion effects and why doubts still exist about hippocampal involvement in context learning (e.g., Gewirtz *et al*., 2000). When "normal" behavior depends upon a configural representation of context, hippocampal lesions will lead to impairment (Nadel, 2008). This should be the case for both acquisition and retention. When a task is used that can be solved with *either* a configural *or* an elemental representation of context, hippocampal lesions will not cause an obvious impairment; rather, special testing methods will have to be used to show that performance differs between animals with hippocampal lesions and control animals. The most obvious method would be to shift the test context. Paradoxically, animals with hippocampal lesions should theoretically be *less*

affected by such a shift than intact animals. In the case of conditioned fear, for example, hippocampally-lesioned rats should show greater-than-normal fear in an out-of-context test. Indeed, Nadel (1968) demonstrated this effect; rats with dorsal hippocampal lesions tested in context B for fear of a CS paired with shock in context A actually showed more fear than did control rats. This parallels observations of Penick and Solomon (1991), and is consistent with the report by Good and Honey (1991) showing that hippocampal lesions impaired rats' ability to learn that a stimulus was reinforced in one context but not in another (see also Lehmann *et al*., 2005; but see Hall *et al*., 1996). It is also consistent with the recent findings that hippocampal inactivation impairs the context specificity of latent inhibition (Maren & Holt, 2000), and extinction (Corcoran *et al*., 2005; Hobin *et al*., 2006), and that reinstatement of conditioned fear in humans is context specific (LaBar & Phelps, 2005).

In *humans*, converging evidence between standard and multiple trace explanations of hippocampal involvement in episodic memory derives from an MRI study conducted by Cipolotti *et al*. (2001) whereby patients suffering both anterograde and retrograde amnesia showed marked hippocampal abnormalities; however, the remainder of both temporal lobes was normal. As such, the researchers suggested that the hippocampus is critical for encoding of new information but also for the recall of episodic information acquired prior to the onset of amnesia. In this light, one can only speculate about the contribution of the hippocampus to long-term memory but it is virtually undeniable that the structure is necessary for *new* memory formation regardless of whether it is semantic or episodic. Indeed, the fact that patient H.M. (Scoville & Milner, 1957), who could not create new long-term memories, but could recall long-term memories that existed prior to his hippocampal ablation surgery, suggests that encoding and retrieval of long-term memory information may also be mediated by distinct systems (see Figure 1.4 below).

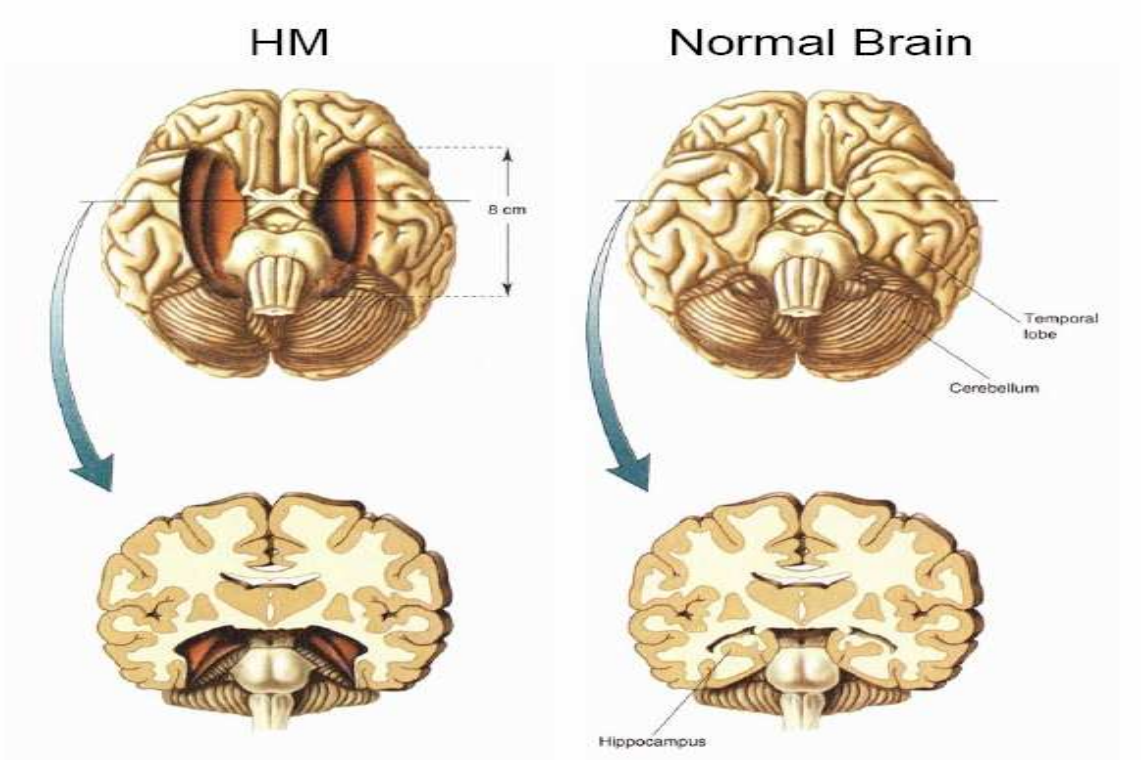


Figure 1.4: Comparison of hippocampal region following hippocampal resection in the case of patient H.M. and in a normal brain.

1.2.3 Context-Dependent Memory in Human-based Research

The term 'context' is quintessentially adopted to refer to spatial, temporal or cognitive information that is present in the environment and surrounds the memory task target but is *irrelevant* or at most *incidental* to the cognitive task being performed. As previously mentioned, the contribution of contextual factors upon learning and memory has been well established and it has been repeatedly shown that returning a participant to the original context in which information was learned results in facilitation for the recall of that information, while altering context can impair recall (e.g., Godden & Baddeley, 1975). Indeed according to the Encoding Specificity Principle (Tulving, 1974; Tulving & Thomson, 1973), memory for *attended* aspects of an encoded event (i.e., item memory) is facilitated

when features of the encoding context are reinstated at test, thereby indicating that item and context features are bound together in memory traces (Smith, 1979). At a basic level, the Encoding Specificity Principle suggests that episodic memory will be improved when contextual cues are provided. The cues will reinstate encoding conditions, and this should increase access to *all* encoded information, including incidentally processed contextual details. Furthermore, the majority of theories concerning memory storage and retrieval incorporate contextual cueing in their models. For example, current models of memory including the Search of Associative Memory (SAM) model (Raaijmakers & Shiffrin, 1981), the Item, Associated Context and Ensemble (ICE) model (e.g., Murnane, Phelps, & Malmberg, 1999), and other theories incorporating models of contextual drift (e.g., Mensink & Raaijmakers, 1988) use context as an integral explanatory variable. Retrieval cues can match both intentionally and incidentally encoded information, and each matching feature increases the summed global activation score for the set of items in memory. Ultimately, if contextual information is associated with target material, then contextual cues should stimulate memory for associated material.

Context can be manipulated in a variety of ways. Some of the first studies involving context effects examined how context can reduce interference. In these studies, participants studied target and interfering lists presented in either the same or disparate contexts. Results showed that learning the target lists in one environmental context, and the interfering lists in different environmental context reduced interference (Bilodeau & Schlosberg, 1951; Dallett & Wilcox, 1968). Memory can also be improved with multiple learning contexts. Participants exposed to material in different environmental contexts or rooms and then tested in an entirely different environmental context show improved memory for the study lists than when learning is confined to a single learning context (Smith, 1988). The improved recall is

presumed to occur because providing multiple learning contexts equips participants with many more cues to aid the retrieval of items. A recent meta-analysis found that interference reduction and multiple learning context paradigms generally produced the most robust context effects (Smith & Vela, 2001).

Another type of context that aids memory is the *incidental* environmental context. An incidental environmental context differs from the contexts described above given that it refers to the spatial and temporal contexts that are not related to the targets of a memory test in an obvious manner. Many dimensions of the incidental environment have been manipulated to investigate indices context-dependent memory. Studies have examined the effect of room manipulations (e.g., Smith, 1979; Smith, Glenberg & Bjork, 1978), changes in the natural environment (e.g., Godden & Baddeley, 1975), changes in the ambient odour (e.g., Herz, 1997; Smith, Standing, & de Man, 1992) and background music (e.g., Balch, Bowman, & Mohler, 1992; Smith, 1985) on participants' memory. When the incidental environmental context is the same at encoding and test, memory is improved as compared to memory when the encoding environment is different from the test environment, an effect referred to as a 'reinstatement effect' (Smith & Vela, 2001).

Reinstatement effects can be understood in terms of the aforementioned Encoding Specificity Principle which, as previously stipulated, postulates that the environmental context can be encoded as part of a memory trace and that this can aid memory for previously stored information when a person is placed in the same context. Thus, because memory is cue-dependent, memory will always be best when the conditions at test match the conditions during encoding (Tulving, 1983). This cue-dependent effect occurs not only for incidental environmental cues, but for semantic contexts also (e.g., Light & Carter-Sobell, 1970). A meta-analytic review of studies of environmental context-dependent memory in humans found that, across all published studies, context manipulations have reliably affected memory

(Vela & Smith, 1992). Not all effect sizes, however, are equal and variations can be found as a function of the memory paradigm employed, the type of input processing given to the targets, and the type of test used to assess memory.

A critical issue concerning contextual cueing effects concerns the nature of the information that is used to reference the target item. Studies have shown that the target is associated with a few local nearby items, rather than with the global pattern or structure created by the elements in the surrounding environment (e.g., Jiang & Wagner, 2004). The vast majority of research within the Encoding Specificity domain has been primarily interested in ascertaining the effect of manipulating global context on memory performance. Other studies investigating the manipulation of both local and global context have been conducted by researchers such as Jiang & Wagner (2004) who found that context-target associations transfer to new contexts with altered global arrangements of elements so long as some local aspects of the learned context are maintained in the new global arrangement. This effect was so powerful that even when the global context of the search arrays was highlighted by a line that connected all distractor stimuli to form a global shape, observers continued to use local cues to locate the target, albeit at a lower rate. This finding suggests that participants employ local cues to identify a target. This finding has also been observed by Olson & Chun (2002), who found that if the positions of some of the elements within a repeated array remain fixed while others vary, contextual cueing occurs only if the target appears within the invariant portion of the display. Thus, variation in the local context immediately surrounding the target prevents cueing, and cueing is possible even if the global structure of all items is never repeated, as long as local context remains constant. However, both of these studies employed non-scene stimuli.

Related to context-dependent traumatic memory, and importantly in terms of possible therapeutic research directions within the realm of reconsolidation, central aspects of

emotional experiences are often remembered at the expense of incidental background details (Payne, Nadel, Britton, & Jacobs, 2004; Reisberg & Heuer, 2004). A real-world example of this trade-off is the weapon-focus effect, wherein victims vividly remember an assailant's weapon but have little memory for other integral aspects of the scene (Stanny & Johnson, 2000; Loftus, Loftus & Messo, 1987). This divergence in memory for central and peripheral aspects of emotional events reflects, at least in part, differential encoding of these two components of the scene. At present, it is unclear how the components of emotional episodic memories are processed and stored and whether they change over time or remain the same. Emotional scenes could be stored as intact units, undergoing some forgetting over time but retaining the same relative vividness for central and peripheral components. Alternatively, the components of the scene could undergo differential processing and storage, perhaps with a selective emphasis on what is most salient and worthy of remembering. Thus, weapons attract witnesses' visual attention, such that other peripheral details receive less perceptual processing than when no weapon is present. Because they are poorly encoded, these peripheral details are not remembered well later (see Kramer *et al*., 1990; Loftus *et al*., 1987). Indeed Payne and colleagues (2008) recently demonstrated that memory for a negative scene develops differentially across time delays containing sleep and wake, with sleep selectively consolidating those central aspects of the emotional memory trace that are of greatest value to the organism.

1.2.4 Context Recognition- The Key to Reconsolidation

Context plays an integral role in the consolidation of a memory trace. The impact of hippocampal lesions on the retention of a context-based task depend upon *when* retention is tested, and upon whether or not the animal was *reminded* of the context before retention was tested. As proposed by Nadel and colleagues above, after some weeks during which a rat is

not returned to the training context, its configural representation of that context weakens, and elemental contextual representations take over. In the absence of reminders that bring the context back into the frame, hippocampal lesions yield little or no effect. However, as various investigators (e.g., Debiec *et al*., 2002; Land *et al*., 2000) have reported in the reconsolidation literature; if animals are reminded of the context before lesions are made, then these lesions subsequently serve to impair retention.

Creating an entirely new representation in response to deciding that one is in a new environment differs from updating an existing representation based on some local change (Nadel, 2008). According to Nadel, this assertion is fundamental to the distinction between memory "consolidation" and memory "reconsolidation". It has long been assumed that a time-dependent stabilization process unfolds after the initial acquisition of a memory (Müller & Pilzecker, 1900). During this time period, termed the "consolidation" interval, memories can be disrupted by new learning experiences, cerebral trauma, hypothermia, electroconvulsive shock, and so on. This idea was initially framed within both physiological and psychological terms, and included the possibility that the content of the memory might itself be transformed during consolidation (Burnham, 1903). Hebb (1949) isolated the physiological process underlying consolidation, thereby providing a comprehensive understanding concerning how exactly memories become stabilized. Hebb assumed that memories are isolated in the brain through changes in synaptic efficacy, and that these changes depend upon complex cellular and molecular mechanisms that lead to structural alterations underpinning potentiated synaptic function. According to Hebb these changes unfolded within the same cell assemblies initially activated by the experience, possibly through reverberations within these assemblies. Study of patient H.M., however, suggested that, in terms of memory for life's episodes, consolidation involves a shift wherein brain structures are critical for memory retrieval. Thus began a long tradition of linking what has

come to be termed systems-level memory consolidation to a shift from hippocampal to neocortical dominance in memory retrieval. The consolidation period was assumed to end when the hippocampal system was no longer essential in retrieval.

It was within this context that the concept of memory reconsolidation first emerged. A number of investigators in the 1960s and 1970s, unconvinced by the concept of consolidation, argued instead that memories were always open to alteration and/or disruption as long as they were in an *active* state (Lewis, 1979; Misanin *et al*., 1968). Memories could be reconverted into an active state through "reminders" such as exposing the organism to the CS used in the learning task, or the context in which learning took place. These ideas, though supported by several well-replicated findings, were neglected in favour of consolidation.

The notion of reconsolidation *re*-emerged in two labs: Sara and colleagues (e.g., Przybyslawski & Sara., 1997; Sara, 2000) and Nader, LeDoux and their colleagues (Nader *et al*., 2000) which both demonstrated that reminders could return well-consolidated memories for maze learning and fear conditioning, respectively, back to a fragile, labile state, and that these newly-fragile memories could be disrupted by the systemic injection of MK-801 (an NMDA channel blocker), or protein synthesis inhibitors into the amygdala, respectively. There followed a proliferation of studies demonstrating the robust nature of 'reconsolidation', its presence in a wide variety of species and learning situations, how it is differentiated from consolidation, and what some of the boundary conditions are that constrain it (refer to Moore & Roche, 2007, for a comprehensive account of the literature).

In a similar vein, a tradition of research using *human* subjects has demonstrated seemingly similar malleability in what should have been consolidated episodically mediated memories (e.g., Loftus, 2005). Much of this research employs a standard procedure wherein subjects are exposed to a complex event, and are later given misinformation concerning some detail of that event. When subsequently asked to recall the event quite often the

misinformation rather than the original detail is remembered. One thing that distinguishes this work on human memory from the animal work discussed previously is the absence of any systematic manipulation of specific reminders.

With the intention of merging these two animal and human based findings, Nadel and colleagues recently developed a paradigm to study reconsolidation in *human* episodic memory that depends upon reminding subjects about what they previously learned (Hupbach *et al*., 2007). In this paradigm, subjects are initially trained on a "list" of objects. These everyday objects are kept in a blue basket and presented one by one to the subject. After all 20 objects are presented, the subject is asked to verbally "recall" the list. This training sequence is continued until the subject recalls at least 18 of the 20 objects (in any sequence). Typically this takes fewer than four training trials. Two days later subjects return to the laboratory and are divided into two groups. Subjects in one group are reminded of their previous training experience, whereas subjects in the other group are not. Subsequently, a second "list" of objects is learned, albeit in a different manner. The objects on this second list are laid out on a table instead of being contained in a basket. Following the learning of this second list recall for both lists is tested either immediately or two days later. In one study, recall of List 1 was tested first, followed by List 2, and in another study recall of List 2 was tested first, followed by List 1. In both studies retrieval performance of subjects that had been reminded was contrasted with subjects that had not.

The results emanating from this research stream can be summarized as follows (see Hupbach *et al*., 2007 for a more detailed account): if, and only if, a reminder was given prior to the learning of List 2, subjects inter-mixed items from List 2 into List 1 when asked to recall List 1. In another study these authors showed that this result is found *only* when recall is tested 2 days later. Intrusions from List 1 into List 2 recall were never observed, whether List 2 is recalled first or second, immediately or 2 days later. Nadel and colleagues

interpreted these results as indicative that the reminder presented prior to List 2 learning reactivated the memory trace for List 1, and thereby triggered an "update" mechanism which caused the subject to confuse the List 2 and List 1 objects. In the absence of the reminder, the subjects treated List 2 learning and List 1 learning as separate episodes and intrusions did *not* occur.

This research team, more recently, has begun to explore exactly what kinds of reminders play a critical role in initiating this "update" mechanism (Hupbach *et al*., 2008). In the original study the reminder involved returning the subject back to the same context, with the same Experimenter, who asked a leading question about the List 1 training experience. The no-reminder group was brought to a different context, with a different Experimenter, and was not asked about List 1 training. In the most recent of such work, these authors systematically manipulated the nature of the "reminders" available to the subjects prior to learning List 2. In one set of studies, only one of the three reminder cues was presented: the original training context, the original Experimenter, or the leading question about the basket in which List 1 objects were kept. Results revealed that only the group that received a *context* reminder showed the memory updating effect. The other two groups showed few if any intrusions of List 2 items into List 1 memory, thereby indicating that updating had *not* occurred in these groups.

Furthermore, in a second set of studies, two of the three cues were provided, either context plus Experimenter, context plus question, or Experimenter plus question, with the intention of investigating the possibility that the failure of the Experimenter or Question to initiate an updating process might have reflected that fact that these are weak cues compared to context, and that by combining these two weaker cues, updating would be demonstrated. Once again, *only* the provision of a *context* reminder, in combination with either the Experimenter or the Question, elicited updating. That these conditions are effective is hardly

surprising since the previous study had shown that context alone is enough to trigger updating.

This set of experiments demonstrates that reconsolidation, as reflected in memory updating effects dependent upon reminding, *can* be observed in *human* learning. They further show that such updating *only* occurs when the context is part of the reminder manipulation, at least in the experimental conditions of these aforementioned studies. Nadel and colleagues conjecture that these results support the idea that context plays a unique role in determining how the memory system behaves. Thus, when in the same context – updating and transformation of an existing memory trace ensues, but when in a new context, an entirely new memory representation is formed.

Thus, it appears that context is an integral component of episodic memory. It is, however, more than just a component of such memory. It also seems to play a determining role in the dynamics of the episodic memory system as a whole. To the extent to which this is the case, further study concerning *how* context is represented physiologically should greatly enhance our understanding of human memory.

1.3 Stress

1.3.1 The Hippocampus and Stress

The hippocampus has a dense concentration of receptors for glucocorticoids (i.e., hormones released during stress; McEwen *et al.* 1986) and is also involved in the consolidation of new memories (Squire, 1982). There is considerable evidence that stress, or the high levels of glucocorticoids accompanying stress, can impair performance on contextual and episodic memory tasks, which are known to require hippocampal function (e.g., Henson, Shallice, & Dolan, 1999; Lupien *et al*., 1998; Nadel & Jacobs, 1998). Indeed, even moderate stress levels

can impair memory function (for reviews, see Lupien & McEwen, 1997; Wolf, 2003). As mentioned previously, there is general agreement that the hippocampal system is important in representing context (Nadel & Willner, 1980), perhaps by binding together elements of the contextual situation and events that make up a given episode (Nadel, 1991). Human and animal studies firmly establish that the high levels of glucocorticoids released *during* stress impair the function of the hippocampus, thereby weakening or completely disrupting those aspects of contextual and episodic memory subserved by this structure (De Quervain *et al.*, 2000, Diamond & Rose, 1994, Lupien *et al.*, 1998; Nadel & Jacobs, 1998; Newcomer *et al.*, 1999). We reason herein that if stress interferes with the *normal* functions of the hippocampus, and the hippocampus is central to context effects in memory, then stress might interfere with those forms of memory dependent upon context and the binding it supports. Thus, we presently postulate that manipulations adversely affecting contextual encoding and retrieval, such as stress, should interfere with memory *retrieval*, thereby allowing us to isolate the effects of blocking the reconsolidation of an episodic hippocampally mediated memory trace. As such, if we are to block the reconsolidation process in *humans*, stress provides a means of impairing protein synthesis.

Exposure to highly stressful events is known to trigger a variety of physiological reactions, of which many are related to the activation of stress-responsive sympatho-adrenal-medullary (SAM) and hypothalamic–pituitary–adrenal (HPA) axes. A plethora of research has revealed that secretion of glucocorticoids (GCs) in response to HPA axis stimulation may modulate memory functioning (e.g., de Kloet *et al*., 1999; McGaugh, 2000; Roozendaal, 2000). However, the precise direction of stress-induced GC effects on memory performance is far from succinct. Animal studies, for example, have shown that GCs can exert *both* facilitating (e.g., on aversive conditioning) as well as impairing effects on memory (e.g., de Kloet *et al*., 1999; Lupien & McEwen, 1997; McGaugh & Roozendaal, 2002). Similarly,

studies employing human participants have reported that acute GC administration may enhance or disrupt memory, yet the precise conditions under which these effects occur are thus far ill-understood (for reviews, see Het *et al*., 2005; Lupien *et al*., 2005; Lupien & Lepage, 2001; Wolf, 2003).

1.3.2 The Physiology of the Stress Response

Although stressors vary widely, the physiological response is relatively *nonspecific*. The term 'stress' was first introduced by Hans Selye (1936), who explained the phenomenon in terms of nonspecific bodily changes that occurred in response to physically harmful stimuli, or "stressors". More recently, stress has come to embody negative effects on the system wherein stressors elicit a bodily response perceived as unrest or one that causes anxiety (Morley, Benton & Solomon, 1991). More appropriately for current circumstances, however, stress is the sum of biological reactions to intrinsic and extrinsic stimuli that culminates in a deviation from homeostasis (Chrousos & Gold, 1992). Initiated by the brain and largely mediated by stress hormones, stress-induced changes include an increase in oxygen intake, redirection of blood flow to the muscles, an increase in blood sugar levels to provide the organism with energy, and a behavioral urgency to act in response to a perceived threat (i.e., *'fight or flight'*). Given that all of these activities involve expending energy, there must be conservation elsewhere in the body. Thus digestion, tissue repair and growth, reproductive activities, and immune function are all inhibited by the stress response (Sapolsky, 1998). The stress response also acts on the brain to presumably affect certain cognitive operations and predispose certain types of behavior. Thus in order to understand the effects of stress upon cognition, it is pertinent to understand the physiological stress response.

Hypothalamic Pituitary Adrenal Axis

The slower hormonal system to be activated during the stress response is the hypothalamic-pituitary-adrenal axis (HPA; Figure 1.5). Unlike the sympathetic-adrenal medulla system (SAMS), which instantly initiates an autonomic response via direct neural stimulation of organs (followed and reinforced by epinephrine release), the HPA stress response relies exclusively on the relatively slower action of adrenal hormones to exert their effect (Sapolsky, 1998). HPA activity thus maintains and builds upon the sympathetic response. Firstly, the paraventricular nucleus of the hypothalamus releases corticotropin releasing factor (CRF), which in turn stimulates the pituitary to release adrenocorticotropin hormone, or ACTH into the bloodstream (for review, see Lovallo & Thomas, 2000; Sapolsky, Romero & Munck, 2000). ACTH makes its way to the adrenal glands, causing the adrenal cortex to release adrenocortical hormones, which are steroids (i.e., lipids derived from cholesterol). There are three classes of hormones produced and released from the adrenal cortex; mineralocorticoids (which help to maintain electrolyte balance), sex hormones, and glucocorticoids (the most important of these in humans is cortisol, while in rodents it is corticosterone; Sherwood, 1997).

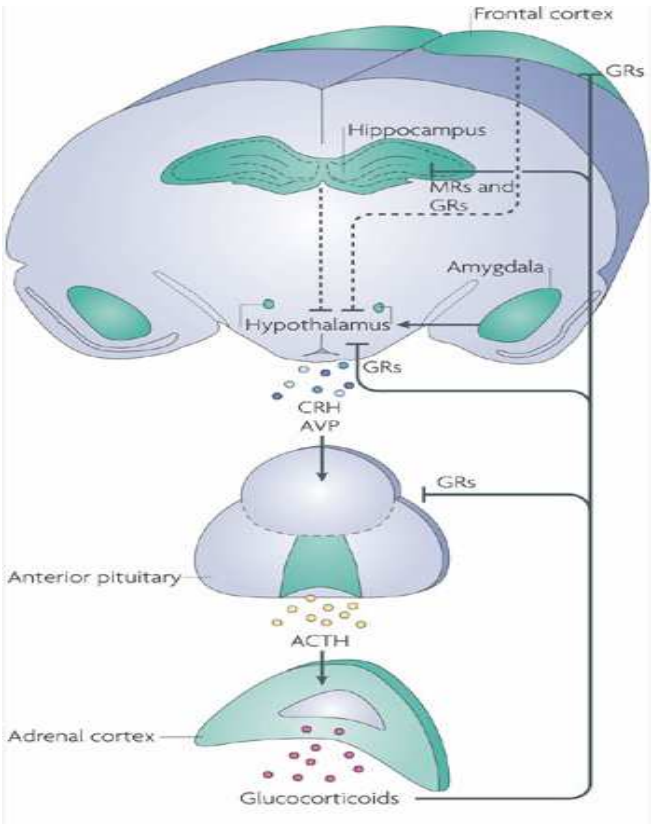


Figure 1.5: Schematic of the hypothalamic-pituitary-adrenal (HPA) axis stress response. Adapted from Lupien *et al.* (2009). © 2009 Nature Publishing Group.

Glucocorticoids such as cortisol play an integral role in raising circulating levels of glucose in the blood to provide muscles and the brain energy for the stress response. Cortisol does this by stimulating the liver to convert glycogen into glucose (which is then released into the blood), inhibiting the secretion of insulin (which takes up glucose for storage), and promoting hepatic gluconeogenesis (converting amino acids into glucose when carbohydrate sources are depleted; Sherwood, 1997). Cortisol also promotes the break-down of protein (i.e., muscle) into amino acids for later gluconeogensis, and fat into fatty acids to provide an additional source of energy for some tissues (although the brain can only use glucose; Sherwood, 1997). While cortisol works to make energy available, it also contributes to the

shut-down of bodily activities that compete for resources—longer-term processes or maintenance activities that can be delayed until after the stressful situation subsides. These include immune function, tissue repair, digestion and energy storage, and certain reproductive activities (Sapolsky *et al*., 2000). Elevated levels of cortisol eventually trigger a negative feedback inhibition process to ensure hormone levels are prevented from rising out of control. High levels of cortisol thus signal the hypothalamus to stop releasing CRF, essentially down-shifting the HPA response. This maintains cortisol at the level necessary to cope with the stressor, or returns cortisol levels to their basal level once the stressor has passed (Bullock, 2001). Indeed, several feedback loops (see Figure 1.6) are involved in regulating the activity of the HPA axis, providing sensitive mechanisms which adjust the circulating cortisol level throughout the day (Pollard & Ice, in Ice & James, 2007).

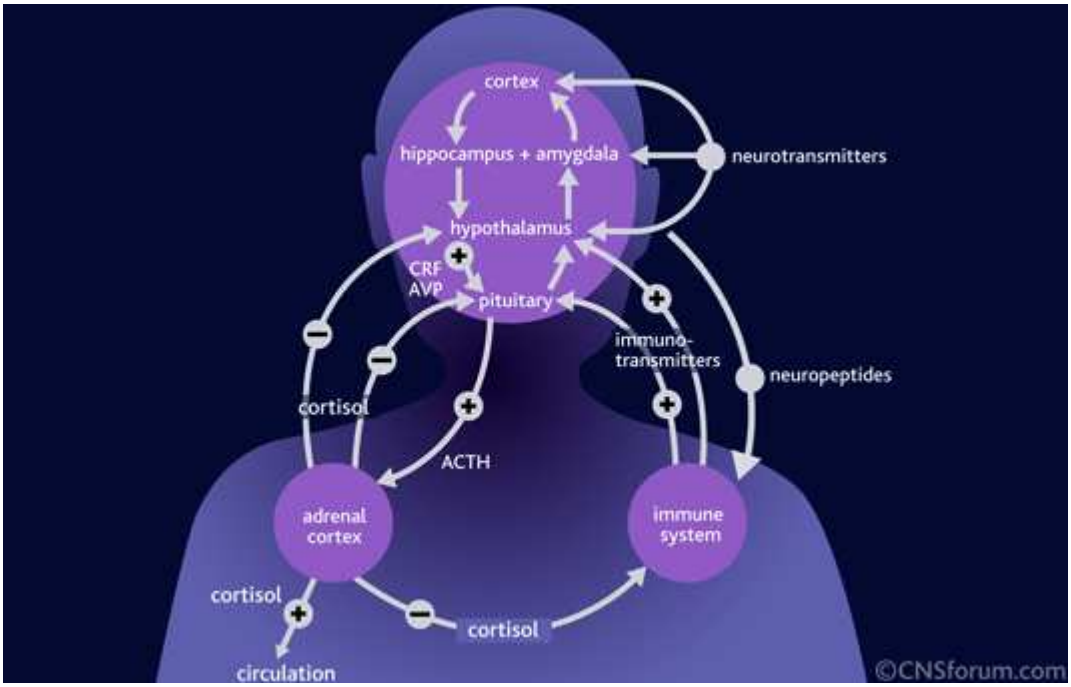


Figure 1.6: The Hypothalamic Pituitary Adrenal (HPA) feedback loop. © CNS Forum: The Lundbeck Institute.

Corticosteroid Receptors

Unlike the catecholamines, adrenocortical hormones pass readily through the blood-brain barrier (Roozendaal, Quirarte & McGaugh, 1997). Evidence suggests that corticosteroids have two methods of receptor activation (Lupien & McEwen, 1997). The first is genomic: once the hormone binds with the receptor, the receptor separates from its attached protein and moves into the cell nucleus, initiating transcription and mRNA protein synthesis. This genomic action eventually alters neuron receptor structure and activity, thus taking hours to weeks to induce an associated behavioral change (Sapolsky *et al*., 2000). The more rapid receptor activation involves corticosteroid interaction with the cell membrane, affecting transmitter response.

As previously discussed, the brain comprises two types of corticosteroid receptors relevant to stress research; mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). These corticosteroid receptors comprise different affinities for endogenous and

synthetic corticosteroids and vary in their distribution in the brain. Both, however, are found extensively in the hippocampus. Recent theoretical and experimental work suggests that the way these receptors function and interact might explain the varied and sometimes inconsistent relationship between corticosteroids and cognition (Lupien & McEwen, 1997; De Kloet, Oitzl & Joels, 1999; Roozendaal, 1999. The MRs are found predominantly in the hippocampus, with some expression in other limbic and brainstem nuclei (McEwen, de Kloet & Rostene, 1986). MRs bind to cortisol (in humans) and corticosterone (in rodents) with high affinity, and are thus largely occupied under non-stressful conditions when corticosteroid levels are low (see McEwen *et al*., 1986, for review). MR activation via low levels of corticosteroids generally results in reduced calcium currents and thus more stable responses to excitatory glutamatergic and biogenic amine inputs. This has lead some to suggest that activation of MRs play a role in maintaining homeostasis (De Kloet *et al*., 1999).

Glucocorticoid receptors have one-tenth the affinity for cortisol and corticosterone (Reul & de Kloet, 1985). Thus as endogenous corticosteroid levels rise under stress and most of the MRs become occupied, GRs gradually become activated. If the stressor is moderate to severe (or a corticosteroid is administered in comparable levels), the percentage of GR occupation increases substantially. GRs are distributed widely throughout the brain, including the limbic system, brainstem, hypothalamic nuclei, and cortex, although they are most concentrated in the hippocampus (McEwen, Weiss, & Schwartz, 1968). GR activation leads to enhanced calcium currents and responsiveness to excitatory neurotransmitters. This activation is generally followed by a decrease in cellular activity, helping to restore cells to their homeostatic state (De Kloet *et al*., 1999). There is evidence, however, that the increase in excitatory activity associated with GR activation can lead to neuron atrophy and death in the hippocampus (see below for further discussion). Given that MRs are largely occupied

during rest and GRs become activated during stress, most researchers have concluded that activation of GRs, rather than MRs, are responsible for stress-related brain and behavioral changes (see Roozendaal, 1999).

Thus stress sets in motion a number of physiological responses, including sympathetic and HPA activation and the release of stress hormones. These hormones exert their action in the brain by activating corticosteroid receptors. The distribution of these receptors in structures involved in memory, particularly the *hippocampus* (which has the largest concentration of receptors) is an important link in understanding the connection between glucocorticoids and cognition.

1.3.3 Stress & Memory: Animal Studies

The animal literature on stress and cognition is vast, providing robust evidence that stress or administered corticosteroids affect both associative learning and spatial memory. Stress manipulations include social stress (dominance struggle), physical restraint, shock, and certain stressful tasks, while corticosteroid administration involves either injection, implanted hormone "beads," or intracerebral administration. Investigators have examined the *modulatory* effects of corticosteroids following adrenalectomy (or other lesion procedure), and the *direct* effects of administered hormones or stress in healthy animals. Researchers have also experimented with the *timing* and *dose* of the manipulation. Together, these studies provide a complex picture, but suggest a *facilitative effect* of *moderate doses* of corticosteroids (or moderate stress) on *encoding and consolidation*, and possibly an *adverse effect* on *retrieval*. Given current limitations, *only* human studies will be discussed.

1.3.4 Stress & Memory: Human Studies

Although research clearly demonstrates that chronically elevated cortisol (from disease, corticosteroid treatment, or aging) is associated with impairments in declarative memory (Lupien *et al*., 2004, 1998; Martignoni *et al*., 1992), evidence for *acute* effects is mixed. Early experimental studies using stress induction or single-dose glucocorticoid administration showed an impairing effect of acutely elevated cortisol on verbal declarative memory (Kirschbaum *et al*., 1996; Newcomer *et al*., 1994; Wolf *et al*., 2001; Wolkowitz *et al*., 1990). However, recent studies investigating *acute effects of cortisol* on word recall either failed to replicate these findings by using cortisol administration (Hsu *et al*., 2003) or psychosocial stress (Wolf *et al*., 2001) or obtained opposite findings (Domes *et al*., 2002).

One explanation for these discrepancies, according to Beckner and colleagues (2006), may be due to differences in dose levels of glucocorticoids. Both animal and human data suggest an inverted U-shaped function between glucocorticoids and memory (see Lupien & McEwen, 1997, for a review). Studies with corticosteroid receptor agonists and antagonists suggest that low levels of corticosteroids (in which MRs are fully occupied) may influence attention to encoding of relevant stimuli, while increasing levels associated with stress (in which GRs start to become occupied) act on consolidation processes (with moderate doses facilitating memory and very high doses impairing it). Thus the majority of human studies, in attempting to approximate moderate stress, may be raising cortisol levels beyond the peak of the inverted-U, thereby resulting in detrimental effects on memory. Animal studies showing a facilitative effect of stress-levels of corticosterone on memory may instead be achieving the peak for those species. Clearly more research on dose-dependent effects in humans is needed to shed light on this issue.

Another important issue, also proposed by Beckner and colleagues, may be related to the timing of the cortisol manipulation. In many of the human studies demonstrating an

impairing effect of elevated cortisol on memory, the stressor or glucocorticoid is applied *before* stimulus presentation and learning, and recall is tested within 1–2 hours. In such a paradigm, cortisol levels are elevated during *all* memory phases: the learning period (initial encoding of the information), consolidation (the continuous transfer of information into longer term storage), and retrieval (recall of information from memory stores). Disruption of any one of these memory processes could account for detrimental effects of stress on memory and might also obscure any facilitated process. Roozendaal (2002) has theorized that under stressful conditions, consolidation of novel information related to the situation is enhanced such that one is more likely to later remember information associated with the stressful experience. However, in order to facilitate this new learning during arousing situations, competing processes of retrieving old information (which could result in retroactive interference) may be inhibited. Thus, it may be *impaired retrieval* that accounts for many of the human findings cited above, rather than stress effects on learning or consolidation.

Indeed, recent studies that have managed to isolate consolidation as a target process point to a *facilitative* effect of stress. These investigations typically administer the stress induction protocol or corticosteroids prior to or immediately following training (i.e., during encoding and consolidation), followed by retention testing at least 24 hr later. Retrieval is therefore tested after corticosterone levels have returned to baseline, thereby isolating the effect of glucocorticoids on consolidation of new memories. Animal studies using this paradigm have generally found a *facilitative effect* of *moderate* levels of *glucocorticoids* on *consolidation* (Conrad, Lupien & McEwen, 1999; Oitzl & de Kloet, 1992; Roozendaal & McGaugh, 1996; Sandi, Loscertales & Guaza, 1997). Several recent human studies have also found a facilitative effect of stress or administered cortisol on encoding and consolidation of visual information with affective content when recall is tested at least 24 hr after learning (Buchanan & Lovallo, 2001; Cahill, Gorski & Le, 2003); an additional study found this for

both emotionally arousing and neutral information (Abercrombie *et al*., 2003). However, the findings for consolidation of verbal information are weak. One study suggested a facilitative effect of administered cortisol on consolidation of word recall when tested after a delay (Abercrombie *et al*., 2003), whereas others have found no difference between cortisol administration (de Quervain, Roozendaal, Nitsch, McGaugh & Hock, 2000) or stress (Wolf, Schommer, Hellhammer, Reischies & Kirschbaum, 2002) and controls. Thus, there is evidence for a facilitative effect of stress and cortisol on the consolidation of visual information, but little for verbal information.

These studies provide stronger evidence of encoding and consolidation effects of stress, although the findings are *mixed*. While one study found a *detrimental* effect on *verbal* memory (Lupien *et al*., 1995), several others found a *facilitative* effect on *visual* memory (Buchanan & Lovallo, 2001; Abercrombie *et al*., 2003; Cahill *et al*., 2003). These studies (with the exception of Cahill *et al*., 2003), however, continue to conflate encoding and consolidation processes. Studies examining attentional effects have generally found that stress and cortisol interfere with selective attention and working memory. Furthermore, none of these studies manipulated either stress or cortisol levels on the day of memory testing in order to determine retrieval effects. Only one human study (de Quervain *et al*., 2000) and two animal studies (de Quervain *et al*., 1998; Oitzl & De Kloet, 1992) have directly tested for the effects of stress during each stage of memory formation and recall. These researchers found evidence of impaired *retrieval*.

Researchers have also recently attempted to parse the effects of glucocorticoids on *retrieval* processes separate from learning and consolidation, and findings provide some support for Roozendaal's (2002) theory that retrieval is impaired by stress. These studies present the stimuli to be learned in the first session under basal conditions and then apply the stressor or glucocorticoid just before retrieval on a subsequent session. Using this type of

design, de Quervain, Roozendaal and McGaugh (1998) found that both shock and glucocorticoids administered just before retention testing impaired retrieval of spatial information in rats. Two pharmacological studies in humans have also shown an impairing effect of elevated cortisol on the retrieval of words learned 24 hr before (de Quervain *et al*., 2000, 2003), and Kuhlmann, Piel and Wolf (2005) similarly found that a psychosocial stressor impaired recall of both positive and negative (but not neutral) words. Wolf and colleagues (2002), however, found no effect of a stressor on retrieval of words learned 4 weeks earlier compared with controls.

Beckner and colleagues (2006) recently addressed these discrepant findings by attempting to parse the effects of an acute psychosocial stressor on these *separate* memory processes by varying the timing of the stressor. The psychosocial stressor (preparation for an expected public speech) was applied at three different time points (and compared with no-stress controls); prior to stimulus presentation and initial learning, immediately after stimulus presentation/learning, and just before memory testing 48 hours later. *Both* verbal and visual memory retention was measured using a film stimulus. Specifically, it was hypothesized that stress would exert a facilitative effect on encoding and consolidation processes and a detrimental effect on retrieval. While De Quervain and colleagues (2000) have used a similar paradigm using glucocorticoid administration as the manipulation, this study was the first to do so employing a *psychological stressor* to investigate the effects of stress and endogeneously-released cortisol on each memory phase in a human sample. Results provided support for the facilitative effect of stress and endogenous cortisol on the consolidation of new information, providing the first evidence that stress enhances the consolidation of *verbal* information. Indeed, this evidence for a facilitative effect of stress on the consolidation of verbal memory stood in contrast with much of the literature. Many studies have found an impairing effect of cortisol on word or narrative recall by using both

psychosocial stress (Jelicic, Geraerts, Merckelbach, & Guerrieri, 2004; Wolf *et al*., 2001) and glucocorticoid administration (Kirschbaum *et al*., 1996; Tops *et al*., 2003), although it is pertinent to note that these studies applied the stressor or glucocorticoid prior to stimulus presentation and tested recall within an hour of the manipulation, thereby elevating cortisol during encoding, consolidation, and retrieval. The detrimental effects of stress on memory in these studies may thus be due to impaired retrieval (Beckner *et al*., 2006).

1.3.5 Stress and Context Dependent Memory

Nadel and Payne (2002) predicted that if binding of the disparate elements that make up a given episode involves spatial context, then stress might disrupt it. However, if spatial context is not involved, stress should be without effect. The researchers induced false memories in participants using the Deese (1959), Roediger-McDermott (1995), or "DRM"[1] paradigm. In brief, participants studied numerous lists of semantically associated words (e.g. candy, sour, sugar, bitter, chocolate, cake, etc.). Each list was followed by a recognition task that consisted of three types of words: words that were actually presented (e.g. sugar), unrelated distractor words that were not presented (e.g. hat), and words that are highly related to the theme or 'gist' of the list, but that were not presented (e.g. sweet), termed "critical lures". Participants generally falsely remember many of these critical lures in DRM Experiments. In fact, the typical pattern of results reveals high rates of false recognition that under some conditions can equal or even surpass true recognition rates for correctly identified words (see Roediger *et al.,* 1998). The researchers were concerned with the fate of false memories in this paradigm if participants were subjected to stress *prior* to performing the task. Participants were exposed to the Trier Social Stress Test (TSST; Kirschbaum *et al*., 1993) or a non-stressful filler task after which they had to listen to 20 DRM word lists, each

[1] This is not to be confused with the 'Day Reconstruction Method' of autobiographical recall.

followed by a computerized recognition task. Compared to controls, participants exposed to the TSST showed elevated rates of false recognition for the critical lures. Thus, stressed participants appeared to lose the ability to distinguish between ‘‘true’’ and ‘‘false’’ memories in the DRM paradigm, which the authors discussed as reflective of the role of both the hippocampal and PFC systems in contextual remembering, and the modulation of these systems by stress. Ultimately, this study demonstrated that moderate psychological stress renders participants unable to distinguish between ‘‘true’’ and ‘‘false’’memories in the DRM paradigm.

In a more recent study, Smeets and colleagues (2008), found that memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Participants were first exposed to a cold pressor task stressor before encoding, during consolidation, before retrieval, or were not stressed and were subsequently subjected to neutral and emotional versions of the DRM word list learning paradigm. Twenty-four hours later, recall of presented words (true recall) and non-presented critical lure words (false recall) was assessed. Results indicated that stress exposure resulted in superior true memory performance in the *consolidation* stress group and reduced true memory performance in the *retrieval* stress group compared to the other groups, predominantly for emotional words. These memory-enhancing and memory-impairing effects were *strongly* related to stress-induced cortisol and sympathetic activity measured via salivary alpha-amylase levels. Neutral and emotional false recall, on the other hand, was *neither* affected by stress exposure, *nor* related to cortisol and sympathetic activity following stress. These results demonstrate the importance of stress-induced hormone-related activity in *enhancing* memory *consolidation* and in *impairing* memory *retrieval*, in particular for emotional memory material.

Thus far we have herein outlined a plethora of research which has revealed that secretion of GCs due to HPA axis stimulation may modulate memory functioning. However, the precise direction of stress-induced GC effects on memory performance is far from clear. Animal studies, for example, have shown that GCs can have facilitating (e.g., on aversive conditioning), but also impairing effects on memory. Similarly, studies relying on human participants have reported that acute GC administration may enhance or disrupt memory, yet the precise conditions under which these effects occur are ill-understood. Recently, Joëls and colleagues (2006) argued that stress will *enhance* memory only when the memory acquisition phase and stressor share the same spatiotemporal context (i.e., context-congruency). Smeets and colleagues (2007) tested this hypothesis by examining whether context congruent stress enhances declarative memory performance, as would be predicted by the encoding specificity principle. Participants were assigned to a personality stress group, a memory stress group, or a no-stress control group. While being exposed to the acute stressor or a control task, participants encoded personality and memory-related words and were tested for free recall 24 hours later. Relative to controls, psychosocial stress significantly enhanced recall of contextually-congruent words, but *only* for personality words. This suggests that acute stress may strengthen the consolidation of memory material when the stressor matches the to-be-remembered information in place and time.

More recently however, Schwabe and colleagues (2009) proposed that stress may actually *impair* the beneficial effect of congruent learning and retrieval environments on memory performance. Indeed, these researchers tested this hypothesis by exposing healthy adults to either a cold pressor stressor or control procedure before they learned an object-location task in a room scented with vanilla. Memory was tested 24 hours later, either in the same or in a different context (unfamiliar room without the odour). Stress administered *prior* to encoding eliminated the context-dependent memory enhancement found in the control

group. Thus, these findings represent the first demonstration of impaired context-dependent memory *following* stress. Thus, stress administered *prior* to encoding impairs context-dependent memory.

1.4 Function of Reconsolidation, Boundary Conditions & Distinguishing Characteristics

The search for an endogenous function for the process of reconsolidation remains a fundamental issue. As noted by Dudai (2007), reconsolidation might not serve any function, particularly given the remote chance of encountering in everyday life the forms of agents used experimentally to induce amnesia. Nevertheless, interference is a potent cause of amnesia in reconsolidation studies (e.g., Walker *et al*., 2003; Hupbach *et al*., 2007) and stress can also be detrimental to reactivated memories (Maroun & Akirav, 2008; Wang *et al*., 2008), thereby suggesting that retrieval-induced plasticity places a memory trace at risk of disruption. As such, reconsolidation has been conceptualized as a fundamental process in the ongoing modification and storage of memories.

Indeed, it has often been suggested that reconsolidation might enable memories to be modified or updated (e.g., Tronson & Taylor, 2007; Dudai & Eisenberg, 2004; Sara, 2000). Generally, memories are retrieved in circumstances wherein additional complementary information is presented. As such, the capacity for plastic alterations in memory strength or content following memory retrieval would appear adaptive in terms of maintaining a memory's relevance with respect to guiding future behaviour (Lee, 2009). Indeed, in terms of human episodic memories, interference congruent with retrieval of a prior memory results in an incorrectly updated memory for a list of items (Hupbach *et al*., 2007), thereby suggesting a role of reconsolidation in updating memories. However, Tronel and colleagues (2005), in a study adopting inhibitory avoidance learning in rats, did not find evidence that

reconsolidation is functionally involved in linking new information to a reactivated memory. Using the doubly dissociable mechanisms of inhibitory avoidance memory consolidation and reconsolidation, these researchers demonstrated that second-order conditioning recruited consolidation processes in a selective manner. However, according to Tronson and Taylor (2007), linking new information to an old memory can be conceptualized as new learning based upon evoked memories, which would be expected to necessitate consolidation mechanisms rather than true memory updating. Lee (2008) recently directly addressed the functional role of memory reconsolidation employing the doubly dissociable mechanisms of consolidation and reconsolidation in hippocampal contextual fear memories, finding that a basic form of memory updating, namely strengthening through a further learning episode, was selectively dependent upon reconsolidation mechanisms. Thus, as suggested by Lee (2009), memory reconsolidation might prove to be the mechanism by which memories are updated through further experience, although it remains to be determined whether reconsolidation has a similar functional role in other forms of memory updating, such as memory weakening or changes in memory content.

Although the mechanisms of memory reconsolidation largely recapitulate those of initial consolidation, there are notable dissociations between the two (see Moore & Roche, 2007 and Alberini, 2005 for a comprehensive review). In particular, there is evidence that reconsolidation recruits specific mechanisms that are not crucially involved in consolidation. The reconsolidation, but not consolidation, of discrete fear memories is vulnerable to ß-adrenoceptor blockade (Debiec & LeDoux, 2004). Moreover, the cellular mechanisms of memory consolidation and reconsolidation for both contextual fear (Lee *et al*., 2004) and inhibitory avoidance (Taubenfeld *et al*., 2001; Milekic *et al*., 2007) are doubly dissociable. As such, reconsolidation is a neurobiologically distinct memory process, which is

increasingly associated with specific cellular mechanisms, such as the expression of the immediate-early gene zif268 (Lee *et al*., 2004, 2005).

The existence of reconsolidation processing is for the mostpart revealed by its absence. Quintessentially, when amnesia for a memory that is one or more days old is induced in a manner that is dependent upon the reactivation of said memory trace through retrieval, reconsolidation is considered to have been impaired (Nader *et al*., 2000; Dudai, 2004). However, similar to other cognitive functions, experimental treatments specifically aimed at targeting memory reconsolidation can also yield subsequent improvements (Tronson *et al*., 2006; Lee *et al*., 2006; Frenkel *et al*., 2005; Rodriguez *et al*., 1999; Blaiss & Janak, 2006). Further, the possibility to improve a memory trace through post-retrieval processing infers a potentially adaptive function for the reconsolidation process. Thus, instead of merely being process that restabilizes a memory following its retrieval, reconsolidation also represents a special state which allows for renewed memory plasticity and modulation (Dudai, 2007). Importantly, such memory-enhancing interventions include naturalistic phenomena such as water deprivation and the administration of glucose (Frenkel *et al*., 2005; Blaiss & Janak, 2006). Therefore, the ability to modify (e.g., strengthen) a previously acquired memory in a potentially adaptive manner is not limited to exogenous pharmacological treatment but is likely to be relevant to naturalistic situations of memory updating.

However, even in paradigms with well-established demonstrations of reactivation-dependent amnesia, there are conditions under which reconsolidation does *not* take place. Therefore, there exist certain boundary conditions around which reconsolidation may or may not be observed. First, temporal dynamics play an important role. In inhibitory avoidance in rats (Milekic & Alberini, 2002), as well as in fear conditioning in the medaka fish (Eisenberg & Dudai, 2004), 14-day-old memories did not demonstrate reactivation-dependent amnesia,

whereas younger memories did show evidence of reconsolidating. However, this is not a universal finding, with contextual fear and appetitive cocaine-related memories showing reconsolidation up to a month following learning (Lee *et al*., 2006; Debiec *et al*., 2002). Nevertheless, it remains possible that all memories possess an age-dependent sensitivity to reconsolidation induced impairment, but with divergent time-courses thus far unaccounted for by the current literature. Alternatively, as suggested by Lee (2009), given that there is an interaction between memory age and the duration of stimulus re-exposure required to successfully reactivate a contextual fear memory (Suzuki *et al*., 2004), it is further possible that all memories undergo reconsolidation regardless of their age, but that previous studies have failed to employ sufficiently strong memory reactivation cues for older memories. However, as further purported by Lee, if the age of a memory does indeed represent a limit on the engagement of reconsolidation mechanisms, this might speculatively fit in with an updating hypothesis. Perhaps the passage of time, under certain circumstances, results in new experiences being more likely to be encoded separately from the original memory. As such it would be predicted that updating an old memory should engage consolidation specific mechanisms [e.g., brain-derived neurotrophic factor [BDNF] in the hippocampus for contextual fear memories (Lee *et al*., 2004)]. Moreover, selective interference with these mechanisms should only affect the new updating information, thereby resulting not in amnesia, as would be expected if reconsolidation mechanisms were being engaged and disrupted, but in a failure to modify the memory.

The issue concerning whether a new experience updates an existing memory trace or triggers new memory trace formation might also underlie the already established constraint that *extinction* places on reconsolidation. Memory reactivation protocols typically involve short extinction sessions. However, lengthier non-reinforced stimulus exposure reverses the impact of amnestic treatment. Therefore, in terms of contextual fear memories, protein

synthesis impairs reconsolidation in order to decrease fear when the context re-exposure is short, but conversely disrupts extinction in order to maintain high levels of fear when the duration of context re-exposure is more prolonged (Suzuki *et al*., 2004). Such a hypothesis has been replicated in cued fear memories (Lee *et al*., 2006) as well as in contextual aversive learning in the crab Chasmagnathus (Pedreira & Maldonado, 2003), although it appears that extinction does not always block reconsolidation from taking place (Duvarci *et al*., 2006). Thus, it is not merely the level of extinction training, but its relationship with initial learning that determines the interaction between reconsolidation and extinction. Protein synthesis inhibition during the same reactivation/extinction parameters has yielded opposing effects when the strength of initial training on a conditioned taste aversion task is varied (Eisenberg *et al*., 2003), which was conceptualised as a trace dominance process, whereby the dominant trace engaged by reactivation/extinction is that which is impacted upon by experimental treatment. However, instead of competition between traces, the extent of extinction training relative to conditioning may determine whether or not a new inhibitory memory is formed. Thus, if stimulus exposure is sufficient to engage extinction learning, this would not concomitantly modify the original excitatory memory. Alternatively, more limited exposure, would serve to trigger memory updating in the absence of new inhibitory learning. Providing support for such a contention is the recent finding in the crab that the transcription factor nuclear factor-kB (NF-kB) reflects a molecular switch between reconsolidation and extinction (Merlo & Romano, 2008). Inhibiting NFkB both impairs reconsolidation (Merlo *et al*., 2005) and enhances extinction (Merlo & Romano, 2008) under the appropriate conditions. Consequently, short memory reactivation induces a functional upregulation of NF-kB, whereas more prolonged extinction results in a functional inhibition. If the assumption is made that NF-kB activity is reflective of a reconsolidation/updating process,

the extinction-induced inhibition would be consistent with a suppression of memory updating in favour of new extinction learning.

A further boundary condition on memory reconsolidation has recently been termed the 'predictability of the reactivation stimulus' (Nader & Hardt, 2009). This condition reflects findings emerging primarily from the crab literature that a mismatch between expected and actual events during reactivation triggers reconsolidation. Pedreira and colleagues (2004) found that reconsolidation only took place, and thus could only be disrupted, when the predictive context ended in the unexpected absence of the aversive outcome. It is not merely the case that memory reactivation must differ in some respect to conditioning, as there are numerous instances whereby reconsolidation impairments have been observed when the reactivation session is operationally identical to training (e.g., using reinforced reactivation procedures in fear conditioning (Eisenberg & Dudai, 2004; Duvarci & Nader, 2004), and in many (Kelly *et al*., 2003; Akirav & Maroun, 2006), but not all (Rossato *et al*., 2007) studies of object recognition memories). Instead, reconsolidation is triggered by a violation of expectation based upon prior learning, whether such a violation is qualitative (i.e., the outcome not occurring at all) or quantitative (i.e., the magnitude of the outcome not being fully predicted). It has thus been predicted that further initial training of fear or object memories would render such memories resistant to reconsolidation impairments through the use of reactivation sessions that are identical to training. Such an interpretation suggests that incompletely, but not fully, learned memories are subject to reconsolidation given the requirement for memory updating to optimize further the predictive accuracy of the memory.

Several hypotheses have been put forth regarding the role of reconsolidation in terms of wider memory processes. Two of these (Alberini, 2005; Dudai & Eisenberg, 2004) have adopted the temporal boundary condition to argue that reconsolidation plays a role in an extended process of memory stabilization. Specifically, Alberini (2005) suggests that

repeated reactivations (which might be implicit during sleep) gradually increase memory stability as part of a lengthy consolidation process, such that when sufficient time has elapsed a memory can no longer be disrupted, *but* it can be added to or modified. Dudai and Eisenberg (2004) similarly integrate reconsolidation within a 'lingering consolidation' process, whereby the reactivation and reconsolidation cycle progressively stabilizes a memory. In contrast to such emphases on reconsolidation enhancing memory stability, memory updating does not require that reconsolidation has an endogenous role to play in the ongoing processing of a memory trace that requires no further modification. Indeed, the reverse has been suggested (see Lee, 2009), in that a memory will persist in a stable and fixed form only if reconsolidation is not engaged, given that reconsolidation is the mechanistic instantiation of memory updating. Thus, reconsolidation *only* plays a role in enhancing memory stability if such enhancement is dependent upon modification of the memory. Instead of focusing on reconsolidation constraints, Morris and colleagues (2006) argue instead for a mode-based explanation of reconsolidation according to which the dual activation of retrieval and encoding states drives reconsolidation processes. This model is well suited to account for situations wherein new experiences result in profound changes to the memory; a change in the location of an escape platform in a water maze being the example used for the delayed non-mapping to place task. However, it is not clear either how it might be adapted to conditions of more negligible memory modifications (e.g., strength), or whether the activation of an 'encoding mode' is sufficient to trigger reconsolidation. For example, extinction training involves both memory retrieval as well as new memory encoding, but under such circumstances reconsolidation is not obviously engaged (e.g., Lee *et al*., 2006; Suzuki *et al*., 2004; Pedreira & Moldonado, 2003). Moreover, the mode requirement appears to be an additional, as opposed to an alternative, boundary condition to those already discussed. Alternately, a hypothesis based upon memory updating incorporates

both the principles of the dual state hypothesis (in that a requirement for updating depends upon the same conditions as those proposed to engage an encoding state), and can potentially account for other boundary conditions.

Further, Ortiz and Bermudez-Rattoni (2007) postulate reconsolidation as an 'updating consolidation' mechanism. Further to demonstrating that fully learned memories are not subject to reactivation-dependent amnesia, these researchers found in both spatial and taste memories that when learning had reached near-asymptotic levels, only partial amnesia resulted from reactivation and protein synthesis inhibition (Rodriguez-Ortiz *et al*., 2005, 2008). This partial amnesia was considered to reflect only the partial destabilization of the existing memory trace to enable updating. As such, this idea is not dissimilar to Alberini's previously discussed contention that old memories can be updated, but not disrupted (2005). Moreover, Rodriguez- Ortiz and Bermudez-Rattoni suggest that reconsolidation associated response decrements do not reflect memory loss for the original consolidated memory but, rather, emanate from a failure to integrate new learning, thereby leading to interference. However, such an interpretation cannot account for recent findings in terms of contextual fear memories (e.g., Lee, 2008). If reconsolidation impairments result from new learning interfering with the stable old memory trace, disruption of the new learning itself should result in an unchanged memory (Lee, 2009). However, in Lee's (2008) recent study, this is not what was observed when the consolidation-specific protein BDNF was knocked down[2] in the hippocampus during memory strengthening/updating. Instead, while knocking down BDNF had no impact on memory strengthening, the modification of the old memory was completely dependent upon the reconsolidation-selective upregulation of zif268. Also,

[2] Gene knockdown refers to techniques by which the expression of one or more of an organism's genes is reduced, either through genetic modification (a change in the DNA of one of the organism's chromosomes) or by treatment with a reagent such as a short DNA or RNA oligonucleotide with a sequence complementary to either an mRNA transcript or a gene.

interference with memory destabilization both protected against the disruptive effects of protein synthesis inhibition and fixed the memory at the same strength despite additional learning. Thus, memory updating requires the destabilization of the original memory in order in integrate new information. Consequently, impairment of the restabilization process (e.g., through protein synthesis inhibition) affects not only the new information but also the reactivated memory, thereby leading to amnesia.

1.5 Conclusions

The aforementioned literature review provides a comprehensive overview of the critical issues underpinning the current research. We primarily provided an overview of the broader context within which the present thesis is framed. An overview of results conducted thus far on animals alone with respect to both demonstrating and blocking the reconsolidation process was elucidated. An overall review of the hippocampal-cortical system set the scene for discussion concerning the role of the hippocampus in episodic memory in humans. Context-dependent research conducted to date in humans was discussed with particular emphasis on the importance of a match between encoding and retrieval. In this case, it has been repeatedly shown that returning a participant to the original context in which information was learned results in facilitation for the recall of that information, while altering context can impair recall. The vast majority of incidental contextual cueing research has been conducted in terms of global, environment-based cues. However, contextual cueing research using non-scene stimuli indicates that participants employ local cues immediately surrounding a target at encoding to identify said target at retrieval to a greater extent than they employ global cues. Furthermore, in terms of context-dependent traumatic memory, important regarding possible therapeutic interventions emanating from the reconsolidation paradigm, central aspects of

emotional experiences (i.e., local cues) are often remembered at the expense of incidental background details (i.e., global cues). Thus, further research into the effects of both local and global incidental cues on the retrieval of target items, together with an investigation into the binding of item and context should allow us to eventually devise a contextual paradigm which promotes reconsolidation processing in humans in a suitable and context-dependent manner. The relationship between the hippocampus and context was subsequently elaborated and the particular role of context recognition in terms of reconsolidation was discussed. The role of context in terms of demonstrating human reconsolidation was emphasized. Overall, it appears that context is an integral component of episodic memory. It is, however, it is more than just a component of such memory. It also seems to play a determining role in the dynamics of the episodic memory system as a whole. To the extent to which this is the case, further study concerning *how* context is represented physiologically should greatly enhance our understanding of human memory.

Human and animal studies firmly establish that the high levels of glucocorticoids released *during* stress impair the function of the hippocampus, thereby weakening or completely disrupting those aspects of contextual and episodic memory subserved by this structure. We reason herein that if stress interferes with the *normal* functions of the hippocampus, and the hippocampus is central to context effects in memory, then stress should interfere with those forms of memory dependent upon context and the binding it supports. Thus, we presently postulate that manipulations adversely affecting contextual encoding and retrieval, such as stress, should interfere with memory retrieval, thereby allowing us to isolate the effects of blocking the reconsolidation of an episodic hippocampally mediated memory trace. As such, if we are to block the reconsolidation process in *humans*, stress provides a non-invasive means of impairing protein synthesis.

Finally, the review finished with a thorough overview of current literature aimed at tackling the important theoretical questions within the reconsolidation sphere such as what is the function of reconsolidation, what are the boundary conditions underpinning the reconsolidation process, and what are the distinguishing characteristics of reconsolidation processing that set it apart from other forms of processing such as consolidation and extinction. Providing succinct answers to such questions is integral given that the reconsolidation phase has been seized upon as crucial for the understanding of memory stability and, more recently, as a potential therapeutic target in the treatment of disorders such as post-traumatic stress and drug addiction. Presently, little is known about the reactivation process, or what might be the adaptive function of retrieval-induced plasticity. Reconsolidation has long been proposed to mediate memory updating, but only recently has this hypothesis been supported experimentally.

1.6 Thesis Objectives

The objectives of this thesis involve exploring the effects of context and stress on episodic memory consolidation and reconsolidation using behavioural and electrophysiological approaches. Specifically, the behavioural effects of global and local context manipulations on episodic memory will be first investigated in order to identify the relative contributions of each form of context to episodic memory encoding and recall (Chapter 3). Subsequently the electrophysiological correlates of local contextual memory facilitation will be examined to further elucidate the cortical nature of these facilitative effects (Chapter 4). Next, behavioural and event-related indices of memory consolidation and reconsolidation will be studied in the context of a memory updating task (the first of its kind to be executed with human participants: Chapter 5). Finally, interactions between psychosocially induced stress and

context on memory retrieval will be investigated in an experiment combining salivary cortisol measures and behavioural indices to explore putative effects of protein synthesis inhibition on memory episodic encoding and retrieval (Chapter 6).

2

Chapter II

Methods: Behavioural, electrophysiological and biochemical

Methods

The purpose of the present Chapter is to provide a more comprehensive and overarching insight into the various methods employed throughout the thesis than allowed for in the experimental chapters. This is important in the respect that it is pertinent to acknowledge *why* exactly particular measures were chosen and *how* exactly these measures relate to the memory processes under investigation. Given the enormous potential scope of this chapter, a brief description of, together with an outline of scoring procedures involved with the various tasks, questionnaires and methods employed will be discussed. The Chapter commences with an overview of the control measures employed throughout. Subsequently, a general *summary* of the visual paired-associates paradigm *only* will be discussed *without* a detailed account of the various paired-associate based tasks employed throughout the course of the present thesis. A detailed overview of the variants of the basic paradigm is provided in the requisite experimental chapters. The focus of the chapter subsequently turns to electrophysiology. In so doing, a comprehensive background will be provided followed by a more detailed overview of the core principles underpinning Event-Related Potentials (ERPs) and Brain Electrical Source Analysis (BESA), both of which are employed presently. Finally, a detailed account of the actual electrophysiological procedure, from set-up and recording to ERP and BESA analysis, tempered with pertinent ethical issues, will be provided. The Chapter concludes with a comprehensive overview of the methods involved in the stress-based research (Chapter 6). Given the enormous lack of cohesion and complicated nature inherent in stress research, we will outline the steps involved in isolating the best method available to induce stress in humans in an ethically responsible manner, as well as to elicit sufficient hormonal and behavioural stress response in *all* participants. Measures of *both* behavioural

and hormonal stress response were obtained, measures and analysis of which are both thoroughly accounted for herein. A detailed account of the Enzyme-Linked Immunoassay (ELISA) technique employed is provided also.

2.1 Control Tasks

2.1.1 National Adult Reading Test (NART)

The National Adult Reading Test (NART; Nelson, 1982; NART-2; Nelson & O'Connell, 1978; Nelson & Willison, 1991) has become among the most widely used retrospective estimators of premorbid level of intellectual functioning in neuropsychological practice and research concerning a wide range of conditions. Its use in estimating patients' intellectual level prior to the onset of suspected dementia, for purposes of making comparisons with current levels of neuropsychological functioning, has become widespread.

The NART list (see Appendix 1) comprises 50 phonetically irregular words (e.g., ache, naïve, thyme). Assuming the participant is familiar with the word, accuracy of pronunciation is used to predict IQ. Given that the words are irregular, phonetic decoding or intelligent guesswork will not provide the correct pronunciation (Nelson & O'Carroll, 1978). The value of the test resides in the high correlation between reading ability and intelligence in the normal population (Crawford *et al*., 1989). In the current thesis, the NART was used as a control measure.

NART scoring

The experimenter determined predicted full scale, verbal and performance IQ estimates based on the number of errors made on the NART with reference to a conversion table provided by Nelson and Willison (1991; see Appendix 1). Each incorrectly pronounced word was counted

as one error. Slight variations in pronunciation were accepted when attributable to regional accents (Spreen & Strauss, 1998). The standard errors of estimate are 7.70, 12.08, and 8.83, for WAIS-R verbal IQ, performance IQ, and fullscale IQ, respectively (Spreen & Strauss, 1998). The range of possible NART predicted IQs is 132-174 for the verbal scale, 123-182 for the performance scale, and 131-175 for the full-scale (Ryan & Paolo, 1992).

2.1.2 Cognitive Failures Questionnaire

The Cognitive Failures Questionnaire (CFQ; Appendix 2) was devised by Broadbent, Cooper, Fitzgerald and Parkes (1982) as a measure of everyday failures of memory and attention. Cognitive failures are cognitive-based mistakes on simple tasks that a person normally should be capable of completing without error (Martin, 1983). Manly, Robertson, Galloway and Hawkins (1999) provided examples of typical cognitive failures, such as tossing out a new pen and keeping the old one or forgetting to take out the trash after being interrupted by a telephone call. Broadbent and colleagues (1982) developed the CFQ to assess the frequency of lapses in three areas: perception, memory and motor function.

CFQ administration and scoring

Participants are asked to indicate the frequency of minor lapses, slips or errors in perception, attention, memory and motor functions they experience on a 25 item scale (see Appendix 2). Participants are asked to indicate, on a 5-point scale (0 = never, 4 = always), how often they have experienced the particular error described by the question (e.g., “Do you bump into people?”, “Do you fail to listen to people’s names when you are meeting them?”, “Do you forget where you put something like a newspaper or a book?”). Total scores range from 0 to 100, from total absence to highly frequent occurrence of lapses.

2.2 Visual Paired-Associates Task

Performance on the visual paired-association (VPA) task measures a form of declarative memory (Manns, Stark & Squire, 2000). The hippocampus appears to be vital for remembering the relations among objects in a scene and also for remembering relations among items that are arbitrarily paired (Hannula, Ryan & Cohen, 2006). Recognition memory is a well-studied example of declarative memory and depends on the integrity of the medial temporal lobe and diencephalic structures (Reed & Squire, 1997; Manns & Squire, 1999). In the VPA task (Fantz, 1964; Fagan, 1970), two identical pictures are presented side by side for a brief viewing period (e.g., 5 sec). After a delay (e.g., 5 minutes; 24 hours), one of the previously viewed pictures is presented along with a new picture. The phenomenon of interest is that individuals will look more at the novel picture than the familiar picture. On the one hand, the task has many of the features of *implicit* memory. No reference is made to a study episode, and performance appears to have an automatic quality that is reminiscent of habituation. In fact, the task is commonly used to assess memory in infants who would certainly not yet understand any explicit instructions even if given (Fagan, 1970). On the other hand however, the direction of gaze is voluntary, and a preference for the new picture could be guided by the same recollective processes that support recognition memory (Manns *et al*., 2000). More specifically, in humans, Manns and colleagues (2000) found that performance on the VPA task was predictive of subsequent recognition memory performance whereas perceptual priming was unrelated to subsequent recognition memory performance. These results are consistent with the data from lesion studies and suggest that performance on the VPA task measures a form of declarative memory. Thus, even though the task requirements are implicit in nature (i.e., no reference is made to the study episode) and even though the memory is observed in the form of a change

in a behavioural bias, the task relies upon the same mechanisms underpinning declarative memory. Furthermore, the task is dependent upon the hippocampus in that no such aforementioned bias between old and new stimuli is observed following hippocampal damage in humans (McKee & Squire, 1993; Manns *et al*., 2000; Pascalis *et al*., 2004), and the monkey (Bachevalier *et al*., 1993; Pascalis & Bachevalier, 1999; Zola *et al*., 2000). Further, in the rat, hippocampal lesions impair performance on an object-exploration task that is analogous to the VPA task (Clark, Zola & Squire, 2000). As stipulated previously, a variant of the basic VPA task constructed especially for studies carried out herein are detailed in the requisite experimental chapters.

2.3 Electrophysiological Analysis

2.3.1 The History of Electrophysiology

Electrophysiology is the study of the electrical properties of biological cells and tissues involving measurements of voltage change (electrical potential) or electrical current flow on a wide variety of scales from single ion channel proteins to whole tissues such as the heart (Ingber & Nunez, 1990; Nunez, 1990, 2000). In neuroscience, it includes measurements of the electrical activity of neurons, and particularly action potential activity. Voltage changes may be investigated either internally or externally, depending upon the area of interest dictated by the research and participant requirements. Single-cell recording and invasive intra-cortical recording through the use of depth electrodes, to obtain an electroencephalogram recording from the cerebral cortex, known as electrocorticography (EcoG), is a common procedure employed in the study of animal neurophysiology and in some patient-based human studies. However, due to the invasive nature of these procedures, their use in humans is rare despite the excellent spatial data available as a consequence of the

preciseness of the method. The ethical issues involved with EcoG, as well as the intricate surgical skills required to carry out the procedure, mean that the preferred method for examining electrophysiological data in humans is by scalp-recorded electrodes, through the process of electroencephalography (EEG). EEG involves the use of an array of scalp-based electrodes which measure voltage fluctuations from the brain through the meninges, skull, and scalp. Thus, they operate over a larger area than EcoG, with an accompanying decrease in precision, yet increase in versatility.

Placing EEG in a historical context, Caton (1875) described the first sensory evoked electrical responses from the surface of the brains of rabbits and monkeys using single electrode recording. Beck (1890) furthered the work of Caton by studying the electrical brain responses of rabbits and dogs to presentation of sensory stimuli. Within 40 years, recordings of electrical brain potentials had moved from animals to humans, and in 1929, Hans Berger published the first recorded study of scalp recordings of human EEGs in which he measured the electrical activity of the human brain by placing an electrode on the scalp, amplifying the signal, and plotting the changes in voltage over time. In these studies, Berger first coined the term "Elektrenkephalogramm". Jasper and Carmichael (1935) and Gibbs, Davis and Lennox (1935) later confirmed the details of Berger's observations. In its raw form however, the EEG is a coarse measure of brain activity, representing a mixed up conglomeration of hundreds of different neural sources of activity, thereby rendering it difficult to isolate individual neuro-cognitive processes. In 1939, Davis published a paper in which he extracted the changes in EEG due to a sensory stimulus, naming it an Evoked Potential (EP). Renshaw, Forbes and Morison proposed the possible relationship between the slow potentials of neurons and the oscillations of the EEG in 1940, leading to the foundation of the American EEG Society. Up until the 1950s there was no set method of electrode placement on the scalp, leading to a committee headed by Jasper developing the international 10-20 placement system. Dawson

(1954) extended the EP extraction techniques introduced by Davis (1939), by averaging large numbers of EPs to increase signal-to-noise ratio thereby reducing the amount of conflicting data being recorded for each response. The averaging procedure allowed for the most prominent and reliable voltage changes to be examined succinctly, without the "noise" of occasional, possibly unrelated, voltage fluctuations from single trials, thereby signaling the birth of Event-Related Potentials (ERPs). The modern era of ERP research commenced in 1964, when Walter and colleagues reported the first cognitive ERP component which appeared to reflect a participant's preparation for an upcoming target, which they termed the 'contingent negative variation' or CNV (Walter *et al*., 1964). The next major advance was the discovery of the P3 component (Sutton, Braren, Zubin & John, 1965). In this case, it was found that the P300 was elicited by the absence of an unexpected stimulus. By the 1970s, ERPs were being widely applied in clinical diagnosis, while Dipole Source Modeling (see below) was introduced in the 1980s in an effort to improve the spatial resolution of ERPs. At present, ERPs are employed to great effect in the investigation of sensory and cognitive processes such as attention, vision and memory. Most impressive insights can be derived from the coregistration of ERPs with other techniques such as functional imaging (e.g., fMRI), transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG).

2.3.2 Event-Related Potentials (ERPs)

More specifically for present purposes, ERPs are changes in the ongoing electrical activity of the brain (electroencephalogram, or EEG) which are caused by the specific occurrence of a cognitive, motor or perceptual event. Any changes in EEG due to the demands of the task are amplified, averaged and extracted as ERP waveforms (see Figure 2.1). These wave-forms are measured as the difference between the electrical activity of a baseline reference electrode attached to an electrically inactive site, such as the mastoid bone below the ear or the naison

on the nose, and the electrical activity of the areas of the brain covered by the electrodes. These changes allow neuroscientists to determine what areas of brain are being stimulated at a given time (and therefore which brain areas are involved in a given process), precisely *when* these areas become activated and what happens in these areas when people make an error. ERPs are calculated through averaging the large number of epochs (i.e., stimuli separated by long periods of time with no ERP-eliciting events) in a recorded EEG which are specifically time-locked to the occurrence of a specific experimental event, generally either the presentation of a stimulus, or the response to a certain stimulus (Handy, 2005). These ERP "waveforms" are plotted by voltage across the y-axis, in microvolts (μV) over time across the x-axis, in milliseconds (ms). This enables the formation of a detailed account of neural stimulation induced by the repetition of a certain stimulus or response. The more repetitions used, the higher the ratio of pertinent signals to background noise. The components involved among the majority of the individual epochs are more profoundly evident in the averaged ERP (Handy, 2005). More specifically, ERPs are calculated by averaging over many events such that the random noise of the background EEG (being uncorrelated with the event of interest) will be averaged out, while the aspects of the ERP waveforms (termed 'peaks' or 'components') that are common among the individual epochs of EEG signal will become apparent (Handy, 2005). ERP topography refers to a neuroimaging technique which calculates intermediary values for spatial points residing between electrodes on the value of the nearby recording sites. This is achieved through mathematical techniques of interpolation and the result is displayed as a coloured isopot map of the head wherein areas of positive fluctuations appear in red and negative activity appear in blue, darkening as a function of amplitude (see Figure 2.10). ERP topography allows for visual inspection of the scalp data and identification of sites of interest for further comparative analyses.

ERPs have been used to study a vast range of cognitive processes, from simple eye-movement and attention tasks (see Kanwisher & Wojciulik, 2000, for a comprehensive review), through to higher cognitive functioning, including language (e.g., Jackson, Swainson, Mullin, Cunnington & Jackson, 2004), learning (e.g., Rose, Verleger & Wascher, 2001) and, importantly for the current thesis, memory (e.g., Cycowicz, Friedman & Snodgrass, 2001; Hornberger, Rugg & Henson, 2006). The simplicity of the procedure, coupled with numerous other benefits, has allowed the ERP method to become one of the most important tools for examining the brain during cognitive processing.

2.3.3 Physiological basis of ERPs

2.3.3.1 Electrical activity in the brain

Communication in the central nervous system takes place through the transmission of electrochemical signals between nerve cells, or neurons (see Figure 2.2). Messages to either excite or inhibit activity in other neurons are passed via the release of neurotransmitter substances from the axon of the efferent (or pre-synaptic) cell to the dendritic tree or cell body of the afferent (or post-synaptic) neuron. The neurotransmitters influence the activity of the neuron by binding to receptors which alter the electrical potential across the membrane of the cell. Due to the constant influx and outflow of both positively and negatively charged ions across this membrane, the equilibrium state, or resting potential, of a neuron is approximately –70 mV. Any deviation from this state will make the cell either more or less likely to generate an action potential. An excitatory signal from a presynaptic cell will cause certain ion channels to open or close, with the result that the membrane potential rises from –70 mV to 0 mV and possibly higher. Such excitatory impulses are termed Excitatory Post-Synaptic Potentials (EPSPs). If the membrane potential rises above a particular threshold level, approximately +30 mV, then an action potential is generated in the neuron, and

neurotransmitter is released onto another cell. The rise in membrane potential due to an EPSP is called depolarisation. In contrast, Inhibitory Post-Synaptic Potentials (IPSPs) render cell firing less likely by lowering the membrane potential, thereby pushing it further from the threshold level for action potential propagation. This lowering of the potential across the membrane is called hyperpolarisation. It is the summated effects of these depolarisations and hyperpolarisations (which may collectively be termed Neural Current Sources), rather than the action potentials themselves, that are recorded by EEG and ERPs.

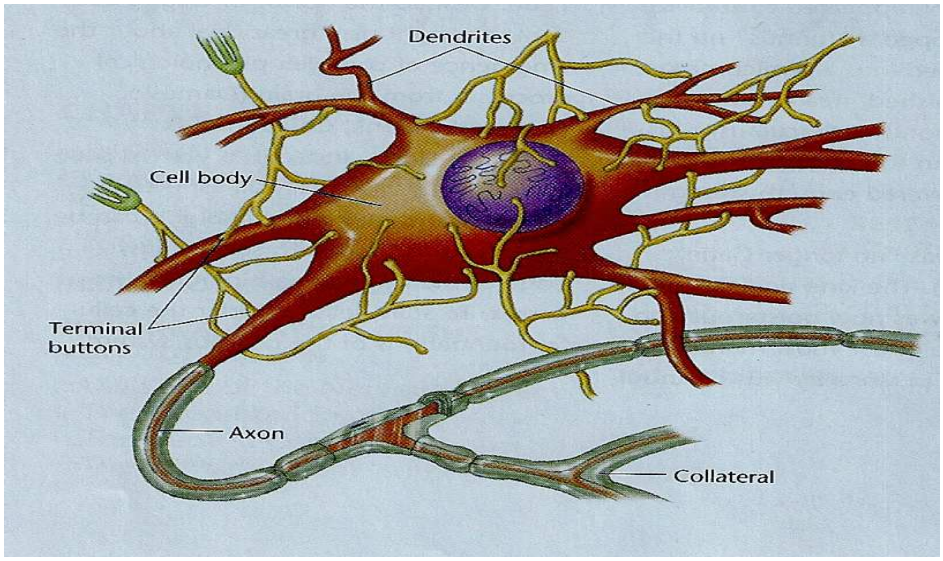


Figure 2.2: Diagrammatic representation of a typical myelinated neuron showing synaptic transmission. Adapted from Smith *et al*. (2003) © Wadsworth, Thomson Learning, Inc.

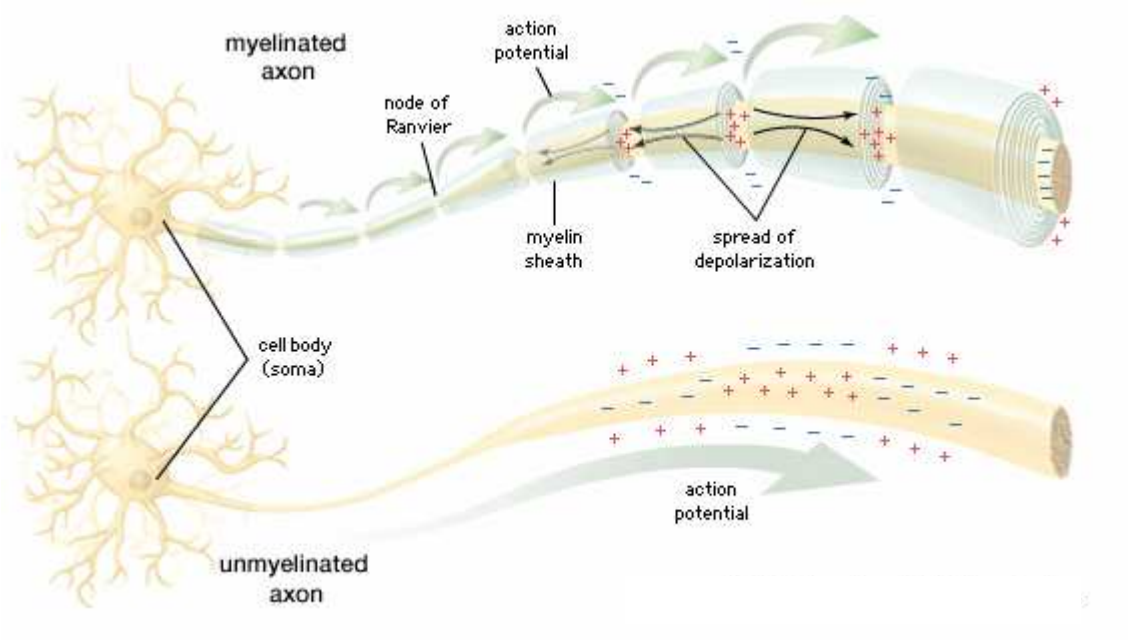


Figure 2.3: Graphical representation showing the course of an action potential. Source © 2002 Encyclopaedia Britannica, Inc.

Neural Current Sources originate at the cell membrane and represent a deviation from the equilibrium state or resting potential. During an EPSP, a local current *sink* is produced, which draws positive ions into the cell, thereby moving the potential closer to 0 mV. A sink may be thought of as a negative source. Local sinks are balanced by distant passive sources; as the sink draws ions into the cell, thus depolarising the membrane, these ions move through the neuron and are ejected at some other location, known as a (positive) *source*. For example, if a sink existed at a branch of the cell's dentritic tree, the distant source might occur at the cell body, or near the axon hillock. The co-occurrence of the positive source at one location, and the negative sink at another, means that the cell may effectively be viewed as a *dipole*. In an IPSP, the opposite situation occurs. A local source is produced, which emits positive ions, thereby lowering the membrane potential. This source is balanced by a distant sink, which takes in ions at another location on the cell. Again, this may be considered as a dipole. The EEG gives a macroscopic view of the activity of these sinks and sources. Although we

can only provide a brief overview here, a detailed account of the workings of this technique is provided by Nunez (1990).

EEG and ERPs record from the scalp the electrical activity (produced by sinks and sources) of populations of pyramidal cells which form the grey matter of the cortical surface. If a scalp potential records activity due to current sources over an area of less than 1 cm^2, then the large number of sources may be considered as a *single dipole source*. Usually, however, scalp potentials are due to larger areas of activity. When a large number of dipoles fire with synchronous activity, and their polarities are the same (i.e. all their positive terminals or sources are adjacent to other positives), as can happen with the densely interconnected pyramidal neurons of the cortical surface, then the group could be considered to form a *homogenous dipole layer*. However, dipole layers rarely occur with completely homogenous polarities of sinks and sources. The more common occurrence is for the layer to consist of a mixture of polarities of dipoles, in which case the overall potential will reflect the majority of dipole polarities.

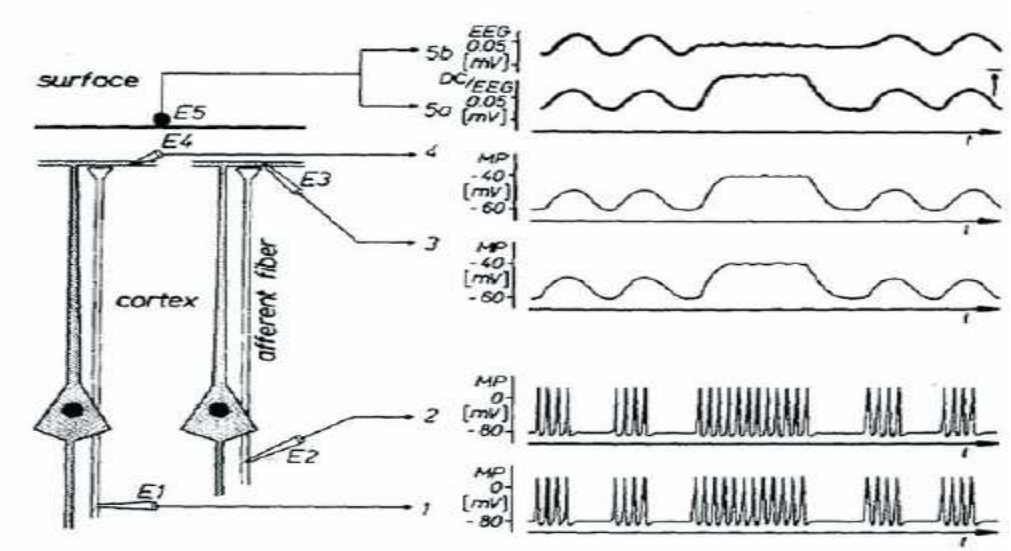


Figure 2.5: A model showing the principles of EEG wave generation. Note that the electrical potentials recorded from the two large pyramidal cells have the opposite polarity at the cortical surface (upper right waveforms) compared to those recorded at E1 and E2 (lower waveforms; from Coenen, 1995).

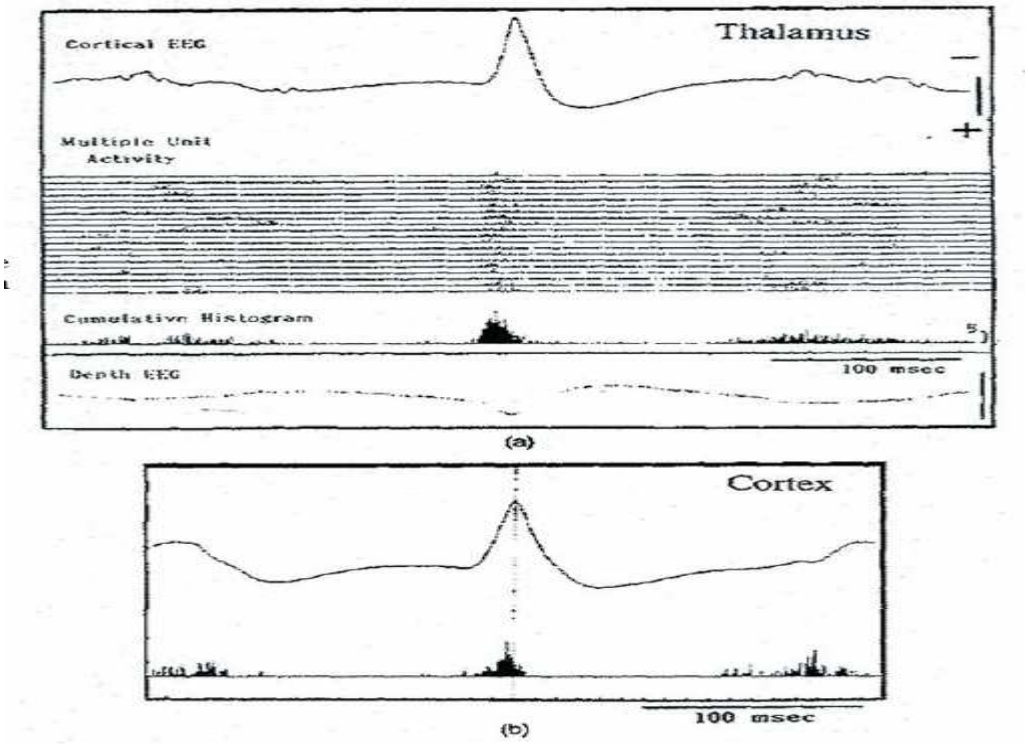


Figure 2.6: Correlation of cortically recorded spike-wave discharges with "multiple unit activity" of (a) thalamic and (b) cortical neurons. Note again the polarity reversal between depth and surface recorded potentials (from Coenen, 1995).

It has been repeatedly demonstrated by correlating scalp-recorded EEG with intracranial neuronal discharges in the monkey and the cat, that the polarity of ERPs, are related to either excitation or inhibition of cells. Comparison of evoked potentials and neuronal spiking activity reveals that neuronal discharges/firing in thalamocortical cells seem to result in negative ERP components, while cellular inhibition underlies positive potentials. Thus EPSPs/depolarisations appear responsible for negative ERP deflections, while IPSPs/hyperpolarisations are the cause of scalp-recorded positivities. Specifically, the scalp recorded negative shifts seem to be due to the depolarisation of pyramidal cell dendrites, which results in an extracellular surface current sink, with the opposite situation the case for scalp recorded positives. The relationship between neuronal activity and scalp-recorded potentials is shown in Figures 2.5 and 2.6 above, from Coenen (1995). Although this polarity reversal between intracranial and scalp recorded activity is true in most cases, the opposite relationship, where scalp positives are due to neuronal excitation and negatives to inhibition, has also been found on occasion.

2.3.4 Temporal and Spatial Resolution of ERPs

The utility of any investigative tool within the realm of cognitive neuropsychology is measured by its performance on two particular dimensions; temporal resolution, its ability to provide an accurate picture of the timing and sequence of occurrence of cognitive events, and spatial resolution, how well it identifies the different anatomical regions of the cortex that are involved in processing. Below is a brief comparison of ERPs with the other main neuropsychological research techniques, along both of these dimensions.

ERPs consist of scalp recorded electrical brain activity. Given that electrical potentials travel through both the bone and skin of the skull and scalp at high speed leading to almost instantaneous recording of the electrical activity of the brain, ERPs provide very

high temporal resolution. The time-course of processing in the cortex may be seen with millisecond accuracy. In this particular facet of functional brain activity recording, ERPs are considerably superior to the other major techniques available such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (*f*MRI). Both of these imaging techniques are constructed upon the concept that increased cognitive processing in an area of cortex requires increased regional cerebral blood flow (rCBF) to support the local energetic demands of the tissue for nutrients and oxygen. There is a significant time-lag involved in such approaches, due to the relatively slow speed at which blood flows through the brain (in comparison to electrical impulses). Also, a blocked design must be used in most imaging studies, such that a real-time record of processing cannot be obtained. Conversely, brain dynamics can be observed in real-time with EEG. For example, the activation time course of the ventral visual stream has been outlined by Doniger and colleagues (2000) with respect to object-recognition and perceptual closure.

A further addition to the neuropsychologist's arsenal of tools is the technique of Transcranial Magnetic Stimulation (TMS; Orrison *et al*., 1995). The method involves applying a powerful magnetic field to a location on the scalp, thereby causing the neurons in the underlying cortical tissue to fire. This effectively precludes that particular area's involvement in any concurrent processing tasks while the stimulation continues. As such, the effect is analogous to a virtual lesion of that region of the cortex. The temporal resolution of TMS is high, enabling one to deduce with precision accuracy at what stage in a processing loop an area is necessary (as indexed by disrupted performance on the task). The most powerful feature of TMS, however, is its functional resolution, a property which no other technique can boast. Functional resolution is the term used to denote the fact that TMS isolates the areas that are required or necessary for the successful completion of a task, rather than areas whose activity is merely correlated with such performance. When used in

conjunction with the other techniques mentioned herein, TMS should provide a significant contribution to understanding of the neural basis of cognitive processing. The spatial resolution is also quite high, accurate to the centimeter, although structures at depths below the superficial layers of cortex are inaccessible to TMS, thereby rendering such a technique insufficient in terms of current concerns.

The most recent addition is magnetoencephalography (MEG; Orrison *et al*., 1995). MEG involves the measurement of the tiny electromagnetic fields that are elicited whenever a neuron fires. Magnetic fields pass through the skin and bone at the same high speed as electric ones, thereby rendering MEG with comparable temporal resolution to ERPs. However, unlike electric potentials, magnetic fields are not distorted by the skull and scalp, therefore much better spatial resolution is possible. At present, the use of MEG is limited due to the massive expense involved.

However, and importantly in terms of present concerns, the major stumbling block encountered with the use of ERPs is the relatively poor spatial resolution it affords both Experimenters and clinicians. Electrical fields are significantly distorted by skull and scalp tissue, such that the pattern of activity recorded on the scalp may bear little resemblance to the regions of cortex responsible for such activity. As such, it is difficult to ascertain with convincing accuracy whether a potential recorded by a dorsolateral prefrontal electrode actually emanated from the dorsolateral prefrontal cortex. PET and fMRI allow for very high spatial resolution, given that the anatomical structures receiving increased blood flow can be represented in three dimensions. Also, because they do not rely on mere scalp recordings, activity in deep sub-cortical regions may also be observed. This disadvantage limits the use of ERPs in Experimental study, and many laboratories have conducted much research on methods to overcome this apparent deficit. However, these methods merely lessen rather than solve the problem of spatial resolution. In sum, ERPs provide excellent temporal

resolution, with relatively poor spatial resolution. Furthermore, regarding source localization in EEG, accurate solutions to the forward problem (see below) allow for the construction of head models which can be compared to recorded data to ascertain estimates of source location, the dipole source localization of which will be discussed in greater detail later in the chapter.

Further, and importantly in terms of studies conducted presently, ERP experiments have various advantages over brain imaging techniques with regard to design and set-up. Participants may experience claustrophobia inside the bore of the magnets involved in MRI. Head movements can have catastrophic consequences in a functional imaging experiment, which are much more easily identified and compensated for by filtering and trial rejection techniques in ERP studies. Magnetic susceptibility is also a problem in MRI experiments. When two tissues with divergent magnetic susceptibilities are juxtaposed, local distortions are created in the magnetic field. Further, there are natural interfaces between air and tissue in the oral and nasal orifices. This yields artifacts in the MR image, mostly a loss of signal, but also a distortion of the image. This particular problem does not affect EEG signals. Finally, in designing experiments, it is easier to incorporate an event-related paradigm into an ERP Experiment given that 'jitter' needs to be included for fMRI studies which typically use blocked designs. The 'event-related' approach allows for measurements of individual trials, or even sub-components of trials (Donaldson & Buckner, 2000).

2.3.5 ERP Localisation: Brain Electrical Source Analysis Technique

The Brain Electrical Source Analysis (BESA) technique employed throughout the current thesis attempts to maximize spatial resolution through the use of multiple source algorithms, creating source montages which have been shown to allow the location of ERP potentials to be displayed at a much higher spatial resolution (Scherg, Bast & Berg, 1999). BESA is based

on the assumption that the spatiotemporal distribution of voltage can be adequately modeled by a relatively small number of dipoles (<10), each of which has a fixed location and orientation but varies in magnitude over time (Scherg, Vajsar & Picton, 1989; Scherg & von Cramon, 1985). Each dipole has five major parameters, three indicating its location, and two indicating its orientation. A magnitude parameter is also necessary, however this parameter varies over time and is isolated somewhat from the location and orientation parameters.

The BESA algorithm commences by positioning a set of dipoles in an initial set of locations and orientations, with only the magnitude being unspecified. The algorithm subsequently calculates a forward solution scalp distribution for these dipoles, computing a magnitude for each dipole at each point in time such that the sum of the dipoles yields, as closely as possible, a fitting scalp distribution in comparison to the observed distribution for each point in time. The scalp distributions from the model are then compared with the scalp distributions at each time point to ascertain how successful the match is. The degree of match is quantified as the percentage of the variance in scalp distribution that is explained by the model; or indeed, alternatively, it can be expressed as the percentage of unexplained variance (i.e., 'residual variance'). The ultimate goal of the algorithm is to isolate a set of dipole locations and orientations that give rise to the lowest residual variance, thereby providing the best fit between the model and the data. This is achieved in an iterative manner. With each iteration, the forward solution is calculated, thereby leading to a certain degree of residual variance. Subsequently, the positions and orientations of the dipoles are slightly adjusted in an effort to reduce the residual variance. This procedure is iterated on numerous occasions adopting a gradient descent algorithm such that the positions and orientations are adjusted in such a manner that there tends to be a decrease in residual variance upon each successive iteration. In the initial set of iterations, the residual variance drops quickly, however after a large number of iterations, the residual variance ceases to decline much from one iteration to

the next, and as such, the dipole positions and orientations become stable. Refer to Figure 2.7 below for an example of the BESA dipole modeling technique.

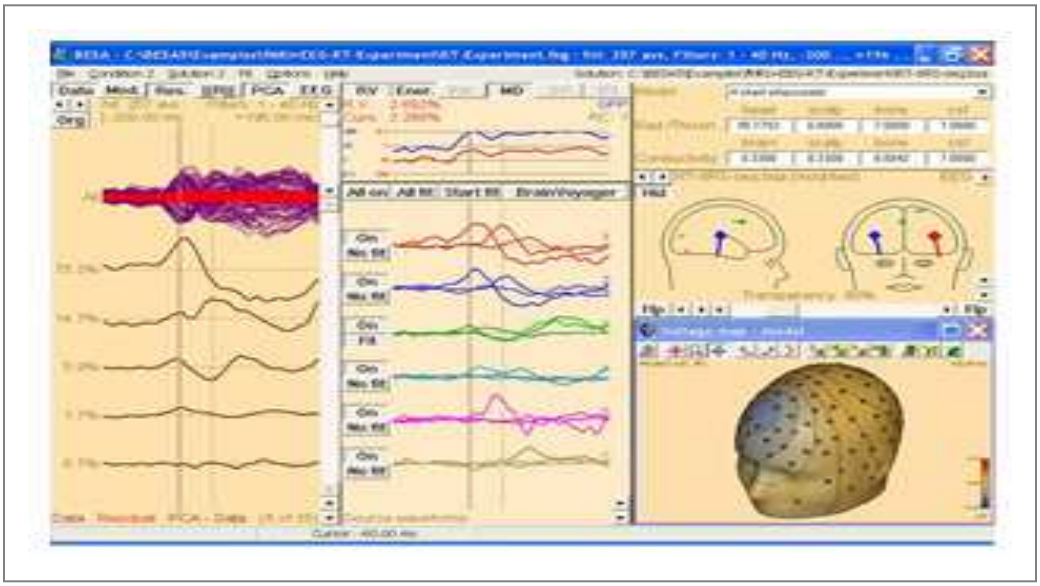


Figure 2.7: An example of BESA dipole modeling procedure. Copyright © 2007 Cortech Solutions, Inc.

2.3.6 Electrophysiological Recording and Setup

2.3.6.1 Preparation: Applying the cap and electro-conductive gel

Participants were fitted with a specially produced electrode placement cap (Easy-Cap), ensuring that the midline electrodes (AFz, Fz, FCz, CPz, Pz, POz, Oz) were positioned straight along the sagittal axis of the head (see Figure 2.8). This cap was mounted in an elastic cap fastened with a chest strap. Electro conductive gel (Abraylt, 2000) was placed into the 128 electrode sites with a 10 ml flat-tipped syringe (see Figure 2.8 for a map of electrode sites). This gel ensures a good conductivity between the scalp and the electrode. The needle was gently swirled in each electrode site to remove any air bubbles or hair that may have obstructed contact between the electrode and the scalp. Tin electrodes (BrainVision; BrainProducts GmbH, Germany) were inserted into the electrode sites following the extended version of the International 10-20 system for electrode placement (American

Electrophysiological Association, 1999; see Figure 2.8), while their plugs were inserted into an amplifier (BrainVision; see Figure 2.9). When all the electrodes were in place, preparation for the reference and EOG electrodes took place. The reference electrode was placed on the naison at the tip of the nose and four EOG electrodes were placed around the eyes to record blinking; that is, two were placed at the external canthi of the eyes to record horizontal movements and another two were placed on the inferior and superior ridges of the orbit of the left eye to record vertical movements (see Figure 2.9). These areas were gently prepared with an alcohol solvent wipe (Sterets) to remove any facial build-up. A non-abrasive electro-conductive gel (Signa-Gel) was then used to apply the facial electrodes. These electrodes were held in place with either electrode pads or surgical tape.

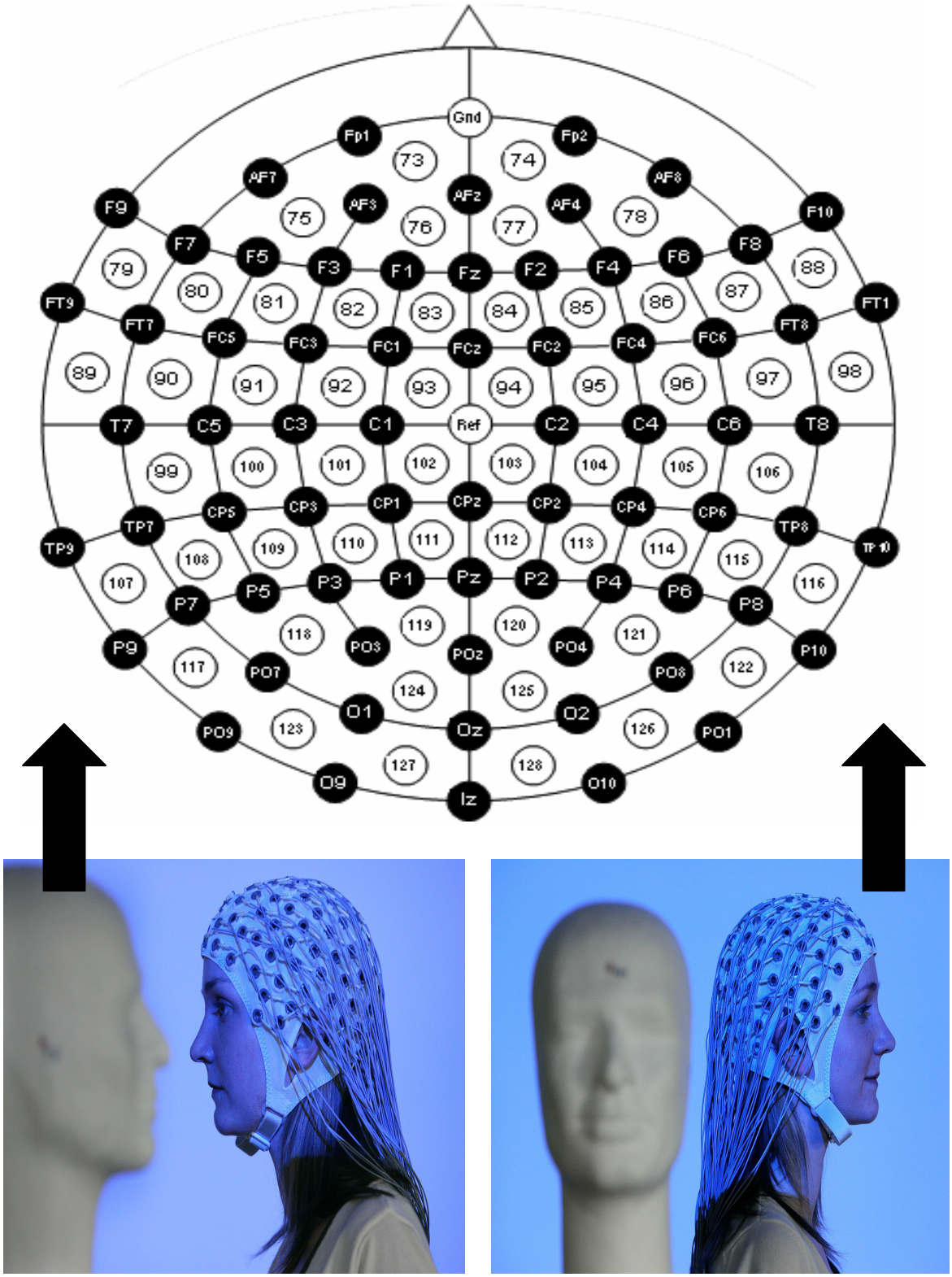


Figure 2.8: The extended version of the International 10-20 system for electrode placement (American Electrophysiological Association, 1999) 128 ERP channel montage (top), together with actual representation of electrode placement, showing left and right sides, used in the present thesis (bottom). Permission for use obtained from the NUIM Psychology Department 2009.

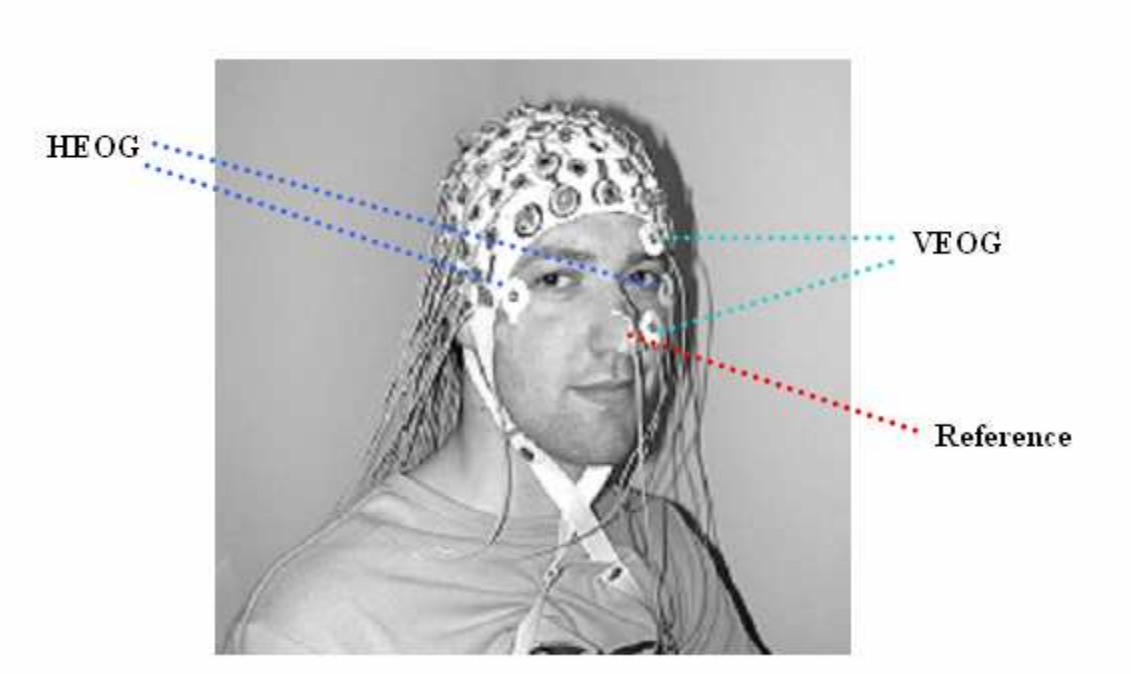


Figure 2.9: An example of a High-Density ERPs Array, used by researchers in NUIM. Figure clearly shows electrode placement together with naison reference, as well as electroencephalography technique used. Permission for use obtained from the NUIM Psychology Department 2009.

2.3.6.2 Testing and reducing impedance

Impedance testing allows one to see how well the electrodes are conducting activity from the scalp. The computer software, BrainVision showed a colour-coded measure of impedance quality at each electrode. At one end of the scale was a red colour, signifying poor impedance, and at the other end was a green colour, indicating low impedance (5kOhms). If the impedance showed all red electrode sites, all connections from the cap to the amplifier were first checked, if they remained red, a cotton bud stick was used to swirl around each electrode cup and more gel was added in order to ensure that the strongest connection possible between the electrodes and the scalp was achieved. In all cases the impedance level was reduced to below 10kOhms before testing began. This process took approximately 50-60 minutes depending upon individual impedances.

After electrophysiological preparation, participants were seated approximately 50cm from an LCD[3] computer screen on their own in a darkened, electrically shielded (i.e., copper) and sound attenuated testing cubicle, measuring 150cm x180cm with access to a mouse for responses. Participants were asked to keep movements to a minimum due to potential artifacts induced by blinks, facial and head movements. All jewellery and mobile phones were removed from the participants and kept in a safe place until the experiment ended. All electrical equipment was removed from the room prior to examination apart from the screen, keyboard and EEG Amplifier. All experiments were constructed using E-Prime® (Psychology Software Tools Ltd., Pittsburgh, USA) which is widely regarded as the most powerful and flexible experiment generator currently available. Upon completion of the experimental task, all electrodes were removed from both the cap and face, and the gel was cleaned off using a paper towel and alcoholic prep pads. Participants were then led to another cubical furnished with a basin and shower hose where the gel was washed-off. The participant was thanked and fully de-briefed while any questions or concerns were wholly answered. When the participant had left, the cap and electrodes were washed carefully in a sink of warm water and all remnants of gel were removed.

[3] Liquid Crystal Display (LCD) screens cause little interference to the EEG signal compared to older Cathode Ray Tube (CRT) monitors.

Figure 2.9: (a) Reducing impedance prior to attaching referential electrodes. (b) Participant seated in front of computer screen in sound attenuating cubicle prior to Experimentation. Amplifier-electrode plug connections also shown in yellow box. Permission for use obtained from the NUIM Psychology Department 2009.

2.3.7 ERP recording and analysis

The raw electrophysiological data recorded from each participant was in the form of a continuous file recorded from 128 channels. The file also contained voltage triggers, sent from the stimulus-presentation computer at the time of stimulus presentation. These triggers allowed for the extracted ERPs to be time-locked to stimulus presentation. The extraction of the ERP signal from the ongoing EEG is referred to "epoching" because the continuous file is divided into individual time epochs. ERPs time-locked to the onset of the stimulus presentations were computed for each subject at all scalp sites with epochs of approximately -100ms to 1500ms (varying across experiment). Blinks were averaged off-line and a blink reduction algorithm was applied to the data off-line in BESA. This algorithm involved automatic artifact correction employing variations of the Berg and Scherg (1994) and Ille *et al.* (2002) strategies. The correction process consisted of four steps. Step one was to define the topography for each type of artifact. Step two determined the brain signal topographies underlying the displayed EEG segment. Step three involved the reconstruction of the artifact signal at each scalp electrode with a spatial filter taking into account artifact as well as brain signal subspace. Finally, step four was to subtract the reconstructed artifact signal from the

original EEG segment. The voltage differences between the 128-channel electrodes and the reference electrode were extracted as electrical waveforms, which were then amplified using a band-pass of 0.16-100Hz and a gain of 1000. The conversion rate was 2000Hz per channel and the range was 150mV. ERP recordings were notch filtered off-line at 50Hz. EEG data were digitized at a sampling rate of 500, and were averaged offline using BESA. Any epochs where the maximum amplitude exceeded 50μV were rejected. Stimulus-locked average ERPs[4] were obtained by averaging the EEG using stimulus presentation as the trigger. ERPs time-locked to the onset of study and test presentations were computed for each participant at 128 electrode sites with epochs of approximately -100ms to 1500ms, which differed according to Experiment.

The average area under the curve (AUC), mean amplitude and latency for defined responses were calculated. For measurements of maximum peak amplitude, the naison electrode was used as the reference. Waveform component structure was assumed in an *a priori* manner with *no* prior knowledge of the pattern of effects. An overall grand-mean waveform was generated for each of the electrodes by collapsing across the conditional ERPs. From this, the latency and AUC of the components of interest could be investigated by visual inspection using BESA. From visual inspection, the time window for each of the components in each of the conditional ERPs were determined. From this inspection, possible comparisons were generated and tested for significance using SPSS© software (Version 13). Only scalp sites selected following a visual analysis of the data were included in the inferential statistics. These sites are representative of the centre of activity differences seen in the topographic maps generated for subtraction waveforms. Although only single sites are displayed (due to figure limitations), clusters of sites were used for analyses.

[4] The term "stimulus-locked" is used here to describe averaging binned by the stimulus. Averages based on stimulus triggers are referred to as Stimulus Triggered Averages (STA)

Applying this form of grand-mean analysis to identify component latencies has the advantage of reducing the number of analyses undertaken. However, the potential is also present to increase the possibility of Type II errors as a consequence of missed effects, given that these latency components represent the activity of simultaneous active neural generators at a given time only (Molholm *et al*., 2004). To account for this potential problem, secondary statistical analyses were carried out using the data set. One-way repeated-measures ANOVAs were used to determine statistically significant differences between various conditions when comparing the latencies or AUCs (DVs) in the components of interest. Greenhouse-Geisser corrections were employed for violations of sphericity. T-tests were employed to examine paired comparisons and elucidate results emanating from the ANOVAs where necessary. Repeated measures ANOVAs attended to Latency and AUC differences for each of the identified components for all comparisons of experimentally defined conditions. A star-based system for significance representing *p*-values of * <0.05, **<0.01, and ***<0.001, respectively, was used throughout.

2.3.8 Brain Electrical Source Analysis

Following completion of ERP analysis, the neural generators of the ERP components were examined by creating a discrete multiple source model with BESA software. This model was used to transform recorded sensory level data (EEG) into brain source space in the form of a 4-shell ellipsoidal head model (Hoechstetter *et al*., 2004). BESA employs a least squares fitting algorithm, over which the user has interactive control. Source localization proceeds by a search within the head model for a location wherein the sources can explain a maximal amount of variance (Scherg & Picton, 1991). The brain source space head model provides source waveforms measuring activities on a trial-by-trial basis from the different regions of the modeled brain. The source waveforms were transformed into time-frequency space using

complex demodulation. This method allows for the separation of the time-frequency content of divergent brain areas even if their activities severely overlap or diverge at the surface (Hoechstetter *et al*., 2004). We conducted whole-epoch modeling as well as individual component modeling using a data-driven step-wise approach and sequential fitting strategies where possible. Individual component modeling was used to generate the possible neural generators of certain components of interest. Single dipoles were added to each model until the solution presented became implausible. Optimal parameters for each dipole in the brain were created by searching for a minimum in the residual variance (RV) function or the percentage of variance in the recorded distribution not explained by the dipole model. For each waveform, the time-dependent RV was computed for the model. Within the predetermined latency window, parameters were optimized for individual data at the time point at which the maximum RV could be computed. Only data with an RV less than approximately 10% were included in the analysis. Refer to Figure 2.10 for example of BESA ERP and dipolar output.

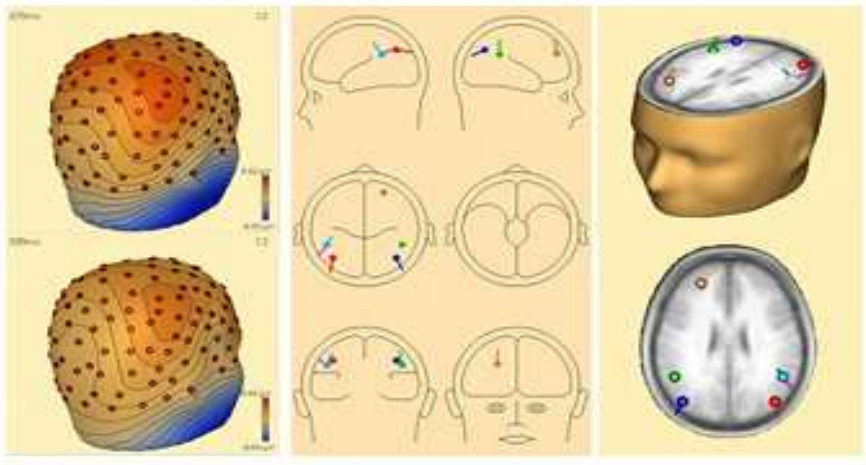


Figure 2.10: BESA source analysis software displaying an example of ERP waveforms and scalp topographies (left), dipole solutions and MRI slices of anatomical locations of brain sources (right).

Source models were estimated for the time windows, in which the components of interest for conditional stimuli waveforms reached peak values. Anatomical loci and Brodmann's areas were estimated using a Talairach Daemon software application© (The Research Imaging Centre, UTHSCSA, Texas, USA). This software maps the X, Y and Z co-ordinates obtained using BESA onto the Talairach co-planar stereotaxic atlas of the human brain (Talairach & Tournoux, 1988) in order to locate the Brodmann's Area and gyrus of each dipole.

Finally, source waveforms were plotted and MRI slices (see Figure 2.10) were also generated in BESA. Transverse MRI slices are included in chapter results. However it is important to note once again at this juncture that the modeled dipoles created by the dipole source analysis represent an oversimplification of the activity in the brain areas and they should not be referred to as exact generators but considered as representative of centers of gravity of the observed activity (Molholm *et al*., 2004; Sehatpour *et al*., 2006).

2.3.9 Ethical Issues

Prior to participating in ERP-based experiments, prospective participants were informed of the general memory nature of the study and that they would be fully debriefed upon completion of the experiment. Those who agreed to participate in the experiment were provided with a consent form which outlined the general nature of the experiment, the expected duration, and a detailed account of the experimental procedure, as well as any legal clauses, and asked to sign it *prior* to taking part in the ERP experiments (see Appendices 17 and 18). Further, participants were made aware that they could withdraw both themselves and/or their data from the study at *any* time, and that any results emanating from each individual's participation were strictly confidential. Upon completion of the experiment, participants were *fully* debriefed and *all* questions or queries were answered by the

experimenter. The participants were asked to keep the nature of the study confidential from potential participants to avoid expectancy confounds. All data obtained from participants remained strictly confidential, and at *no* time during data analysis was the participant's identity revealed, with participants instead identified through randomly allocated participant numbers.

2.4 The Stress Task

2.4.1 Trier Social Stress Task (TSST)

An extensive animal and human literature reports that psychological factors can influence the hypothalamic–pituitary–adrenocortical (HPA) axis, which regulates the release of cortisol (see Chapter 1). Over the past half century, many studies have specifically focused on the effects of psychological stressors on cortisol activation. Despite the extensive magnitude of this research, Dickerson and Kemeny (2004) drew two broad conclusions from this literature as a whole. First, like physical stressors, psychological stressors are indeed capable of activating the HPA axis; a number of studies have reported that laboratory tasks such as public speaking or mental arithmetic can increase cortisol levels (e.g., Kirschbaum, Pirke, & Hellhammer, 1993). Second, the effects of psychological stressors on this physiological system are highly variable. Many studies have failed to find cortisol changes (e.g., Manuck *et al.*, 1991), and recent reviews have highlighted the inconsistent effects of psychological stressors on cortisol activity (e.g., Biondi & Picardi, 1999). The vast heterogeneity in the literature indicates that all types of negative situations may not uniformly trigger cortisol changes (Mason, 1968).

In order to select the most *effective* stressor for the purposes of the present research, it was pertinent to ascertain the conditions under which a cortisol response is sufficiently

induced. The literature in this area however is vast and for the mostpart, impenetrable. Hans Selye (1956) argued that the stress response, which includes HPA activation, was nonspecific: all stressors, whether physical or psychological, would elicit the same physiological reaction. Others have concluded from the early work investigating the effects of severe physically traumatic experiences on cortisol activity (e.g., electric shock, injury) that only extreme or prolonged stressful conditions trigger cortisol elevations. Some have focused on the specific characteristics of the stressor, hypothesizing that contexts that are novel (Rose, 1980), unpredictable (Mason, 1968), uncontrollable (Henry & Grim, 1990; Sapolsky, 1993), or threatening, with the potential for harm or loss (Blascovich & Tomaka, 1996; Dienstbier, 1989), would be most likely to activate this system. However, even though a range of hypotheses have been put forward, the vast majority has not been empirically investigated, and the evidence, where present, is not conclusive.

However, in a recent meta-analysis of 208 laboratory stress studies, Dickerson and Kemeny (2004; see paper for a detailed account of the available literature) investigated conditions capable of eliciting HPA axis stress responses. These researchers found that only certain types of acute laboratory stress tasks elicited a cortisol response. Evaluative tasks, such as ones that involved public speaking, produced greater cortisol responses than non-evaluative tasks (e.g., watching an emotion-eliciting video). Uncontrollable tasks yielded greater cortisol responses than tasks that were controllable. The largest effects sizes were found for motivated performance tasks (i.e., tasks that required active responses) that combined social-evaluative threat with uncontrollability. Finally, the meta-analysis found that tasks in which the evaluator was present (e.g., audience members for the speech task) produced greater cortisol responses than tasks wherein the evaluator was less salient (e.g., speech task that was videotaped for later evaluation). Overall, these findings suggest that, in a

laboratory context, motivated performance tasks that involve salient social-evaluative threat and uncontrollability result in the greatest activation of the HPA axis.

The Trier Social Stress Test (TSST, Kirschbaum, Pirke & Hellhammer, 1993) is a highly standardized laboratory psychosocial stress task, which is characterized by *both* uncontrollable and social-evaluative elements. The TSST is one of the few available stress protocols which satisfies the aforementioned criteria of a motivated performance task that combines elements of uncontrollability and high levels of social-evaluative threat. The TSST has become a standard tool for the experimental induction of psychological stress in healthy subjects as well as clinical populations, investigating a wide range of different outcome variables ranging from subjective-verbal stress reports to objective behavioral and biological stress responses including parameters of the hypothalamus-pituitary-adrenal, sympathetic-adrenal-medullary axis and the cardiovascular, immunological, and blood coagulation systems. The TSST is a motivated performance task consisting of a brief preparation period followed by a test period in which the subject is asked to deliver a free speech and perform mental arithmetic in front of an audience (see Chapter 7, for comprehensive account of procedure employed in the current context). The TSST can be applied in younger and older adults, in children as well as in clinical populations (for recent reviews see Kudielka *et al*., 2007a; 2007b). It has been repeatedly shown that the TSST is a valid and reliable instrument to induce physiological stress responses (Kudielka *et al*., 2004).

2.4.2 Measuring Emotional and Behavioural Response

Although the present research was most interested in disseminating the HPA response to the TSST, it was deemed necessary to measure behavioural response to the stress task as a control measure to account for any unexpected results as well as to ensure participants were

indeed ‘stressed’. Emotions are thought to mediate the effects of appraisal of environmental circumstances and coping resources on autonomic and endocrine systems such as the HPA axis (Pollard & Ice, 2007). Importantly, it is generally assumed that endocrine and psychological stress responses represent indicators of the same construct and thus a high psycho-endocrine covariance should be expected (Hellhammer *et al*., 2008). On a neuroanatomical level this hypothesis is corroborated by close links between the HPA and cortical and limbic structures, which are important mediators of subjective-psychological stress responses (Feldman *et al*., 1995; Lopez *et al*., 1999; Buijs & Van Eden, 2000; Heckmann *et al*., 2005; Herman *et al*., 2005; Wang *et al*., 2005).

To measure stress *appraisal*, a quick visual analog scale rating of how ‘stressed’ the participants currently felt (1=not at all stressed to 10= extremely stressed; see Appendix 3) was used initially as a *global* measure of stress and subsequently as a measure of *subjective* appraised stress levels at various stages throughout the stressor task (i.e., post-rest, post-anticipation, post-stressor, post-distractor, post-experimental task, post-recuperation). As such, these measures required immediate assessments of appraisal following exposure to various situations.

Given that psychopathology and mood state of the person both affect appraisal and the reporting of stress (Aldwin *et al*., 1989; Cohen *et al*., 1988; Lazarus & Folkman, 1984), it was deemed necessary to include control measures taking all of the aforementioned into account. Participants were screened for recent Depression and/or Anxiety related diagnoses (see Chapter 7). Further, the State-Trait Anxiety Inventory (STAI) was used to determine both state anxiety at various time points throughout the experiment (i.e., post-rest, post-anticipation, post-stressor, post-distractor, post-experimental task, post-recuperation) as well as the individual’s more stable trait anxiety rating. Ultimately, the question concerns whether appraisal is a reflection of underlying processes that are themselves responsible for incurring

vulnerability, or whether appraisal is the determinant of vulnerability directly (Monroe & Kelley, 1995). By including measures of the antecedents and components that contribute to appraisal, then, these competing views concerning the role of appraisal related to the stress task can be understood. Taking environmental factors into account, it was decided to use the Positive and Negative Affects Scale (PANAS; Watson, Clarke & Tellegen, 1988) to measure mood and affective response to the stressor task at the aforementioned time points to measure both mood and whether the stress task impacted on changes in subjective ratings. Taking personal resources into account, it was decided to take measures of general health using the General Health Questionnaire (GHQ; Goldberg, 1978), stable self-esteem using the Rosenberg Self-Esteem Scale (RSE; Rosenberg 1965), the 10-item Resilience Scale (Wagnild & Young, 1993) to measure hardiness, and the STAI, state and trait forms, to measure both stable and more temporary anxiety experienced throughout the stress task. Other salient variables were accounted for throughout using more qualitative measures given the length of the Experiment and potential for participant tiredness.

2.4.2.1 State Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) was initially conceptualized as a research instrument for the study of anxiety in adults (Spielberger *et al*., 1970). The STAI is a self report measure designed to differentiate between the temporary condition of “state anxiety” and the more general and long-standing quality of “trait anxiety” in adults. According to the author, state anxiety reflects a transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity. State anxiety may fluctuate over time and can vary in intensity. In contrast, trait anxiety denotes stable individual differences in anxiety propensity and refers to a general tendency to respond with anxiety to

perceived threats in the environment. The STAI contains four-point Likert items. The STAI Form Y is an administered analysis of reported anxiety symptoms. The first subscale measures state anxiety, the second measures trait anxiety, each comprising twenty questions (see Appendices 4 and 5, respectively). The range of scores is 20-80, the higher the score indicating greater anxiety (Spielberger *et al*., 1970). Some of the questions relate to the absence of anxiety, and are reverse-scored. STAI results can be used in the formulation of a clinical diagnosis; to help differentiate anxiety from depression; for psychological and health research; and for the assessment of clinical anxiety in clients in medical, surgical, and psychiatric settings (Mindgarden, 2008). Another feature of the scoring key addresses if three or fewer questions were skipped, providing an alternative scoring procedure.

2.4.2.2 Mood Measure: Positive and Negative Affects Scale (PANAS)

The Positive Affect Negative Affect Schedule (PANAS; Watson *et al*., 1988; see Appendix 6) is a psychometric scale developed to measure the largely independent constructs of positive and negative affect both as states and traits. Further, Positive and negative affect have been shown to relate to other personality states and traits, such as anxiety (Tellegen, 1985). Numerous PA (Positive Affect) and NA (Negative Affect) scales have been developed and studied in a variety of research areas. The findings from such studies indicate that the two mood factors relate to different classes of variables. Anomalous and inconsistent findings have also been reported. For example, some mood scales have been developed through factor analysis (e.g., Stone, 1981), while others have been constructed on a purely ad hoc basis with no supporting reliability or validity data (e.g., McAdams & Constantian, 1983). As such, there was a need for reliable and valid PA and NA scales that are also brief and easy to administer.

The development of the new scale by Watson and colleagues (1988) was based on previous measures that existed in the area. The starting point was 60 terms included in the factor analyses reported by Zevon and Tellegen (1982). Through a factor analysis the aforementioned researchers reduced the terms pool and devised a final list of 10 descriptors for the PA scale (attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong and active); and 10 descriptors for the NA scale (distressed, upset-distressed; hostile, irritable-angry; scared, afraid-fearful; ashamed, guilty; nervous, and jittery). Preliminary analyses revealed no systematic differences between undergraduate and non-student responses, and they have been combined in all analyses. Subjects were asked to rate how they felt during seven different time periods: (1) present moment; (2) today; (3) past few days; (4) past week; (5) past few weeks; (6) past year; (7) in general. The PANAS scales demonstrated a significant level of stability across all time frames. Importantly, for the purposes of the present research requirements, the PANAS can be used as a state or trait measure, and as such was employed at various time points throughout the stressor task to ascertain variations in mood (see above). Further, no consistent sex differences have been found.

2.4.2.3 The Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale (RSE; Rosenberg, 1965, see Appendix 7) was devised in an attempt to achieve a unidimensional measure of global self-esteem. Self-esteem refers to how much value an individual places on themselves (Baumeister, Campbell, Krueger & Vohs, 2003; Leary & Baumeister, 2000), or the amount of positive feelings an individual associates with the self (Kunda, 1999). The scale was originally designed as a Guttman scale, in that the RSE items were to represent a continuum of self-worth statements ranging from statements that are endorsed even by individuals with low self-esteem to statements that are

endorsed only by persons with high self-esteem. Rosenberg (1965) scored his 10-question scale that was presented with four response choices, ranging from “strongly agree” to “strongly disagree” as a six-item Guttman scale. The first item included questions 1 through 3 and were denoted a positive score if two or three of its questions were answered positively. Questions 4 and 5 and questions 9 and 10 were aggregated into two other items that were scored positively, if both questions in the item had positive answers. Questions 6 through 8, counted individually, formed the final three items. For the negatively worded RSE questions, responses that expressed disagreement and, hence, were consistent with high self-esteem, were considered positive.

2.4.2.4 Resilience Scale (RS)

The 25-item Resilience Scale (RS™; Wagnild & Young, 1993) is a self-report measure of the extent of appraised individual resilience. Resilience has been described as an individual’s capacity for maintenance, recovery or improvement in mental health following life challenges (Ryff *et al*., 1998), successful adaptation following exposure to stressful life events (Werner, 1989), and an individual’s capacity for transformation and change (Lifton, 1993). All items are scored on a 7-point scale ranging from 1 = disagree, to 7 = agree. All items are worded positively and reflect accurately the verbatim statements made by participants in the initial study on resilience conducted by Wagnild and Young (1993). Item responses are summed and then averaged. Possible scores range from 25 to 175 with higher scores reflecting higher resilience. The shortened version of the 25-item scale, the RS_{10} was used in the present research (see Appendix 8), given time limitations and possible participant fatigue. The shorter versions of the scale are derived from a factor analysis reported by Neill & Dias (2001).

2.4.2.5 The General Health Questionnaire (GHQ)

The General Health Questionnaire (GHQ; Goldberg, 1978, see Appendix 9) is the most common assessment of mental well-being. Developed as a screening tool to detect those likely to have or be at risk of developing psychiatric disorders, it is a measure of the common mental health problems/domains of depression, anxiety, somatic symptoms and social withdrawal. Available in a variety of versions using 12, 28, 30 or 60 items, the 28-item version is used most widely. Examples of some of the items in use include 'Have you found everything getting on top of you?'; 'Have you been getting scared or panicky for no good reason?' and 'Have you been getting edgy and bad tempered?'. Each item is accompanied by four possible responses, typically being 'not at all', 'no more than usual', 'rather more than usual' and 'much more than usual', scoring from 0 to 3, respectively. The total possible score on the GHQ 28 ranges from 0 to 84. Reliability coefficients have ranged from 0.78 to 0.95 in various studies.

2.4.3 Measuring Hormonal Variation in the HPA Response

2.4.3.1 Cortisol as a "stress hormone"

Salivary cortisol is frequently used as a biomarker of mental stress (e.g., Evans & Steptoe, 2001; Fischer *et al*., 2000; Pruessner, Hellhammer & Kirschbaum, 1999). Most studies consider salivary cortisol levels a reliable measure of HPA axis adaptation to stress (Hellhammer, Wüst & Kudielka, 2009).

The HPA axis is responsible for the secretion of the stress hormone cortisol. Numerous studies have indicated that both physical and psychological stress lead to a significant activation of the HPA axis. Stressors can override the negative feedback loop at the pituitary and hypothalamus, leading to increased frequency and amplitude of cortisol pulses. For example, marathon runs (Cook *et al*., 1986) and exercising on a bicycle ergometer

(O'Connor & Corrigan, 1987) are among the physical strains that are capable of activating the HPA axis. More importantly for current purposes however, psychological loads can activate the HPA axis as much, or more so than physical stimuli do. In early work, Mason (1968) reported that psychological influences are among the most potent natural stimuli known to affect HPA activity; his work emphasized the importance of situational characteristics as novelty, unpredictability, uncontrollability, anticipation of negative consequences, and personal involvement in activating the HPA axis. In addition, academic examinations (Kahn *et al*., 1992), public speaking (Bassett, Marshall & Spillane, 1987), parachute jumping (Deinzer *et al*., 1997), hostage imprisonment (Rahe *et al*., 1990), and psychosocial stress tasks in laboratory research all have been found to stimulate the HPA axis. Indeed, participation in the Trier Social Stress Task (TSST; Kirschbaum *et al*., 1993) has induced considerable changes in the concentration of ACTH and cortisol in many previous studies (see Rohleder *et al*., 2007) and repeatedly shows cortisol responder rates of over 70% (Kudielka *et al*., 2007).

2.4.3.2 Measuring Cortisol

A large proportion of cortisol is bound to transport proteins, such as cortisol-binding globulin and albumin that prevent the hormone from acting on target cells. Only 2-15% of secreted cortisol circulates unbound (Kirschbaum & Hellhammer, 2000). Only this "free" hormone fraction is biologically active (Mendel, 1989; Robbins & Rall, 1957), and as a consequence, it is usually free cortisol that is measured in field studies. Although blood contains both bound and unbound cortisol, only the free hormone fraction is able to get into saliva through passive diffusion. Although levels of cortisol in saliva are lower than those in blood, correlations between salivary cortisol and unbound blood cortisol levels are high ($r \sim .90$); hence, salivary cortisol provides an index of the biologically active fraction of this steroid

hormone (Kirschbaum & Hellhammer, 2000). Thus, the measurement of cortisol in saliva is the method of choice in psychoendocrinology studies and indeed for current purposes. Further, blood collection was not deemed practical for current purposes given it is invasive, requires medically trained personnel, is ethically problematic in the demands it makes of participants, and can itself cause a stress reaction thereby affecting cortisol levels. Saliva collection was deemed most appropriate, given that it is less invasive than obtaining blood, and more convenient than collection of timed urine samples (Ellison, 1988; Kirschbaum & Hellhammer, 1994; in Ice & James, 2004). Also, as it was necessary to collect samples at several different time points throughout the experiment, saliva collection was preferable.

To complicate matters, a substantial number of potential sources of inter- and intra-individual factors can affect salivary cortisol response to acute stressors. Important determinants of salivary cortisol responses to acute stress in humans incorporate such factors as age; with age there may be a decreased ability of the HPA axis to return to baseline following a stressor (McEwen, 1998; Sapolsky, 1992) and gender; higher cortisol levels and a greater cortisol response to laboratory stressors in men have been reported in some studies (Kirschbaum *et al*., 1992), endogenous and exogenous sex steroid levels (e.g., the female menstrual cycle, use of oral contraceptives and hormone replacement therapy); the use of oral contraceptives leads to an increase in cortisol binding globulin levels, such that more of the total cortisol is bound and less is available as free hormone (Kirschbaum & Hellhammer, 2000), pregnancy; levels of cortisol are elevated during the final trimester of pregnancy (Kirschbaum *et al*., 1992) and the cortisol response to stressors may also differ across trimesters (Obel *et al*., 2005), lactation and breast-feeding; in animals, lactation has been associated with attenuated hormonal responses to different kinds of stressors (Carter & Altemus, 1997) and breastfeeding decreases basal levels of ACTH and total plasma cortisol in lactating women (Amico *et al*., 1994), smoking; nicotine causes increased levels of cortisol

(Kirschbaum & Hellhammer, 1989) and Wüst *et al*. (1992) found that smoking two cigarettes resulted in elevation of salivary cortisol levels, peaking 25-35 minutes after smoking, coffee and alcohol consumption as well as dietary factors (e.g., fasting); eating and caffeine consumption causes rises in cortisol levels, peaking around 40-45 minutes following consumption (Smyth *et al*., 1998; see Pollard & Ice, 2007) and plasma cortisol levels rose following alcohol consumption in various studies (see Prinz *et al*., 1980; see Pollard & Ice, 2007); use of certain medications which may affect cortisol levels (e.g., glucocorticoids), presence of certain diseases which may result in an increase or decrease in cortisol levels, recent exercise level; cortisol levels appear to rise during exercise and peak approximately 20-30 minutes afterwards (Kindermann *et al*., 1982; Kirschbaum & Hellhammer, 1994; Filaire *et al*., 1996; Jacks *et al*., 2002; Tremblay *et al*., 2004; see Pollard & Ice, 2007) and sleep quality the preceding night, as well as various personality-based factors; in general, research suggests that negative effect is associated with a rise in cortisol levels (Pollard & Ice, 2007).

As such, these factors were stringently controlled for in the current study through various means. First, participants were given a participant details form prior to partaking in the experiment (see Appendix 10) upon which all of the aforementioned details were noted. Further, a pre-experiment screening questionnaire was administered (see Appendix 11), and exclusion criteria included currently taking beta-blockers, steroids, or any medication which may affect central nervous system functioning or endocrine systems, anyone suffering from Cushing's syndrome, Syndrome X or any other metabolic syndromes which may affect cortisol readings, recent diagnosis of depression or anxiety related disorders, history of head injury, current smoker, above average weekly alcohol intake, recent cold/flu-like symptomology, current pregnancy, recent shift work, and recent insomnia, as well as age exceeding 40 years. Although higher cortisol levels and a greater cortisol response to

laboratory stressors in men have been reported in some studies (Kirschbaum *et al*., 1992), Dickerson and Kemeny (2004), in their meta-analysis of laboratory studies, found there were no sex differences in cortisol effect sizes in response to experimental stressors. Therefore, *both* male and female subjects were included in the current study. Given that the majority of available participants were recruited from an undergraduate psychology pool, comprising mainly females, it was decided to merely take note of menstrual cycle stage and use of contraceptive pill rather than exclude these potential participants (see Appendix 10). Subsequently, participants were given strict guidelines regarding salivary cortisol analysis 24 hours prior to participating (see Appendix 12). To further ensure adherence to exclusion criteria and guidelines provided prior to salivary cortisol collection, a post-experiment screening questionnaire (see Appendix 13) was also administered.

Although there are several 'techniques' for saliva sampling, the easiest and most hygienic way is to collect saliva with the so called “Salivette™” device (Sarstedt, Inc., Rommelsdorf, Germany). This device mainly consists of a small dental cotton roll which the participants gently chew on for 30-90 seconds until they feel that the swab is sufficiently soaked with saliva. When finished, participants were instructed to place the cotton roll in a small tube with a hole which was located within a standard centrifuge tube. Salivette swabs are available with a citric acid infusion to stimulate saliva flow, but the citric acid is liable to affect pH levels of samples, and is thus to be avoided. Since the untreated pure cotton swabs, employed herein, supplied with standard Salivette tubes usually collect a sound sample of 1 ½ - 2 ml of saliva after between 60-80s of chewing, obtaining a sufficient sample is usually unproblematic (Kirschbaum & Hellhammer, 2000). Prior to saliva collection participants were equipped with strict rules and instructions governing saliva sampling (see Appendix 12). Immediately prior to sampling, participants were first asked to rinse their mouths with clean water and then examined for oral bleeding given that food and blood can contaminate

samples (Ellison, 1988; Flinn, 1999; see Pollard & Ice, 2007). To avoid a low pH which can potentially yield false high values, participants were instructed not to consume drinks with low pH immediately before saliva collection (see Appendix 12 for Participant Instruction Sheet).

As suggested by Kudielka and Kirschbaum (2005), several samples were collected per participant over the course of each stress session to cover basal HPA axis functioning, the initial response phase, and the recovery phase. Initial free salivary cortisol responses can be observed 5–20 min after stress with peak levels 10–30 min *after* cessation of the stressor. Basal levels are typically regained after 60–90 min. Thus, it was decided to obtain saliva samples at six time points throughout the stress task (see Appendix 14 for a detailed outline of procedural timing protocol and Appendix 15 for salivary cortisol sampling time record sheet). The first sample was taken immediately upon the participant entering the lab. The participant was subsequently given a 30 minute 'rest' period in a relaxing environment. The second sample was taken at the end of this 30 minute rest period. These first two samples provided an index of basal salivary cortisol levels. The participant was then exposed to a 10 minute stress anticipation period. The third sample was taken at the end of this anticipation period. Participants were then exposed to the stressor task and the fourth sample was taken upon completion of this task. A fifth sample was collected following the experimental task. Given that salivary cortisol levels peak 10-30 minutes post stressor, we hypothesized peak values during the experimental task. Participants were then given a 30 minute 'recovery' period during which they were re-exposed to the relaxing environment previously encountered. The final samples were obtained at the pre- and post- recovery period. Using the two pre and post stress periods, an artificial baseline was created, also known as the 'artificial baseline', which indicated basal salivary cortisol values (see Method section in Chapter 7 for greater detail). A further more stringent baseline, also known as the 'practical baseline', was

created using the first and last sampling times only to ensure that the baseline concentration was unaffected by the stressor (given that coritsol can remain elevated 50 minutes post-stressor (Kirschbaum *et al*., 1989). Unstimulated (i.e., presumably unaffected by stressors or other factors – 'normal'/baseline level) cortisol follows a diurnal rhythm that is dictated by the sleep-wake cycle, rather than a light-dark cycle: there is a typical and consistent flood of cortisol in the body upon awakening, generally declining thereafter, and cortisol secretion follows a series of peaks and troughs throughout the day, with a small peak associated with a lunch-time meal (Preussner *et al*., 1997, in Pollard & Ice, 2007; Kirschbaum & Hellhammer, 2000), which tends to taper off to a more steady, less steep decline in the afternoon. It is for this reason that laboratory studies examining cortisol generally schedule post-noon testing sessions. Therefore, all participants were scheduled to commence the session at 3pm in the current study (see Appendix 14). Variations in this cycle are seen in clinical populations – for instance, a blunted response has been demonstrated in individuals with depression and those experiencing socioeconomic hardship, while extremely elevated, or again, blunted cortisol release can result from a variety of medical conditions. Cortisol secretion can be affected by everyday factors such as consumption of food or beverages prior to sampling, or disrupted sleep patterns. As a result, stringent guidelines were set forth to control for these factors, and various control measures were distributed (see above) to screen for possible psychopathologies (see Appendices 10 and 11).

Cortisol in saliva is a particularly robust biologically-active compound, and samples remain viable for several days at room temperature, as well as when frozen and refrozen. In the current research, after having obtained the samples, they were immediately stored at -20º C degrees for hygienic reasons, as well as to prevent a significant degradation of the steroid. For the purposes of cortisol evaluation, participants were asked to report time of waking, exercise, smoking, caffeine, medication and food intake (van Eck & Nicholson, 1994;

Ockenfels *et al*., 1995; Smyth *et al*., 1998; in Pollard & Ice, 2007) all of which are known to influence cortisol (see Appendix 12).

2.4.4 Assay Technique Employed: ELISA

Salivary Cortisol ELISA Technique: EIA Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics™; State College, PA).

Day 1:

To prepare the samples, all frozen samples were thawed completely, vortexed, and centrifuged at 1500 x g (@3000 rpm) for 15 minutes. All samples were brought to room temperature before adding to the assay plate. Given that particulate matter may interfere with antibody binding, leading to falsely elevated results, clear samples were pipetted into appropriate wells as defined by the three pre-prepared plate layouts (Appendix 11). Each kit comprised 96-well microtitre plates which were *pre*-coated with monoclonal anti-cortisol antibodies. Plates were covered with tinfoil and incubated overnight at room temperature (i.e., 2 - 8°C).

Day 2:

Plates were washed once in Phosphate Buffered Saline (PBS) Wash Buffer (1X) (140 mM NaCl; 2.7 mM KCl; 10 mM Na2HPO4; 1.8 mM KH2PO4, dissolved in distilled, autoclaved water; 0.05% Tween v/v; 100 mL of 10X wash buffer to 900 mL of deionized H_20). The pH was adjusted to 7.4 using hydrochloric acid. Cortisol in saliva samples and in a set of standards (termed 'cold' cortisol) was added to wells of the microplate. 25 µL of standards, controls, and unknowns were pipetted into appropriate wells. Standards, controls, and unknowns were assayed in duplicate. 25 µL of assay diluent (63mL of a PBS containing a pH indicator and a non-mercury preservative) was pipetted into 2 wells to serve as the zero. 25µL of assay diluent was also pipetted into each non-specific binding (NSB) well. The

cortisol standards comprised 6 vials, 500 μL each, labeled A-F, containing cortisol concentrations of 3.000, 1.000, 0.333, 0.111, 0.037, and 0.012 μg/dL in a synthetic saliva matrix with a non-mercury preservative (values in nmol/L are 82.77, 27.59, 9.19, 3.06, 1.02, and 0.33 nmol/L, respectively). A 1:1600 dilution of the enzyme conjugate (50 μL of a solution of cortisol labeled with horseradish peroxidase) was obtained by adding 15 μL of the conjugate to the 24 mL of assay diluent prepared previously. The diluted conjugate solution was mixed immediately and 200 μL was pipetted into each well using a multichannel pipette. The plate was mixed on rotator for 5 minutes at 500 rpm and incubated at room temperature for an additional 55 minutes. Plates were washed 4 times with 1X PBS wash buffer. Washing was achieved by pipetting 300μL of wash buffer into each well, and then discarding the liquid by inverting the plate over a sink. After each wash, the plate was thoroughly blotted on paper towels before being turned upright. 200 μL of TMB (Tetramethylbenzidine) solution was added to each well with a multichannel pipette. Plates were mixed on a plate rotator for 5 minutes at 500 rpm and incubated in the dark at room temperature for an additional 25 minutes. 50 μL of stop solution (12.5mL of sulphuric acid solution reconstituted with 12.5mL of deionized water) was added with a multichannel pipette. The plates were subsequently mixed on a plate rotator for 3 minutes at 500 rpm. The bottom of the plate was dried with a water-moistened, lint-free cloth. Plates were read A_{450}nm in a 96-well plate reader within 10 minutes of adding stop solution, and cortisol concentrations were estimated for the standard curve.

Calculations

The average optical density (OD) was calculated for all duplicate wells. The average OD for the NSB wells was subtracted from the average OD of the zero, standards, controls, and unknowns. The percent bound (B/Bo) for each standard, control, and unknown was

calculated by dividing the average OD (B) by the average OD for the zero (Bo). Concentrations of the controls and unknowns were ascertained by interpolation using software capable of logistics. A 4-parameter sigmoid minus curve fit was used.

3

Chapter III

Behavioural correlates of local versus global contextual processing in episodic memory retrieval

Abstract

The contribution of contextual factors upon learning and memory has been well-established, and it has been repeatedly shown that reinstating a learning context facilitates, while changing context impairs, retrieval. Here, we attempted to ascertain whether context reliably facilitates episodic item recognition in the same way that it influences episodic word recognition and semantic object identification. Second, we wanted to determine the relative effects of local and global background context, encoded implicitly, on episodic item retrieval. In so doing, we attempted to delineate whether the binding of item and context occurs implicitly, or whether item and context are separate entities in this regard. We achieved this aim through adopting context-dependent measures such as the context-shift decrement, as well as employing a visual paired-associate task, known to elicit episodic processing. Third, we decided to investigate the impact of both local and global context on true and false recognition measures, given the importance of true and false recognition within the premise of implicit-explicit, unconscious-conscious, familiarity-recollection and item-inter-item (i.e., binding of item and context) dichotomies, respectively. To achieve this, we used the 'old/new' paradigm, wherein participants were required to judge whether items presented during the test phase were previously encountered during the initial study phase. Experiment 1 was concerned with ascertaining the implicit effect of local context cue congruency or incongruency on true versus false episodic recognition. Conversely, Experiment 2 was concerned with determining the impact of global contextual cue congruency or incongruency on true versus false episodic recognition. Predicted congruency effects were found across both local and global Experiments, with participants responding more accurately to 'false', as opposed to 'true' previously presented stimulus pairs. We suggest that the increased false over true recognition findings, indicate that perhaps such episodic processing is taking place

on a conscious, item-familiarity based level. Further, the context-dependent congruency results infer that context facilitates episodic stimulus recognition in the same way that it influences episodic word recognition and semantic object identification.

3.1 Introduction

3.1.1 General Introduction

An extensive empirical literature demonstrates that reinstatement of context wherein a target was originally learned facilitates several forms of memory retrieval (e.g., free recall, Eich, 1985; Godden & Baddeley, 1975; Parker & Gellatly, 1997; Parker, Gellatly & Watermann, 1999; cued recall, Smith *et al*., 1978; serial recall, Jensen, Dibble & Anderson, 1971; and perhaps less consistently, recognition, Smith, 1985; Canas & Nelson, 1986; Dougal & Rotello, 1999; Russo *et al*., 1999; but see Smith *et al*., 1978; Fernandez & Glenberg, 1985; Godden & Baddeley, 1980; Murnane & Phelps, 1993, 1994, 1995). An episodic memory trace consists of both focal information towards which attention is focused and peripheral information comprising factors such as details of the physical environment in which learning occurred and the emotional or physiological state of the learner, quintessentially referred to as "context". Context plays an integral role in reinstating the original episode, given that it comprises a large proportion of the memory trace of the episode. According to Isarida (2005), different forms of context aid in reinstating different portions of an episode. For example, in terms of a list-learning episode, semantic context (which incorporates semantic features from the set of items being processed) changes quite rapidly, and as a consequence will become associated with only a single item. Alternately, global environmental cue-based context, which is composed of the incidental physical features of the environment wherein participants process focal information, can become associated with the entire list-learning event, given that environmental context remains stable throughout the event and is thereby associated with all the elements of the event. The second idea that provides a foundation for understanding episodic memory is that the match between information available in a retrieval cue and information stored in memory is a critical determinant of retrieval success. The

higher the degree of match, overlap, or similarity between the information contained in a retrieval cue and the information stored in memory, the higher the probability that the information from memory will be successfully retrieved. Thus, the best cue for retrieving a target item from memory is information that is stored in memory along with the target item. Tulving (1983; Tulving & Thompson, 1973) referred to this concept as the Encoding Specificity Principle (see Chapter 1).

In accordance with the widely held assumption that episodic memory is context-specific, researchers have quintessentially sought evidence that a change in context between learning and test exerts a detrimental effect on the ability to discriminate previously learned items (i.e., targets) from new items (i.e., distractors) in a recognition paradigm (Smith, 1988). Previous research finding such a deteriorative effect, with lower performance in different-context test conditions than in same-context test conditions has been reported (e.g., Geiselman & Glenny, 1977; Geiselman & Bjork, 1980; Smith, 1986; Smith & Vela, 1992). However, there have also been numerous failures to produce such context-dependent effects with changes in environmental context (e.g., Smith *et al*., 1978; Godden & Baddeley, 1980; Fernandez & Glenberg, 1985; Murnane & Phelps, 1993, 1994, 1995). Murnane and Phelps (1993, 1994, 1995), adopting a global activation approach, have presented the most thorough attempt in the recent literature to resolve such anomalous findings. Global activation theories of memory (e.g., Gillund & Shiffrin, 1984; Murdock, 1982), which view memory as a function of the total level of activation of information stored about a learning episode in response to an item-plus-context retrieval cue, predict that a study-test context mismatch should decrease recognition performance. Murnane and Phelps (1993, 1994) argued that in order to find effects of changed context on measures of recognition, the changed context test condition must use a context previously unencountered during the learning phase. This follows from the global activation approach, which asserts that if an item-plus-context test

cue contains context information that was previously encoded during the study phase, even though the particular item was actually presented in a different context at study than the one in which it is presented at test, then the activation of context information within the memory representation will be equal under both same- and different-context conditions. Thus, in order for different levels of activation to occur in same- and different- context conditions, the different-context condition must involve presentation of items in a novel context that has not been previously encoded into the memory representation.

In response, Murnane, Phelps and Malmberg (1999) proposed a theory of cueing effects that assumes that there are three general types of information that can match between encoding and retrieval: Item information, Context information, and Ensemble information (thus, it is called the ICE theory). Item information refers to features that received focal processing at encoding (e.g., the conceptual features of the studied words). Context information refers to incidentally-processed features that are bound in a memory trace although they are not central to the memory task at hand. This type of information is also known as associated context. Ensemble information refers to contextual features that are meaningfully integrated with the item information. According to the ICE model, when associated context information is provided in a test cue, the relevant contextual feature is activated across an entire set of items in memory. However, providing integrated context information at retrieval activates contextual features that are uniquely associated with a single item in memory. Ultimately, the ICE model specifies a global matching model that is capable of producing the complete pattern of context-dependent recognition effects, according to which specific predictions depend upon patterns of match and mismatch for associated context and ensemble information.

Contexts can differ in terms of their position on a local-global continuum (e.g., Dalton, 1993; Glenberg, 1979). The vast majority of context-based research has thus far

investigated *only* the influence of extra-item, global contexts encoded incidentally (see Mori & Graf, 1997), with changes in context between learning and retrieval generally exerting a detrimental effect on memory performance (e.g., Godden & Baddeley, 1975; Eich, 1985). Further, the majority of context-dependent research has been conducted in one of only two environmental or *global* contexts, subsequently testing memory retrieval in either in the same or an alternate environmental context.

Other contextual manipulations have focused on more *local* aspects of visual context combined with predominantly verbal materials, such as text colour, background color, or font. Dulsky (1935), in a series of experiments, reported a decrease in memory performance when the background colour of target nonsense syllables changed between study and test. Since then, many experiments have demonstrated decreased retrieval performance with changes between encoding and retrieval in the local verbal context (Tulving & Osler, 1968; Light & Carter-Sobell, 1970), font format and orientation (Graf & Ryan, 1990), background colour (Mori & Graf, 1996), or foreground and background colour (Dougal & Rotello, 1999). In a comprehensive series of experiments, Murnane and Phelps (1993, 1994, 1995) manipulated context by changing foreground (colour of the word), background (colour of computer screen), and the location of the word (upper left, lower right, and so on). In multiple experiments, a context shift decrement (i.e., decreased memory for items presented in different contexts at study and test) was observed. The context shift decrement was significantly enhanced when the words were originally studied in a visually rich context (computer-generated virtual reality scenes, such as on a chalkboard in a classroom) relative to simple visual contexts (coloured font, coloured background), or in various locations on the computer screen (Murnane *et al*., 1999).

The association between viewed items and the context in which they appear has been termed *contextual binding* (Chalfonte & Johnson, 1996; Mitchell *et al*., 2000). The capacity

to encode such associations can be distinguished from the ability to separately encode either the item or its context. Prior research has established that contextual details are bound to item information (Chalfonte & Johnson, 1996). The majority of research into *contextual binding* between *objects* and context stems primarily from studies conducted on object perception or object identification in humans, which has typically shown that contextual information enhances object identification (Palmer, 1975; Biederman *et al*., 1982; Boyce & Pollatsek, 1992; Davenport & Potter, 2004). Such experiments focused on pre-existing, *semantic* relationships between objects and their associated contexts. For example, Bar and Ullman (1996) showed that the presence of a clearly identifiable object facilitated identification of an ambiguous object when the identifiable object was semantically related, as did the presentation of realistic spatial relationships between related objects. However, the implicit influence of visual context on memory for specific, episodically-mediated abstract paired-associates remains to be elucidated (however see Hayes, Nadel & Ryan, 2007 for episodic object recognition).

Neuroimaging studies of scene processing (Epstein & Kanwisher, 1998), object identification (Bar & Aminoff, 2003), and *intentional* retrieval of visual context information (Hayes *et al*., 2004) suggest that the medial temporal lobes, most likely the parahippocampal cortex (PHC), may be involved in visual context effects mediating episodic object recognition. Indeed, Hayes and colleagues (2007) recently found that the PHC is important not only for processing of scene information, but also plays a role in successful episodic memory encoding and retrieval. Further, the hippocampal and PHC regions have been shown to be responsible for the association of objects with their spatial location in the stimulus environment (Burgess *et al*., 2002). Other neuroimaging evidence indicates that these regions are also involved in relational processing (Cohen *et al*., 1999), that is, in integrating or binding disparate elements in a complex scene to form a meaningful representation. For

example, greater activation of the HF and PHC region occurs when stimulus elements are encoded relationally or *bound* together rather than encoded individually (Henke *et al*., 1997, 1999). Thus far, *in vivo* demonstrations of HF and PHC activations during binding operations have used paradigms that required *effortful encoding* (Henke *et al*., 1997, 1999; Montaldi *et al*., 1998). However, behavioral data suggest that these processes operate *without explicit intention* (Luck & Vogel, 1997; Cohen *et al*., 1999). In line with Goh and associates (2004) who demonstrated the engagement of MTL areas in contextual binding *without* explicit task instructions to relate picture elements, we sought to identify behavioural correlates of contextual binding without explicit instruction to do so, in an episodic hippocampally-mediated visual paired-associates task

Contemporary theories of recognition view performance as a derivative of at least two forms of processing: one subsuming conscious recollection of the initial learning event and another upon which a general 'feeling' of familiarity may be based (e.g., Gardiner & Java, 1993; Jacoby, 1991; Mandler, 1980). Research tends to converge on the view that recollection is based on effortful, elaborative, inter-item processing (e.g., word-word associations, word-image associations, word-context associations, and so on). Conversely, evidence suggests that familiarity is based on an automatic, integrative, item-based process (i.e., the process involved in representing the item itself in terms of perceptual features and so on, independent of the representation of other items). According to this perspective, it has been suggested that context-shift decrement effects should occur only for measures of recognition based on elaborative processing (i.e., recollection), whereas recognition emanating from purely item-based processing (i.e., familiarity) may remain unaffected by study-test context changes. This proposition is supported by findings demonstrating that the encoding of context information requires effortful, elaborative processing (e.g., Naveh-Benjamin, 1987, 1988). If it is the case that automatic, integrative processes, assumed to belie

feelings of familiarity at retrieval, are purely item-based and do not involve processing of context information, it would be predicted that if recognition is based primarily on familiarity, no context-shift decrement will be found.

ICE theory (see above) makes predictions about context effects on different measures of recognition, including 'true' recognition rate (i.e., proportion of old items correctly identified as old), 'false' recognition rate (i.e., proportion of new items identified as old), and the discrimination measure (i.e., composite measure of recognition memory that index an individual's ability to distinguish old from new items). The predicted patterns of context effects are different depending on which information is stored in memory and used in the retrieval cue, either item and associated context only, or item, associated context and integrated item and context. ICE predicts that if only item information and associated-context information are used in the global match, then the global match for target items tested in the same context is higher than the global match for targets tested in a different context. Consequently, context effects are expected in terms of true recognition. Also, the global match for distractors tested in a context that the participant has experienced during encoding ("same context") is predicted to be higher than the global match for distractors presented in a new ("different") context. Thus, context effects are also predicted in terms of false recognition. Because an associated-context match increases the global match to both targets and distractors, it is not likely to enhance discrimination. Thus, if only item and associated context are used, we should not predict a context effect on discrimination between old and new items. If, however, participants use item information (I), associated-context information (C), *and* an ensemble (E) in the global match, then the ensemble is an additional source of match for targets tested in the same context. As a consequence, the global match for targets tested in the same context is increased compared with the case in which no ensemble is used. The global match for distractors tested in a formerly presented context, however, is not

increased compared with the no-ensemble case, because an ensemble cue formed from a distractor does not match any ensembles stored in memory. Given that an ensemble match increases the global match to targets but not to distractors, it contributes to enhanced recognition memory as indicated by the discrimination measure. Thus, when I, C, and E are used, context effects are predicted in terms of true and false recognition, as well as discrimination between the two.

Slotnick and Schacter (2004) further hypothesized that true recognition is associated with greater contextual reactivation than false recognition. Recent memory retrieval-based studies have provided converging evidence for true recognition-related sensory reactivation of the same cortical regions involved in processing stimulus materials during encoding, including reactivation of motor processing regions during memory for motor sequences (Nyberg *et al*., 2001), reactivation of auditory processing regions during memory for sounds (Nyberg *et al*., 2000; Wheeler, Petersen & Buckner, 2000) and reactivation of visual processing regions during memory for pictorial stimuli (Wheeler & Buckner, 2004; Wheeler & Buckner, 2003; Vaidya *et al*., 2002; Wheeler, Petersen, & Buckner, 2000). Slotnick and Schacter tested their hypothesis in the visual system, given its well-known hierarchical functional-anatomic cortical processing architecture. Using abstract shapes in an old-new recognition memory task, they expected to observe greater true as compared to false recognition-related visual cortical activity.

The researchers reported evidence of a functional-anatomic dichotomy between forms of access to late and early visual processing regions: late visual processing regions supported conscious recognition (and were associated with *both* true and false recognition), whereas early visual processing regions supported implicit memory (and were preferentially associated with true recognition, as opposed to false recognition). Such results provide direct evidence that previously-reported memory-related reactivation in late visual processing

regions (Wheeler & Buckner, 2004; Wheeler & Buckner, 2003; Vaidya *et al*., 2002; Wheeler *et al*., 2000) is accessible to conscious recognition, which previously has only been assumed. Furthermore, this finding purports that the previously reported true-greater-than-false activity assumed to reflect sensory or contextual memory (Schacter *et al*., 1996; Cabeza *et al*., 2001) is largely inaccessible to conscious recognition.

3.1.2 Motivation behind and overview of Experiments

Context has been previously hypothesized to influence how a perceptual description of an object is matched against long-term memory representations (Biederman, 1972). Chun (2000) proposes that a coherent visual context can facilitate the detection and identification of *objects* and this contextual knowledge is often acquired through *implicit learning*. Implicit learning is advantageous, as it allows more information to be acquired than is possible through consciously mediated channels. Much of the early work on context has focused on global context, with a paucity of research considering *local* context. Moreover, the act of learning associations between stimuli and their contextual backgrounds is a fundamental requirement of everyday memory; however, relatively little is known about the behavioural correlates subserving contextual binding of background context with episodically-mediated stimulus items. Furthermore, disorders such as post-traumatic stress and drug addiction, purported therapeutic targets of reconsolidation, are characterized, created and perpetuated by implicitly mediated subconscious episodic context cues (see Chapters 1 and 7 for a more comprehensive discussion). If we are to use reconsolidation to target such memory disorders, it is imperative that we first ascertain the impact of local and global contextual cues, encoded implicitly on episodic memory as opposed to semantic memory which is replete with experimental research. For example, there is a multitude of research conducted in frontal cortical regions and their role drug addiction circuitry (see Goldstein & Volkow, 2002) and

explicit processing of drug cues. Conversely, a paucity of research has focused on the subconscious processing which may take place within the medial temporal regions (see Chapter 1 for discussion of Classic Consolidation Theory and Multiple Trace Theory). In this regard, it is important to ascertain whether the binding of item and context occurs unconsciously, or whether item and context are separate entities in this regard. Isolating such variables would allow for greater strides to be made in terms of targeting the specific encoding and retrieval processing occurring in both traumatic and addiction related psychopathologies. Further, the findings herein will provide the most accurate means of isolating reconsolidation processing of episodic memory traces in Chapters 5 and 6.

The current set of experiments was motivated by three main questions. First, we attempted to ascertain whether context reliably facilitates episodic stimulus recognition in the same way that it influences episodic word recognition and semantic object identification. As such, we used abstract stimulus pairings in order to prevent possible confounding effects of pre-existing semantic object associations. Second, we wanted to determine the relative effects of local and global background context, encoded implicitly, on episodic item retrieval. In so doing, we attempted to delineate whether the binding of item and context occurs implicitly, or whether item and context are separate entities in this regard. We achieved this aim through adopting context-dependent measures such as the context-shift decrement. Third, we decided to investigate the impact of both local and global context on true and false recognition measures, given the importance of true and false recognition within the premise of implicit-explicit, unconscious-conscious, familiarity-recollection and item-inter-item (i.e., binding of item and context (e.g., ICE model ensemble information) dichotomies, respectively. To achieve this, we examined “source memory”, that is, the recollection of details about the encoding context of a recognized item, confirming retrieval of a specific episode. In so doing, we used the ‘old/new’ paradigm, wherein participants were required to judge whether

items presented during the test phase were previously encountered during the initial study phase.

Specifically, Experiment 1 was concerned with ascertaining the implicit effect of *local* context cue congruency or incongruency on true versus false episodic recognition. Conversely, Experiment 2 was concerned with determining the impact of *global* contextual cue congruency or incongruency on true versus false episodic recognition. Global activation memory models do not provide response latency predictions with respect to global cue manipulations. Nevertheless, in line with encoding specificity, showing a target stimulus pair plus congruent cue information should facilitate the accuracy and speed of correct recognition decisions in comparison with a target stimulus pair presented with incongruent cue information. Longer reaction times for responses made in incongruent context conditions also are predicted, as recognition decisions should take more time when nominal stimulus and context cue information conflict.

3.2 Experiment 1: Local Context

3.2.1 Introduction

Experiment 1 attempts to determine the behavioural correlates associated with *local context memory* through an episodically-mediated visual paired-associate (VPA) task. The unique aspect of this study involved the presentation of a different local contextual background with each pair. In doing so, every time a stimulus pair was presented during encoding, its distinct contextual background (i.e., colourful landscape) was also presented. Participants were given *no explicit instructions* to memorise these background pictures. During the test phase, participants were shown a probe stimulus (i.e., a single stimulus presented on a contextual background), which was followed by a full pair, in order to examine whether the paired-associates were encoded in an implicit manner with the context as a complete trace or whether each element was associated with disparate parts of the scene in a separate manner. The participants were required to judge whether the two stimuli had been previously learned during the study phase (*true-pair*) or if the stimuli were recombined pairs (*false-pair*). Each pair continued to be presented along with a landscape mediated background; however, half of the pairs were presented on a congruent background whereas the other half were presented on an incongruent background. Consequently, there were four test conditions: true-congruent condition, true-incongruent condition, false-congruent condition and false-incongruent condition.

It was predicted that upon encoding of the stimulus pairs, participants would implicitly associate each pair with a contextual background. Further, it was predicted that participants would be more likely to remember a stimulus pair if it was presented along with its congruent local context. Thus, it was hypothesized that accuracy would decrease in the incongruent condition, whereas RT would increase. Furthermore, in line with research

stipulating that true recognition supports contextual processing to a greater extent than false recognition, if implicit associations were made between item and context during encoding, we expected to find increased accuracy and lower RTs in true-pair conditions as opposed to false-pair conditions.

3.2.2 Method

3.2.2.1 Participants

Participants comprised 48 experimentally naïve undergraduate and postgraduate students (32 female; 16 male) recruited from the NUI Maynooth campus. Participants were aged between 18 and 40 years, with a mean age of 22.2. All participants reported normal visual acuity and were fluent English speakers. Further, all participants were screened for possible confounding cognitive lapses with the CFQ, with all results within the normal range. All participants were screened for possible drug and alcohol consumption within the preceding 24 hours which may have adversely affected cognition. Two participants' data were removed from analysis due to E-Run® software recording malfunctions. Informed consent form relevant to this study is shown in Appendix 16.

3.2.2.2 Stimuli

The task used for this study was a standard VPA task which was created using the E-Prime experimental presentation program. The task incorporated eight pairs of stimuli, as well as eight local contextual backgrounds. Each stimulus pair was presented in front of a distinct background. The eight stimulus pairs and their associated backgrounds are shown below in Figure 3.1. The pairs of stimuli to be learned comprised 16 non-verbalisable achromatic visual figures obtained from a graphic design website. The backgrounds were eight distinct landscape scenes; four were taken from the sample pictures provided with all Microsoft computer packages, whereas the other four were obtained from a landscape scenery-based website. The experiment took place in the Department of Psychology at the National

University of Ireland, Maynooth on a Dell Personal Computer with Pentium 4 processors (3.00GHz CPU) and standard LCD monitor and computer.

3.2.2.3 Procedure

Study Block

The task consisted of a study block containing 48 trials, followed by a test-block containing 128 trials. The study block involved presenting the eight study pairs six times each in a pseudorandom order (objects were presented randomly in a run of 8 which was repeated 6 times), such that consecutive presentations of the same object did not coincide (Figure 3.1). During this study block, each stimulus pair was presented for 3500ms with a 750ms inter-trial interval consisting of a fixation-cross. Participants were required to learn which stimuli formed a stimulus pair and to remember these pairs for the test phase. No explicit instructions were given regarding the learning of the local contextual backgrounds.

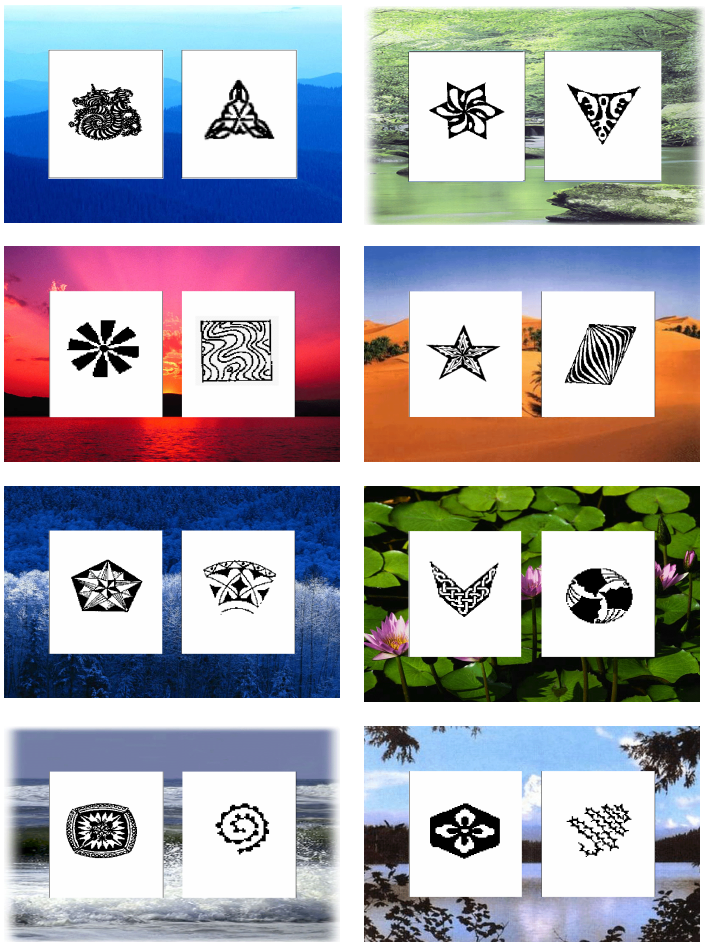


Figure 3.1: Complete set of visual paired-associate stimulus pairs with contextual backgrounds presented during the study block (48 trials presented).

Test-block

During the test-block (Figure 3.2), a probe stimulus was first presented for 1000ms in order to examine whether the paired associates were encoded in an implicit manner with the context as a complete trace or whether each element was associated with disparate parts of the scene in a separate manner. A probe stimulus consisted of one half of a stimulus pair with a contextual background. The probe stimulus was positioned in either the right or left – hand side of the screen, depending upon where it had been positioned during the study phase. This was followed by a full pair (the same probe and background along with the second stimulus), which remained on screen until the participant responded. The full pairs can be referred to as

the test pairs given that participants were required to judge whether the pair had been previously viewed during the study phase (i.e., a true-pair) or whether it was not presented during the study phase (i.e., a false-pair). The false-pairs consisted of the same stimuli shown in the study phase, however the pairs were rearranged. No feedback was provided for any of the trials throughout the experiment. Each trial comprised a probe stimulus, immediately followed by the test pair. Prior to the onset of the next trial, a fixation cross appeared for 750 ms.

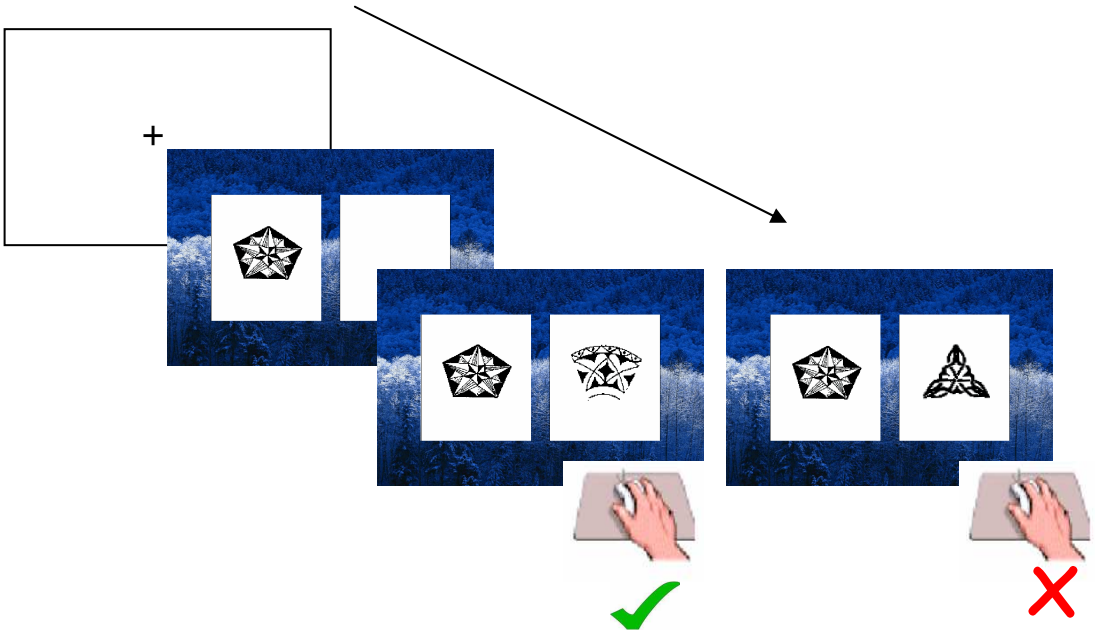


Figure 3.2: Diagrammatic representation of test-block displaying fixation and probe stimulus together with true and false stimulus pairs.

To test for the impact of implicit local context effects on memory, the backgrounds were manipulated during the test phase. There were four different test conditions, each comprising 32 trials. Each of the 16 stimuli, learned in the study phase, was presented twice each as probes. The four test conditions were devised through manipulating the background wherein the probe was presented and by following the probe with either a true or false-pair.

True-pairs (i.e., one of the eight pairs learned during the study phase) were either presented along with their original background (congruent context condition) or they were presented on one of the seven incorrect backgrounds (incongruent context condition). The same concept applies to the false-pairs. Thus the test pairs contained four conditions: true-congruent; true-incongruent; false-congruent and false-incongruent (Figure 3.3 below). Presentation of these conditions was randomised and this random order was the synonymous for all participants.

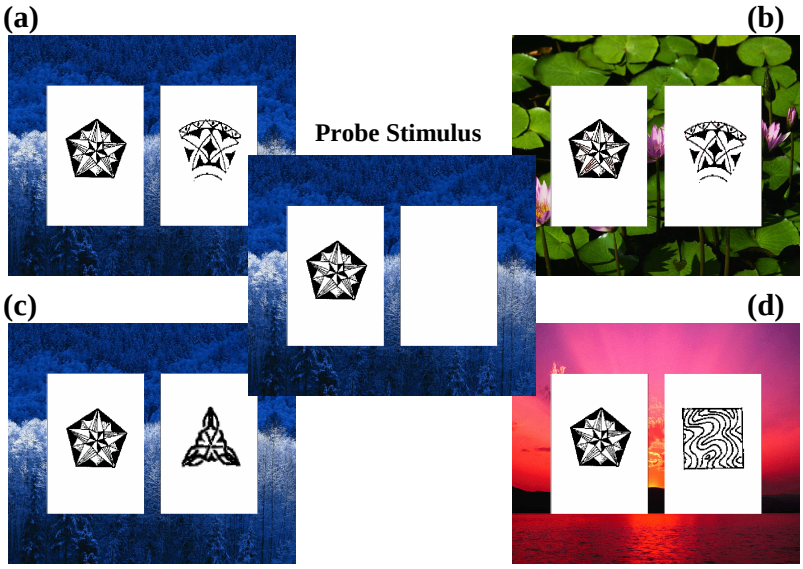


Figure 3.3: Example of the four test conditions: (a) true-congruent (b) true-incongruent (c) false-congruent and (d) false-incongruent together with probe stimulus (center).

During the test phase, both accuracy and RTs were recorded. A *correct* response was elicited when participants pressed the left mouse button, with their index finger, when a true-pair was presented; and the right mouse button, with their middle finger, when a false-pair was presented, *regardless* of the contextual background. RTs were measured as the interval between presentation of the stimulus and the response and were recorded for both correct and incorrect trials. Failure to respond was classed as incorrect. E-Prime logged RT and accuracy data for each participant.

3.2.2.4 Statistics

The experiment employed a 2x2 repeated-measures factorial design; i.e., two *within group* Independent Variables were manipulated. The first was local *context*, operationalised at two levels: 'congruent' context and 'incongruent' context, and the second was *stimulus type*, also operationalised at two levels: true-pairs and false-pairs. This design enabled the measurement of four different conditions: *true-congruent, true-incongruent, false-congruent and false-incongruent*.

All statistical analyses of collated data were performed used SPSS statistical package (Version 13 for Windows). Extreme outliers exceeding 1.5 times the interquartile range were removed from analysis. A series of 2x2 repeated measures ANOVAs were conducted for both Accuracy and RT data, in order to identify whether there was a significant main effect of stimulus type or context and any interaction effect that may have occurred therein, as well as possible differences across stimulus type and response type (i.e., correct or incorrect). Bonferroni-corrected paired t-tests were subsequently carried out to further investigate these effects where appropriate. A star-based system for significance representing *p*-values of $p<0.05$ *, $p<0.01$ **, and $p<0.001$ ***, respectively, was employed throughout. The symbol ± was employed throughout to indicate standard deviation from the mean. In accordance with stipulations put forth by Polit and colleagues (2008), data obtained for accuracy were converted to percentage as opposed to absolute values. RT data is presented in terms of milliseconds. Bonferroni-corrected *p*-values are presented only once in cases where similar *p*-values were adjusted. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

3.2.3 Experiment 1: Results

3.2.3.1 Accuracy

In terms of accuracy (Figure 3.4), a mixed factorial 2x2 repeated measures ANOVA revealed an overall main effect for stimulus type (i.e., true-pairs versus false-pairs); Wilks' Lambda= .671, F(1,41)= 20.111, $p<0.005$, $\eta_p^2= .329$. Further, an interaction effect between stimulus type and context was also identified; Wilks' Lambda=.901, F(1,41)=4.526, $p=.039$, $\eta_p^2= .099$. The main effect for context was non-significant at the $p>0.05$ level. Subsequently conducted paired samples t-tests revealed that, in general, false stimulus pairs were remembered more accurately than were true stimulus pairs. There was a significant increase in percentage accuracy from the true-congruent condition (84.57±12.04) to the false-congruent condition (93.90±4.30), $t(41)= -3.941$, $p<0.005$; Bonferroni-corrected, $p=0.02$), and the false-incongruent condition (93.82±4.75; $t(44)= -4.371$, $p=0.02$; further, there was a significant increase in percentage accuracy from the true-incongruent condition (82.18±14.80) to the false-congruent condition (93.90±4.30; $t(41)= -4.454$, $p=0.02$, as well as the false-incongruent condition (93.82±4.75; $t(44)= -4.965$, $p=0.02$. Also, there was a significant decrease in percentage accuracy from the true-congruent condition (84.57±12.04) to the true-incongruent condition (82.18±14.80; $t(46)= 3.207$, $p=.002$: Bonferroni-corrected, $p=.012$). However, no such difference was observed in terms of false stimulus pairs.

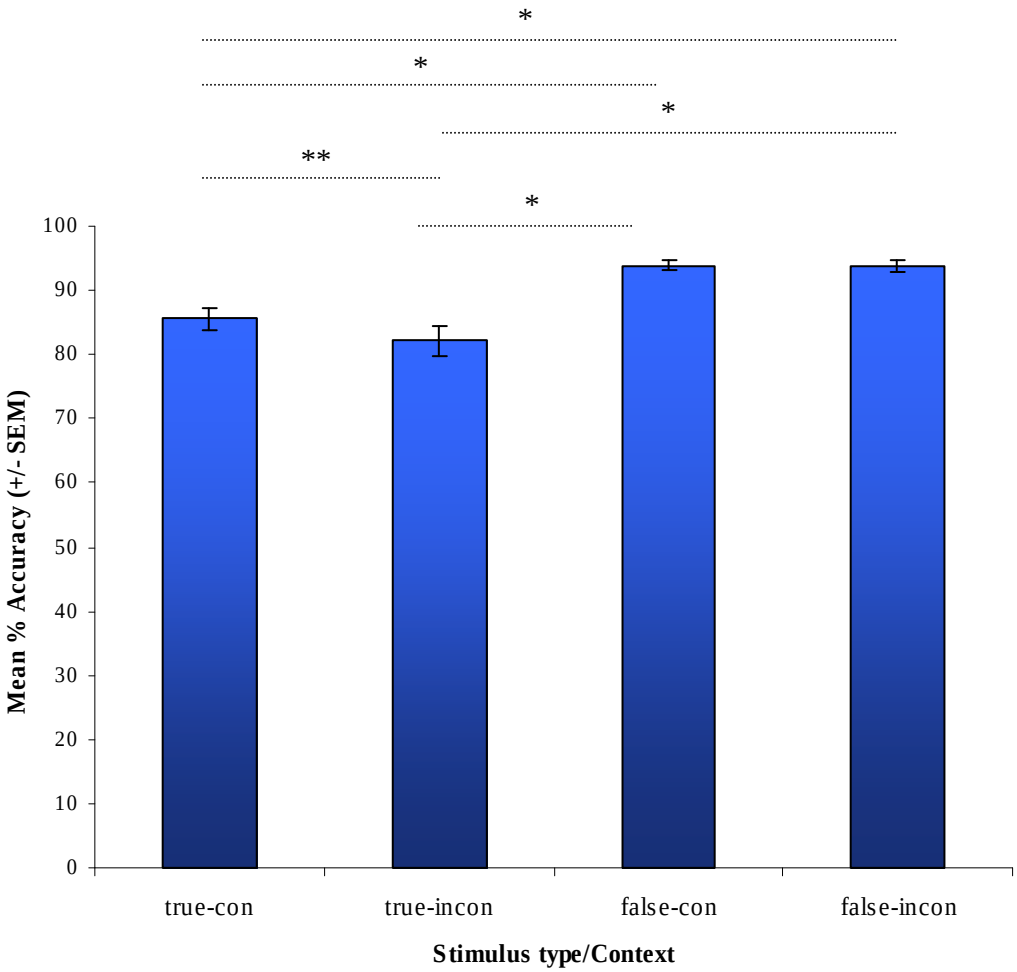


Figure 3.4: Mean percentage accuracy across stimulus type (true or false-pair) and context (congruent or incongruent; +/- Standard error mean: SEM). In terms of true versus false stimulus pairs, Bonferroni-corrected *p*-values are shown.

3.2.3.2 Reaction Time

In terms of RT for correct responses (see Figure 3.5), a mixed 2x2 repeated measures ANOVA yielded non-significant effects in terms of stimulus type [$F(1,44)= .127$, $p= .724$, $\eta_p^2 =.003$], context [$F(1,44)= .021$, $p= .885$, $\eta_p^2 = .001$], or interaction between stimulus type and context [$F(1,44)= .586$, $p=.448$, $\eta_p^2 = .013$]. Regarding incorrect responses (see Figure 3.6), a further 2x2 repeated measures ANOVA revealed once again, non-significant effects in terms of stimulus type [$F(1,35)= .838$, $p= .366$, $\eta_p^2 = .023$], context [$F(1,35)= .002$, $p= .966$,

η_p^2 = .001] and interaction between stimulus type and context [F(1,35)= .790, *p*= .380, η_p^2 = .022].

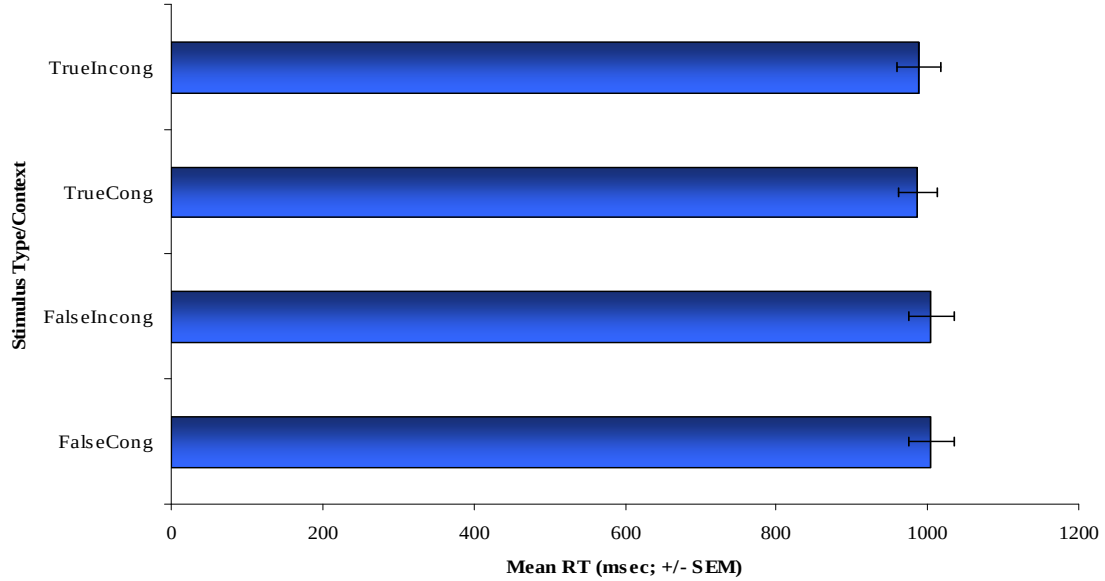


Figure 3.5: Mean RT (msecs) across true and false-pairs for correct responses (+/- SEM).

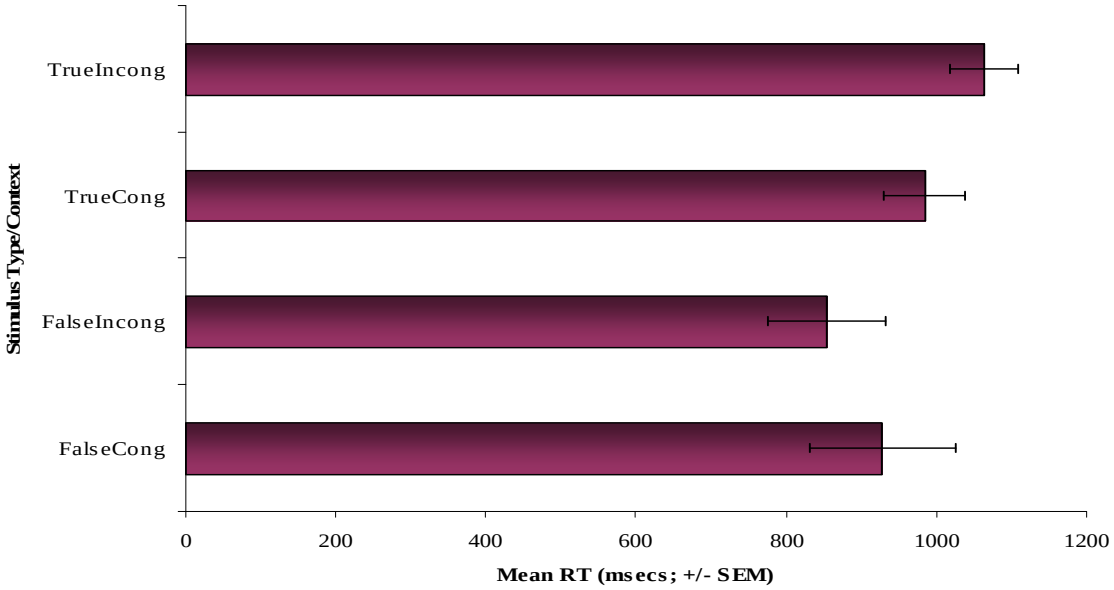


Figure 3.6: Mean RT (msecs) across true and false-pairs for incorrect responses (+/- SEM).

3.2.4 Experiment 1: Brief Discussion

It was predicted that upon encoding of the stimulus pairs, participants would implicitly associate each pair with a contextual background. Further, it was predicted that participants would be more likely to remember a stimulus pair if it were presented along with its congruent local context. As such, it was conjectured that accuracy would decrease in the incongruent condition, whereas reaction time (RT) would increase.

Accuracy: In terms of accuracy, contrary to expectations, false-pairs elicited the highest accuracy, with no differences found between congruent and incongruent contexts. Further, in terms of congruency effects, in line with predictions, decreased accuracy for incongruent context for true-recognition was identified. Interestingly, for true-pairs mean accuracy was higher for the congruent condition compared to the incongruent condition; however, for false-pairs the opposite was true. Given that a significant main effect was found for stimulus type (i.e., true-pairs versus false-pairs), together with an interaction effect between stimulus-type and context, it is possible that local context exerted an effect on true-pair recognition in particular, given the finding of a performance decrement for in response to incongruent context.

Reaction Time: In terms of Reaction Time, no significant differences were found irrespective of context or pairing. Descriptively, in terms of RT for correct responses, participants responded quickest to true-pairs, with a slightly quicker advantage for congruent contexts. Such a finding contrasts with the accuracy findings of lower accuracy for true recognition. Thus, these results could represent some form of speed-accuracy trade-off.

However, participants took longer to respond to false-pairs, with the congruent context slightly slowest. As such, it could be the case that participants took longer to decide whether these pairs were viewed previously as they did not conform to expectations.

3.3 Experiment 2: Global Context

3.3.1 Introduction

Environmental context (EC) effects upon memory performance are assumed by all theories of memory given that all theories purport that spatiotemporal context provides the basis for discriminating relevant from irrelevant episodic traces (Parker & Gellatly, 1997). However, in practice, EC effects are not readily obtained, even though room environments involved in experiments which have considered EC effects have generally been rendered as noticeably different from each other as possible (Dolinsky & Zabrucky, 1983; Eckert, Kanak & Stephens, 1984; Mayes, Meudell & Som, 1981; Smith, 1979; 1985a; Greenspoon & Ranyard, 1957). Environments have also been varied on several sensory dimensions while the room environment remained constant. The addition of a single unisensory cue, such as music (e.g., Balch, Bowman & Mohler, 1992; Smith, 1985b) and odour (e.g., Baker *et al*., 2004; Aggleton & Waskett, 1999; Herz, 1997; Parker & Gellatly, 1992; Schab, 1990; Cann & Ross, 1989) has been shown to facilitate recall performance. The range of environmental manipulations has been manifold. For example, in their seminal study, Godden & Baddeley (1975) found that a word list learned on land was better recalled when tested on land, whereas information learned underwater was better recalled underwater. Such results infer that aspects of the environment, whether extreme changes such as on land/underwater, or subtle unisensory cues, when available at memory encoding and retrieval can assist in explicit memory recall.

More typical laboratory demonstrations of the reinstatement effect have similarly shown that memory recall is superior when study and test are performed in the same rather than in different rooms (Smith, 1979; Smith, Glenberg & Bjork, 1978; Jensen, Dibble &

Anderson, 1971; Jensen, Harris, & Anderson, 1971). However, many such studies have also failed to detect environmental context effects (e.g., Alonso & Fernández, 1997; Fernández & Alonso, 1994; Bjork & Richardson-Klavehn, 1989). In a series of eight experiments, Fernández & Glenberg (1985) failed to detect reliable variations in memory performance as a consequence of altering environmental context from study to test. Similarly, Saufley *et al*. (1985), in a series of experiments, found that test scores of university students did not reliably vary as a function of the classroom wherein the test was administered (i.e., same or different classroom from the lecture room). Eich (1985) reported a reinstatement effect, but only when participants were *explicitly* instructed to associate an ambient background environment with target materials (in the form of an interactive image). As such, it appears that it is not enough to simply state that similar context conditions yield better memory performance than different context conditions. Rather, context effects appear to be complex and, at present, not well understood, and the literature concerning manipulation of global environmental context is highly variable.

Episodic memory is often imbued with multisensory richness, such that the recall of an event can be comprised of the sights, smells and sounds of its prior occurrence. Therefore, remembering a previous episode often relies upon the reactivation of associations that span multiple sensory domains. The hippocampus organises the various distributed representations that together form an episodic memory, without itself becoming their physical repository, thereby ensuring the remembrance of the original trace and enabling access to the entire engram via partial cues from different sensory modalities (Mesulam, 1998). When multisensory information is spatially or temporally congruent and can be integrated into a unitary concept, it can enhance task performance (Eimer *et al*., 2002; Spence *et al*., 2004; Dhamala *et al*., 2007). Further, studies under controlled laboratory conditions have

demonstrated that multisensory input can facilitate behaviour by speeding reaction times (Hershenson, 1962; Gielen *et al*., 1983)

Experiment 2 attempts to ascertain the impact of both manipulating and reinstating contextually enriched *global* environment contexts during cued recall of a paired-associates task embedded on a white background. Similar to Experiment 1, participants were *not* explicitly instructed to bind global context and stimulus pair item information at encoding. Thus, in terms of the ICE model, item information should theoretically be bound to globally associated context in an implicit manner.

Two different contextually-enriched environments were used; namely, a contextually 'bright' room layout, and a contextually 'dark' room layout. There were four conditions; Conditions 1 and 2 involved reinstating congruent global environmental context for across study and test phases, whereas Conditions 3 and 4 involved manipulating global environmental context between study and test. Again, participants were given *no explicit instructions* to memorize these environmental cues. During encoding trials, all stimulus pairs were presented on white backgrounds and participants were required to remember which stimuli formed stimulus pairs. During the test phase, participants were shown a probe stimulus (i.e., a single stimulus presented on a white background), which was followed by a full pair (refer to Experiment 1 for reasoning behind employing probe stimulus). The participants were required to judge whether the stimulus pair had been previously learned during the study phase (*true-pair*) or if the stimuli were rearranged pairs (*false-pair*). There were four test conditions: true-congruent, true-incongruent, false-congruent, and false-incongruent.

It was predicted that upon encoding of the stimulus pairs, participants would implicitly associate each pair with a *global* contextual background. Further, in accordance with Isarida (2005) who conjectured that global environmentally-based context (which is

composed of the incidental physical features of the environment wherein participants process focal information) can become associated with the entire encoding event, given that environmental context remains stable throughout the event and is thereby associated with all the elements of the event: it was predicted that participants would be more likely to remember a stimulus pair if it was presented along with a congruent global context. Thus, it was hypothesized that accuracy would decrease in the incongruent conditions, whereas RT would increase. Again, we expected to find increased accuracy and lower RTs in true stimulus conditions as opposed to false stimulus conditions, thereby indicating contextual facilitation of episodic memory in global contexts.

Therefore, the central theoretical questions underpinning the current study concern whether incidental globally mediated background cues are stored in memory, to what extent they are stored in memory and whether such stimuli can cue memory of materials that are studied contiguously with these incidental contexts. It is pertinent to clarify the cue-related elements that function in environmental context-dependent processes given the importance of environmental cues to traumatic and addiction related memory traces. Given that the retrieval of environmental contextual information can benefit the retrieval of episodically associated events, we are presently concerned with both the cuing properties of environmental-cue dependent context as well as the retrieval of contextual episodic-based memory tasks.

3.3.2 Experiment 2: Method

3.3.2.1 Participants

Participants comprised 40 undergraduate and postgraduate experimentally naïve students recruited through posters placed throughout the NUI Maynooth campus. Of these 36 were female and 4 were male. Participants were aged between 18-42 years, with a mean age of 21.4. Participants were randomly assigned to one of four experimental groups (i.e., AA, AB, BA, or BB). In the AA group, participants were aged between 18-30 years, with a mean age of 23.1. In this group, 2 participants were male and 8 participants were female. In the AB group, participants were aged between 19-22 years, with a mean age of 20.9. All participants in this group were female. In the BA group, participants were aged between 18-22 years, with a mean age of 19.9. In this group, 1 participant was male, while the remaining 9 were female. Finally, in the BB group, participants were aged between 18-42 years, with a mean age of 22.2. In this group, 1 participant was male, while the remaining 9 were female. All participants reported normal visual acuity and were fluent English speakers. Further, all participants were screened for possible confounding cognitive lapses with the CFQ, with *all* results within the normal range. All participants were screened for possible drug and alcohol consumption within the preceding 24 hours which may have adversely affected cognition. Three participants were removed form analysis due to non-conformity with experimental instructions. All excluded participants were replaced by additional participants. Informed consent form relevant to this study is shown in Appendix 16.

3.3.2.2 Stimuli

The task used for this study was a standard VPA task (see Chapter 2) which was created using the E-Prime experimental presentation program. The task incorporated eight pairs of stimuli, all presented on a white background. The pairs of stimuli to be learned were made up of 16 non-verbalizable achromatic visual figures obtained from a graphic design website. The paired-associate item pairings employed were *identical* to those used for Experiment 1 (see Figure 3.1), albeit with the exclusion of local contextual backgrounds. The experiment took place in the Department of Psychology at the National University of Ireland, Maynooth on a Dell Personal Computer with Pentium 4 processors (3.00GHz CPU) and standard LCD monitor and computer.

In terms of Global Context, two testing rooms were used as experimental contexts. Participants were trained and tested in either a contextually congruent or incongruent 'bright' or 'dark' setting, each comprising a mulisensory stimulus array which aimed to increase EC-dependent contextual disparity between the two settings. For the same-context groups (i.e., AA, BB), all phases of the experiment took place in the same environmental context. For the different-context groups (i.e., AB, BA), the study and test phases took place in a different environmental context. Context A comprised a domestic 'bright' stimulus array, with brightly coloured visual stimuli, ambient music and light olfactory cues. This setting, measuring 4.10m x 6.0m x 4.70m contained a standard desk upon which a blue and white checked tablecloth was placed, brightly coloured contemporary paintings, large windows, a soft reclining chair, a brightly coloured floor rug, several plants, potpourri, a magnolia and cherry blossom air freshener, and dried flower arrangements, with ambient instrumental music entitled 'Fantasias and Sonatas' composed by Mozart playing in the background.

Conversely, Context B was designed as a more contextually 'dark' setting, comprising a 'dark' stimulus array, with darkly coloured visual stimuli, heavy darkly themed

music and heavy olfactory cues. This setting was a typical laboratory setting in a windowless sound attenuating $2x3m^3$ cubicle painted black, containing a standard table and chairs, a strategically positioned black and blue coloured movie poster, overhead 'blue' lighting, a vanilla and festive spice air freshener, with the composition 'Minas Morgul' from the Lord of the Rings soundtrack, playing in the background.

3.3.2.3 Procedure

Study Block

Details *identical* to Experiment 1, with the exception that stimulus pairs were presented on a blank white as opposed to local, context background. Participants were required to learn which stimuli formed a stimulus pair and to remember these pairs for the test phase. No explicit instructions were given regarding the learning of the surrounding global environmental contexts.

Test-block

Details *identical* to Experiment 1, again with the exception that no local context background was provided at test. To test for the impact of incidental global environmental context effects on retrieval, the environment cue backgrounds were either reinstated or manipulated during the test phase. There were four different test conditions, each comprising 32 trials. Each of the 16 stimuli, learned in the study phase, was presented twice each as probes. The four test conditions were depicted by following the probe stimulus with either a true or false-pair. True-pairs (i.e., one of the eight pairs learned during the study phase) were either presented along with a congruent or incongruent environmental context. The same concept applies to the false-pairs. Thus the test pairs contained four conditions: true-congruent; true-incongruent; false-congruent and false-incongruent. Presentation of these conditions was

presented in a sequential order and this was synonymous for all participants. Refer to Experiment 1 (method section) for details concerning the recording of accuracy and reaction time.

3.3.2.4 Statistics

The experiment employed a 2x4 mixed factorial design. The within-subjects variable was 'stimulus type' (two levels; true-pairs and false-pairs), while the between-groups variable was the 'context' to which each group was exposed to, whether reinstated in a congruent (i.e., AA, BB) or incongruent (i.e., AB, BA) testing environment, thereby rendering four levels (AA, AB, BA, BB).

All statistical analyses of collated data were performed used SPSS statistical package (Version 13 for Windows). A series of two-way mixed between-within ANOVAs were conducted for both Accuracy and RT data (correct and incorrect response), in order to identify the main effect of stimulus type and context and any interaction effect that may have occurred therein, with further Tukey HSD *post hoc* tests used where appropriate. Paired t-tests were subsequently carried out to further investigate these effects where appropriate. A star-based system for significance representing *p*-values of $p<0.05$ *, $p<0.01$ **, and $p<0.001$ ***, respectively, was employed throughout. The symbol ± was employed throughout to indicate standard deviation from the mean. Mean percentage accuracy was detailed throughout, with RT data presented in terms of milliseconds. Bonferroni-corrected *p*-values are presented only once in cases where similar *p*-values were adjusted. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

3.3.3 Experiment 2: Results

3.3.3.1 Accuracy

Descriptively, in terms of percentage accuracy, in line with predictions, congruent contexts yielded higher accuracy than did incongruent contexts for *both* true and false stimulus pairs (see Figure 3.7). In contrast to predictions, yet similar to Experiment 1, false-pair recognition was consistently more accurate than true-pair recognition across groups. A two-way mixed factorial between-within ANOVA revealed a significant main effect for stimulus type (i.e., true-pairs versus false-pairs); Wilks' Lambda= .699, $F(1,36)= 14.526$, $p<0.001$, $\eta_p^2= .301$. However, there was no interaction effect observed between stimulus type and context group; Wilks' Lambda= .915, $F(3,36)= 1.109$, $p=.358$, $\eta_p^2= .084$. Likewise, the main effect for context group was non-significant at the $p>0.05$ level. Subsequently conducted paired samples t-tests revealed that participants in the AB group performed significantly more accurately for false-pairs (74.78±7.71) than for true-pairs (67.58±4.86; $t(9)= 11.493$, $p<0.001$). Similarly, participants in the BA group performed more accurately for false-pairs (84.07±8.15) than for true-pairs (74.09±12.63), albeit at the threshold of significance; $t(9)= 2.182$, $p=.057$. Comparing *all* accuracy percentage scores, irrespective of assigned group, participants responded significantly more accurately to false-pairs (83.22±16.94) than to true-pairs (76.55 ±16.54; $t(39)= 3.924$, $p<0.001$).

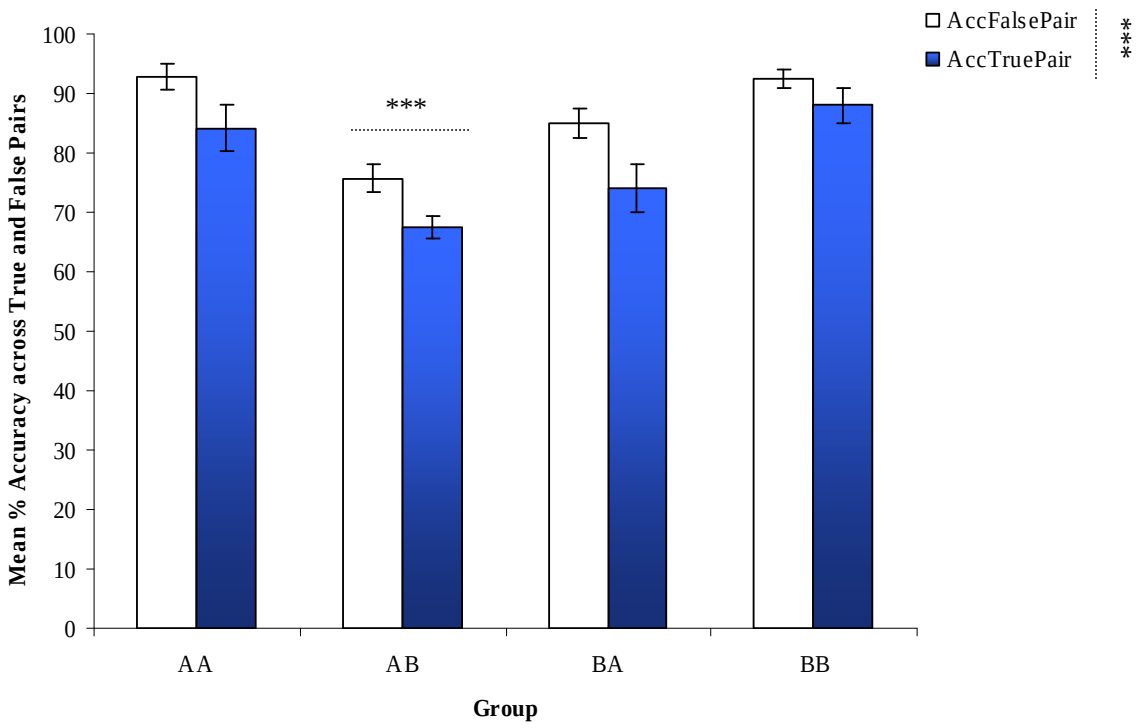


Figure 3.7: Mean percentage accuracy across stimulus type and context (+/- SEM).

3.3.3.2 Reaction Time

When participants responded correctly (see Figure 3.8), a two-way mixed factorial between-within ANOVA revealed a significant main effect for stimulus type (i.e., true-pairs versus false-pairs); Wilks' Lambda= .811, F(1,36)= 8.405, p=0.006, η_p^2= .189. However, there was no interaction effect observed between stimulus type and context group; Wilks' Lambda= .910, F(3,36)= 1.189, p=.328, η_p^2= .090. Likewise, the main effect for context group was non-significant at the p>0.05 level. Subsequently conducted paired samples t-tests revealed that participants in the AB group responded quicker to true-pairs (999.70±136.75) than to false-pairs (1062.66±82.09; t(9)= -2.686, p=.025). Comparing *all* correct RTs, irrespective of assigned group, participants responded significantly quicker to true-pairs (1024.18±236.24) than to false-pairs (1060.25 ±233.67; t(39)= -2.878, p=0.006). Conversely, when participants

responded incorrectly (see Figure 3.9), a two-way mixed factorial between-within ANOVA revealed non-significant main effects for either stimulus type or context group, together with a non-significant interaction effect, at the $p>0.05$ level.

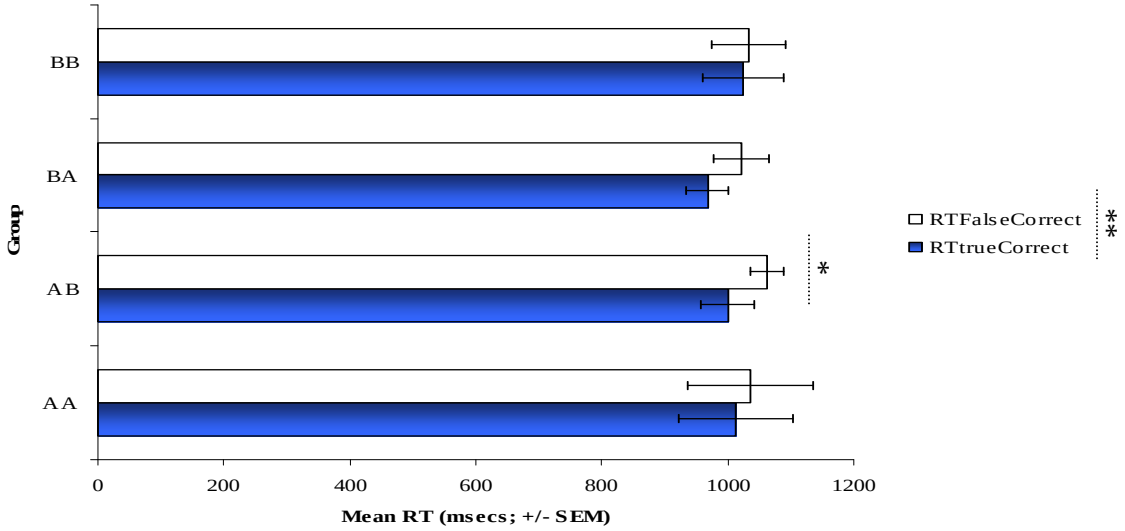


Figure 3.8: Mean RT (msecs) across true and false-pairs for correct responses (+/- SEM).

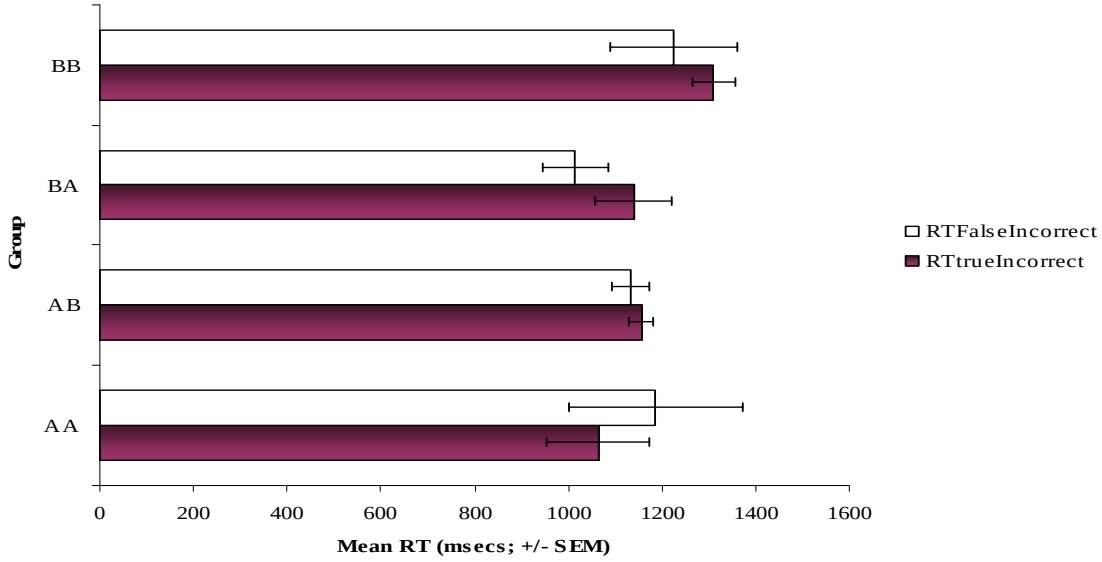


Figure 3.9: Mean RT (msecs) across true and false-pairs for incorrect responses (+/- SEM).

3.3.4 Experiment 2: Brief Discussion

Accuracy: The findings of this experiment indicate that participants performed significantly more accurately on the (local context-free) paired-associates task in congruent global settings when compared to incongruent global settings. There was a statistically significant main effect for stimulus type, with false recognition higher than true recognition in both incongruent groups (i.e., AB and BA). Irrespective of group, participants responded significantly more accurately to false-pairs than to true-pairs. Unexpectedly therefore, yet similar to Experiment 1, false-pair recognition (i.e., stimulus pairs not learned previously in the study phase) was significantly more accurate than true-pair recognition (i.e., previously learned stimulus pairs) across groups.

Reaction Time: In terms of correct response, there was a significant main effect of RT for stimulus type, with non significant effects for the interaction between stimulus type and context group and a non-significant main effect for context group. For the incongruent AB group true-pair recognition was significantly quicker than false-pair recognition. Non significant main effects for stimulus type and context group together with a non-significant interaction effect were found for incorrect response. Irrespective of group, participants responded significantly quicker to true-pairs than to false-pairs

3.4 Comparison of Experiments: Results

Accuracy and reaction time results were compared across experiments in terms of stimulus type (i.e., true or false-pair) and congruency type (i.e., congruent or incongruent). In so doing, it was hoped that the facilatory effects of either local or global context would emerge in a more succinct manner than comparing across stimulus type and congruency type for each separate experiment. For Experiment 2, we averaged the percentages for congruent and incongruent conditions, thereby rendering percentage accuracy values for the four stimulus types (i.e., true-congruent, true-incongruent, false-congruent, false-incongruent). No such collapsing of percentages was required for local context-based experimental data.

3.4.1 Accuracy

A mixed between-within repeated measures ANOVA was conducted to ascertain differences in percentage accuracy between global and local context (Figure 3.10), with stimulus type (i.e., true-congruent, true-incongruent, false-congruent and false-incongruent) as the within-groups variable and experiment (i.e., global or local) acting as the between-groups variable. A significant main effect was found for stimulus type, Wilks' Lambda= .494, $F(3,57)= 19.465$, $p<0.001$, $\eta_p^2 =.506$. Greenhouse-Geisser corrected values remained significant at the $p<0.001$ level. Further, a significant interaction effect was found between stimulus type and experiment, Wilks' Lambda= .661, $F(3,57)= 9.734$, $p<0.001$, $\eta_p^2=.339$. Greenhouse-Geisser corrected values remained significant at the $p<0.001$ level. An Independent samples t-test was conducted to further investigate these differences. Significant differences were identified for both incongruent stimulus types; in the true-incongruent condition, accuracy was significantly higher for local (82.18±14.80) than for the global context [70.84±10.15; $t(54)= -$

3.506, p= 0.001], with similar results obtained for the false-incongruent condition (global- 80.42±9.07 and local- 93.82±4.75; $t(26)$= -6.081, p<0.001).

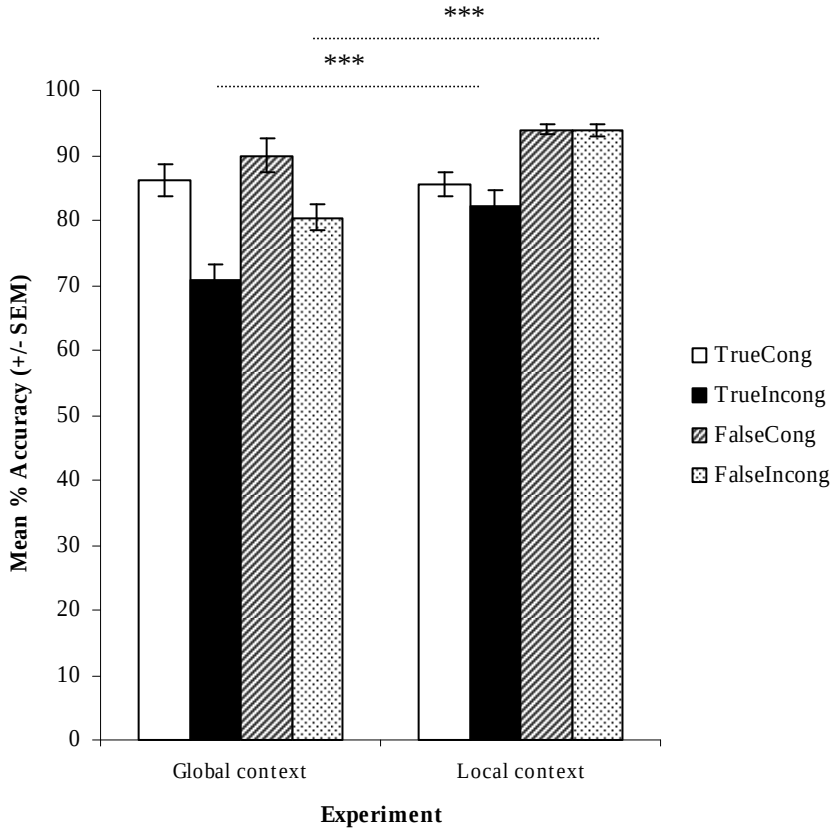


Figure 3.10: Mean percentage accuracy across stimulus type and context per Experiment (+/- SEM).

3.4.2 Reaction Time

A mixed between-within repeated measures ANOVA similar to that conducted for accuracy was conducted to ascertain RT differences across stimulus type and context. In terms of both correct (Figure 3.11) and incorrect response (Figure 3.12), a non-significant main effect was found for stimulus type, together with a non-significant interaction effect between stimulus type and experiment at the p>0.01 level (more stringent significance level applied due to diverging n between groups).

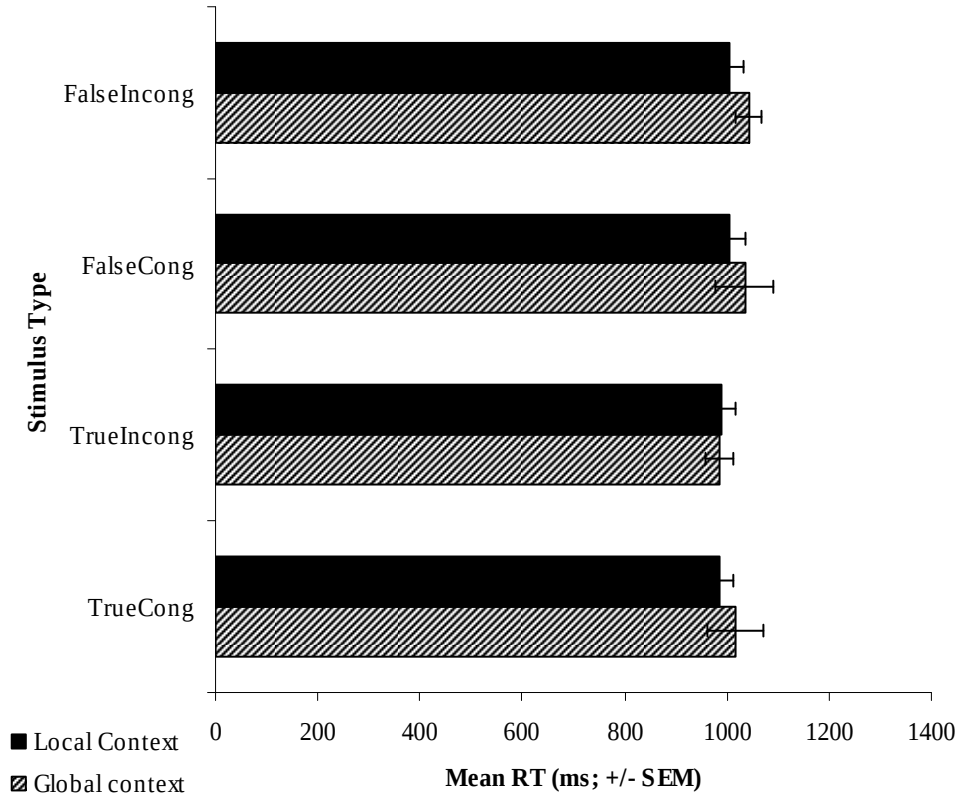


Figure 3.11: Mean RT (msecs) for stimulus type (y-axis) across local and global context (bars) for correct response (+/- SEM).

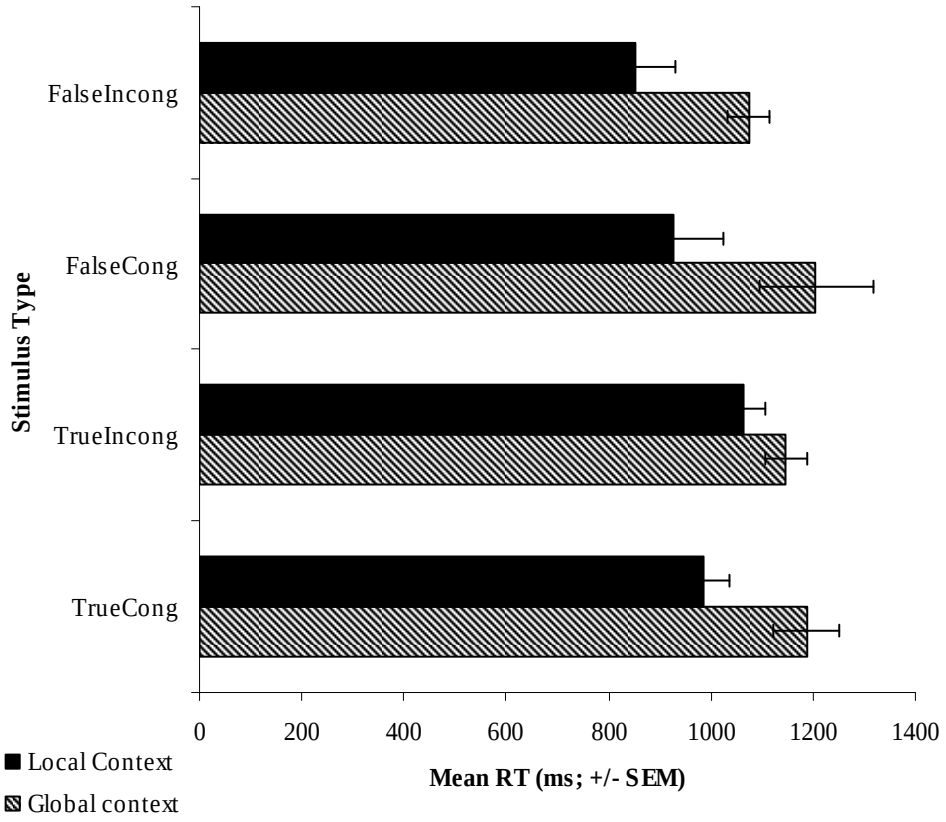


Figure 3.12: Mean RT (msecs) for stimulus type (y-axis) across local and global context (bars) for incorrect response (+/- SEM).

3.4.3 Summary

Accuracy: Accuracy was lowest for the true-incongruent condition across both local and global contexts, with highest accuracy for false-pairs across both congruent and incongruent local context. Greater context effects were observed for both true- and false- pair recognition in the global context. There was a significantly higher accuracy for both true- and false-incongruent conditions in local as opposed to global context. A significant main effect was found for stimulus type, together with an interaction effect between stimulus type and experiment.

Reaction Time: In terms of RT, negligible differences were observed between local and global contexts for correct response. However, a slower RT across all conditions for global context was found in terms in incorrect response. A non-significant main effect for stimulus type, together with a non-significant interaction effect between stimulus type and Experiment was found.

3.5 General Discussion

Results from these experiments indicate that the prior history of the stimulus type—namely, the degree of familiarity—is a critical parameter in modulating the effect of both local and global context. Interestingly, in this regard, false-pair recognition of unfamiliar stimulus pairs was higher than true-pair recognition of familiar stimulus pairs across *both* local and global contexts. Such a finding, tempered with non-significant main effects for context and significant main effects for stimulus type, would suggest that perhaps memory facilitation is mediated by item recognition alone given that previous research suggests that true recognition supports contextual processing to a greater extent than false recognition. We discuss these findings in light of implicit-explicit, unconscious-conscious, familiarity-recollection and item-inter-item (i.e., binding of item and context (e.g., ICE model ensemble information) dichotomies.

Regarding the local context manipulation in Experiment 1, context effects were observed in terms of accuracy for true and false stimulus pairings without a significant main effect for local context. In this regard, false-pairs were remembered significantly more accurately than were true-pairs. Similarly, in terms of the global context cue manipulation in Experiment 2, congruency-based context effects were observed in the respect that performance was more accurate for false-pairs as opposed to true-pairs with a significant main effect found for stimulus type and non-significant effects found for global context.

Interestingly, in both experiments, false-pair recognition (i.e., stimulus pairs not learned previously in the study phase) was significantly more accurate than true-pair recognition (i.e., previously learned stimulus pairs). If implicit memory were mediating accuracy, greater true-versus-false performance would be expected in line with early

processing regions. However, evidently this was not the case. As such, it is possible that later consciously mediated, familiarity-based processing regions must be responsible for this effect. Certainly, the slower RTs obtained in terms of correct responding for false recognition across both experiments supports such a possibility. However, such a finding may also represent a problem inherent in the task design. It is possible that using permutations of learned stimuli as false items together with the relatively high numbers of the latter (i.e., 48 encoding items and 128 test items, the majority of them false) may have created substantial interference between items.

A further potential confound related to task design is that at test, the staggered presentation of the pairings (i.e., the presentation first of a single probe stimulus) may have produced priming effects or initiated retrieval processes prior to the presentation of the test pair. However, the implementation of such an experimental design is justified in the respect that we were interested in ascertaining whether the paired associates were encoded in an implicit manner with the context as a complete trace or whether each element was associated with disparate parts of the scene in a separate manner, an issue which electrophysiological data presented in Chapter 4 will shed further light upon.

Furthermore, comparing accuracy results obtained across both local and global experiments, local context appeared to show higher percentage accuracy across all conditions, except the true-congruent condition. However, the greater accuracy in the true-congruent condition for global context did not prove significantly higher than that obtained with local context. Interestingly, RT showed that the true-congruent condition, in response to local context, yielded the quickest RT across both local and global domains. Thus, it is suggested that participants employed unconsciously mediated implicit processing resources when they encountered true previously encountered stimulus pairs for local context, and conversely consciously mediated processing resources when exposed to conditions which did

not meet with expected items or context. Additionally, accuracy for incongruent conditions for both true and false recognition was significantly higher when local context was employed. RT results are generally in line with these findings for both correct and incorrect response. However, participants responded slightly quicker in the true-incongruent condition in response to global context than they did in response to local context. This finding would infer that disparity between global cues present at study and at test are implicitly aiding memory for previously encountered stimulus pairs. However, the difference in RT between local and global context is marginal. Importantly, participants were least accurate in this condition with global cues available compared to all other conditions, both locally and globally. Indeed, this finding was found to be significant. Thus, it is possible that a speed-accuracy trade off is instead responsible for these findings.

Alternatively, the cue-overload hypothesis (Earhard, 1967; Watkins, 1979; Watkins & Watkins, 1975) states that as more target items are associated with a particular cue, so it becomes less likely that the cue will evoke any of the target items. Indeed, when comparing both experiments, as mentioned previously, local context (wherein one background context was matched with one stimulus pair thereby leading to eight stimulus pair-background pairings) during encoding yielded higher percentage accuracy across all conditions except the true-congruent condition than global context (wherein one global background was matched with eight stimulus pairings), with significantly higher accuracy for both true and false recognition in incongruent contexts. Indeed, Smith (1988, 1994) suggests cue-overload as a candidate to explain the unreliability of environmental context-dependent memory effects. Thus, it could be the case that cue-overload in the global condition is responsible for these effects in the current study. If this is the case, future studies should aim to counterbalance the number of target items to-be-remembered relative to local and global contextual cues. Indeed,

the cue-overload hypothesis is supported by empirical evidence (Earhard, 1967; Watkins, 1979; Watkins & Watkins, 1975).

Results obtained herein could also be explained by the Outshining Hypothesis, according to which memory retrieval determined primarily by strong stimulus item cues conceals any influence of weaker context retrieval cues and, conversely, lowering stimulus item cue strengths relative to the strength of context cues enhances context-dependent memory effects (cf. Dalton, 1993; Lockhart & Craik, 1990; Nixon & Kanak, 1985; Eich, 1980; Geiselman & Bjork, 1980). Smith (1986, 1988, 1994; Smith & Vela, 2001) labelled this phenomenon the 'outshining hypothesis', drawing an analogy between the way a bright light outshines and effectively hides any changes in a dim light, and the way high-strength stimulus item cues mask any influence of lower strength context cues. Thus, a cue's effectiveness depends upon the presence of better cues. However, what renders one cue better than another? According to Smith (1988), the potential cuing derived from a piece of information can be increased by a number of factors. For example, the less overloaded a cue (i.e. the fewer items associated with a cue), the better the cue (Watkins & Watkins, 1975). Cues should also be better the more deeply processed they are, the more repetitions they have received, and the better integrated they are with their targets. Regarding the present set of experiments, on the basis of such aforementioned assertions, it would be expected that local context, wherein there were fewer associations between item and context together with the fact that contexts were better integrated with their targets, should yield higher accuracy and quicker RT than the global context. Indeed, descriptively this was the case, with the exception of quicker RT in the true-incongruent condition in the global context. However, interestingly, accuracy was significantly higher for local context when compared to global context for true and false incongruent contexts. Thus perhaps, it could be the case that

participants recognize an incongruent background to a greater extent when said context is local as opposed to global.

The integral role of stimulus familiarity, as previously discussed by Dalton (1993), is supported by the studies conducted presently. Thus, stimulus parameters appear to influence the degree of context-dependency in terms of both local and global context, with false recognition higher than true recognition. Empirical support for the notion that stimulus familiarity plays a role takes several forms. Davies and Milne (1982) showed participants pictures of both novel and famous faces while varying background, pose, and expression. They found reduced recognition performance for novel, but not famous, faces as a function of all three changes, thereby demonstrating differential local context effects for familiar as opposed to novel faces. As such, it would seem plausible that modulation by the environmental context might differ for novel and familiar stimuli. In any case, the important role of stimulus familiarity is also supported by findings within the domain of animal learning, whereby context effects on recognition-like tasks have traditionally been more reliable. Recognizing the importance of the relation between stimulus and context, Lubow, Rifkin, and Alek (1976) showed that exposing a stimulus prior to presenting it in a novel environmental context (i.e., making it familiar) enhanced perceptual learning, in comparison with the simple presentation of a novel stimulus in the learning context.

There are other salient reasons why a stimulus attribute such as familiarity might be a parameter of contextual modulation. Whether contextual attributes such as temporal or spatial information are present or absent constitutes one of the critical distinctions that Tulving (1972) makes between episodic and semantic memory systems. According to Tulving, multiple presentations of an item allow that item to be abstracted from its context. As the item representation becomes progressively more semantic in nature, its reliance on specific contextual attributes for recognition is diminished. The representation can be

considered in a state of "decontextualization," whereby it can be activated and the corresponding item can be recognized without the reinstatement of cues present at encoding.

In a number of studies of face recognition, somewhat similar to abstract stimulus recognition, changes in local contexts such as semantic labels, face associates, or background cues have resulted in decreased recognition accuracy. In addition, in several demonstrations, changes in global context have resulted in decreased recognition for unfamiliar faces (e.g., Cann & Ross, 1989; Gage & Safer, 1985; Malpass & Devine, 1981). Abstract stimulus recognition, like face recognition, may rely on context reinstatement to a greater extent than word recognition does because of the importance of stimulus novelty. With verbal stimuli, the identification of a letter string as a word requires experience with that particular letter string; hence it can hardly be considered a novel stimulus.

In contrast to the aforementioned face recognition research, using abstract non-verbalisable stimulus pairs, we presently found that changes in local context yielded a significantly greater context effect (i.e., decreased recognition accuracy) for true (i.e., familiar) as opposed to false (i.e., unfamiliar) stimulus pairs. Further, we found that false stimulus pair recognition was significantly higher than true-pair recognition. Regarding global context, changes in global cues between study and test resulted in decreased recognition for both true (i.e., familiar) and false (i.e., unfamiliar) stimulus pairs, with recognition for false-pairs higher when cues were kept congruent between study and test. Thus it would appear that, in terms of local context, stimulus pair familiarization actually increased dependence upon accompanying contextual information when compared to recognition of unfamiliar stimuli, and decreased dependence on accompanying contextual cues in congruent as opposed to incongruent contexts.

Alternately, if global context encoding and specificity is a function of stimulus familiarity, the familiar stimuli should be less dependent on the reinstatement of the

environmental context than the novel ones. However, in the current study we found that stimulus pair familiarization, paired with contextual incongruity, increased dependence upon accompanying global cue information when compared to true (i.e., familiar) and false (i.e., unfamiliar) stimulus pairs presented in a congruent environment. Such findings contradict those observed by Dalton (1993) wherein recognition impairment was found for both novel and familiarized faces when local context was changed from study to test, and room context change only exerted a detrimental impact for novel faces when the environmental context was changed from study to test. However, it must be emphasized that the current study involved implicit contextual processing, whereas previous studies have generally incorporated intentional contextual processing. Indeed, Baddeley and colleagues (Baddeley & Woodhead, 1982; Godden & Baddeley, 1980) have proposed that recognition, unlike recall, is not contextually dependent unless context and stimulus are interactively encoded or integrated at study. Thus, the contextual encoding of the environmental features that took place did so in the absence of demands for intentional interactive processing.

Difficulty with interpretation between local and global context effects presently may be also attributable to the between-group design employed. The need for a within-subjects design with respect to global context manipulations is evident when one considers the potential for significant criterion changes for study items tested in different environmental conditions. A within-subjects design would avoid this problem in the global context manipulation. Therefore, we reasoned that the following study should incorporate local context manipulations within both congruent and incongruent global settings. Furthermore, regarding the Experimental Context hypothesis, Fernández and Glenberg (1985) proposed that laboratory context manipulations are inherently ineffective because, from the subject's perspective, all environmental context changes occur within the broader "Experimental context." This overriding experimental context diminishes the salience of any environmental

manipulations between study and test. Fernández and Glenberg's proposal has received some empirical support from a study in which a radical context change was employed, with subjects' recognition memory being tested over the telephone when they were at home (Canas & Nelson, 1986).

Taken together, the present Chapter presents evidence that, similar to studies conducted on verbal recall, changing both local and environmental context can have detrimental effects on episodic recognition when attention is turned to properties of the stimulus rather than that of the context. Further, the increased false- over true- pair recognition findings, indicate that perhaps such episodic processing is taking place on a conscious, item-familiarity based level. The following Chapter attempts to ascertain the electrophysiological and neural correlates of local contextual processing in episodic memory given that it has been previously demonstrated in numerous studies (e.g., Olson & Chun, 2002; see Chapter 1) that participants employ local cues to a greater extent than global cues to identify a target and the neural underpinnings of implicit item/context binding of episodic memory have not thus far been isolated in terms of the available literature.

4

Chapter IV

Electrophysiological correlates of local contextual processing in episodic memory

We wish to thank Sarah Cassidy for assistance with data collection.

Abstract

Previous neuroimaging research indicates that there are unique medial temporal, parietal and prefrontal areas associated with context-dependent and context-independent episodic memory representations. Using a local context paired-associate task paradigm, we attempted to isolate the electrophysiological and source correlates underpinning the retrieval of episodic local contextual memory. In so doing, it was hoped that electrophysiological indices could shed some light on contentious issues within the field such as implicit item-context binding, together with the functional role of MTL regions in episodic retrieval. Eight pairs of stimuli were learned during the study phase, with each pair presented superimposed upon a unique contextual background. The test phase involved the presentation of a single visual stimulus on a contextual background (i.e., probe stimulus), which was followed by a full stimulus pair. Participants were required to judge whether a presented stimulus pair was 'true' (previously presented during the study phase) or 'false' (rearranged pairs), irrespective of background, allowing for the manipulation of implicit local contexts. Electrophysiological data revealed statistically significant context effects on the P1-N2 latency for the four test conditions occurring maximally over parietal electrodes, with the true-congruent condition peaking approximately 30ms earlier than the incongruent conditions. Results indicate that implicit local context interacted to affect learning of visual pairs at a relatively early stage in the information-processing stream, and that such scenes were processed as a unitary percept rather than as a set of linked elements. When compared to behavioural findings showing superior retrieval of false-pairs, the electrophysiological data implies that the association between context and stimulus pair occurs unconsciously and somewhat separate from later processing. Sources were located for false-pairs in the superior temporal gyrus, suggesting conscious item-based processing, whereas sources located for true-pairs within the medial temporal lobe

suggest unconscious context-based processing. The data suggest that implicit contextual processing of episodic memory remains within the remit of MTL regions, whereas explicit item-based processing no longer relies upon MTL regions at this juncture.

4.1 Introduction

Due to its dense connectivity with sensory areas, the hippocampal formation (HF) is a strong candidate for a role in the initial processing and subsequent reinstantiation of context, particularly during learning. Memory performance depends upon the similarity between information stored in memory and that available at retrieval. However, much controversy has prevailed as to the significance of a congruent context for memory formation, and therefore the effect of context on cortical brain activation still leaves room for discussion. Moreover, the act of learning associations between stimuli and their contextual backgrounds is a fundamental requirement of everyday memory; however, relatively little is known about the electrophysiological correlates and functional neuroanatomy subserving this process.

What *is* known is that the hippocampus and adjacent MTL structures are critical for the encoding and retrieval of episodic information (Cohen & Eichenbaum, 1993; Squire, 1992; Squire & Zola-Morgan, 1991). The MTL structures are likely candidates for contextual learning (i.e., the binding of multiple cues) in the brain. Furthermore, relational memory (i.e., memory for associations among stimuli) has been strongly linked to the medial temporal lobes (for review, see Eichenbaum *et al*., 1994) and the prefrontal cortex (PFC; for review, see Moscovitch, 1994) in various neuroimaging studies (e.g., Giovanello *et al*., 2004; Lepage, Habib & Tulving, 1998; Ranganath *et al*., 2000). Also, functional neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have contributed to our understanding of the relationship between the MTL structures and episodic memory encoding or retrieval, or both (Schacter & Wagner, 1999; Lepage *et al*., 1998). In a review of MTL activations detected by PET, LePage and colleagues (1998)

conjectured that posterior regions of the MTL are associated with episodic retrieval, whereas anterior regions are associated with episodic encoding.

Regarding the functional role of the MTL structures in memory, although there is a general consensus that episodic memory is supported by the hippocampus, the specific nature of the neuronal processing that occurs there is a subject of ongoing debate (Meltzer & Constable, 2005; see Chapter 1). Several researchers have proposed that the MTL structures may be related to learning and consolidation of declarative memory (Squire & Alvarez, 1995; Squire & Zola-Morgan, 1991), novelty assessment and encoding (Tulving *et al*., 1996), formation and storage of multiple traces binding separate components together (Fujii *et al*., 2000; Nadel & Moscovitch, 1997), retrieval of deeply encoded items (Rugg *et al*., 1997), and spatial learning (Henke *et al*., 1999a; Maguire *et al*., 1997; 1998; O'Keefe & Nadel, 1978). More specifically, Squire (1992) proposed the Classic Consolidation Theory which postulates that the hippocampus stores memories as a result of encoding, but the memories are then consolidated over time to more stable cortical areas (see Chapter 1). However, in Nadel & Moscovitch's (1997) Multiple Trace Theory, the authors propose that the hippocampus is involved in episodic and spatial memories for as long as they exist with only a time-limited contribution to other forms of memory (i.e., semantic) which are stored elsewhere in the brain (see Chapter 1). Essentially, the hippocampus appears critical for encoding of new information but also for the recall of episodic information acquired prior to the onset of amnesia. In this light, one can only speculate about the contribution of the hippocampus to long-term memory but it is virtually undeniable that the structure is necessary for new memory formation regardless of whether it is semantic or episodic. Indeed, the fact that patient H.M. (Scoville & Milner, 1957; see Chapter 1) could not create new long-term memories, but could recall long-term memories that existed prior to his hippocampal ablation

surgery suggests that encoding and retrieval of long-term memory information may also be mediated by distinct systems.

Evidence for the role of the MTL structures in context memory, more specifically, has been supported by studies of amnesic patients and imaging studies. Huppert & Piercy (1978) found that Korsakoff amnesics had difficulty making use of temporal context compared with normals. Furthermore, an fMRI study conducted by Bar and Aminoff (2003) revealed strong activation of the posterior portion of the parahippocampal cortex (PHC) and the parahippocampal gyrus while participants viewed objects strongly associated with a particular context, (e.g., traffic-lights) compared with those taking place when a non-context specific object was presented (e.g. fly). The authors also reported activation of the retrosplenial cortex during strong contextual pictures. This is consistent with findings from Andreasen *et al.* (1995) and Fink *et al.* (1996). Epstein and Kanwisher (1998) have reported that the PHC is activated during encoding of houses and environmental landmarks. It is possible, then, that the area is responding to the processing of places and not context *per se*. Bar and Aminoff (2003) tested this possibility by comparing spatial and non-spatial contextual stimuli and revealed that both types significantly activated the PHC and the retrosplenial cortex. They concluded that these areas mediate general analysis of contextual associations, and not only of place-related information. In a virtual reality experiment, Burgess and colleagues (2001) examined memory processing using event-related functional magnetic resonance imaging, and found that there are unique MTL, parietal and prefrontal areas associated with context-dependent and context-independent episodic memory representations. They also suggested that activation of the left and right MTL differentiates between spatial and non-spatial memory processing in a way that is consistent with previous work in human amnesia and non-human animal studies.

Understanding of the neural underpinnings of contextual memory, episodic memory and relational memory has been further advanced through various electrophysiological studies (e.g., Brown & Aggleton, 2001; Rhodes & Donaldson, 2007; see Eichenbaum *et al*., 2007, for a review). Several researchers have attempted to delineate cognitive and neural processes involved in human long-term memory by recording ERPs while participants simultaneously engage in tasks involving episodic memory encoding and/or retrieval (for general reviews, see Friedman, & Johnson, 2000; Friedman, 1992; Halgren & Smith, 1987; Rugg, 1995a,b).

Many ERP studies of recognition memory have been interpreted within dual-process frameworks that differentiate between familiarity and recollection (Brainerd *et al*., 1995; Hintzman & Curran, 1994; Jacoby, 1991). Though details differ between theories, familiarity is generally considered to reflect an assessment of the global similarity between study and test items (Hintzman, 1988; Gillund & Shiffrin, 1984), whereas recollection allows for the retrieval of detailed information concerning study items such as physical attributes or associative/contextual/source information. Within the context of such theories, studies indicate that an ERP old/new effect occurring between 400ms and 800ms is related to putative memory retrieval processes (Johnson, 1995; Rugg, 1995). The earlier right frontal aspect of the ERP old/new effect (300–500ms) may be related to *unconscious* familiarity whereas the later left parietal aspect (400–800ms) may be related to *conscious* recollection (see Friedman & Johnson, 2000; Mecklinger, 2002 for reviews; Düzel, Vargha-Khadem, Heinze & Mishkin, 2001; Guillem, Bicu & Debruille, 2001; Nessler, Mecklinger & Penney, 2001; Rugg *et al*., 1998). The 300–500ms familiarity-related effect has been termed the 'FN400 old/new effect' (Curran, 1999; 2000) and is identifiable by a positive shift which is maximal over right frontal electrodes. Rugg and colleagues (1996) obtained direct evidence from positron emission tomography (PET) that the activity of the right prefrontal cortex

varies in accordance with the probability of successful retrieval, thereby demonstrating that neural activity within this region is greater during the processing of 'old' as opposed to 'new' recognition memory test items. The 400–800 ms recollection-related ERP effect has been termed the 'parietal' old/new effect (Allan, Wilding & Rugg, 1998; Rugg, Schoerscheidt & Mark, 1998; Rugg *et al*., 1998; Wilding & Rugg, 1996, 1997) and is characterized by a positive shift in ERPs for correctly identified old recognition test items relative to new items. Thus, on the basis of functional neuroimaging (Cabeza *et al*., 1997) evidence, it is suggested that the frontal effect is sensitive to item retrieval (i.e., familiarity), whereas the parietal effect is sensitive to context retrieval (i.e., recollection).

The evidence for relating the parietal old/new effect to recollection is particularly strong. Further, according to Donaldson and Rugg (1999), the effect is an indirect reflection of the contribution of the MTL memory system to episodic retrieval. The findings from numerous studies suggest that this left parietal effect is elicited selectively by test items that engender retrieval of contextual information from their encoding episode (for reviews, see Rugg & Curran, 2007; Friedman & Johnson, 2000; Rugg & Allan, 2000; Allan *et al*., 1998). This hypothesis is supported by an array of evidence. First, the functional properties of the effect would suggest that it is elicited in circumstances wherein the MTL would be conjectured to be engaged during memory retrieval. Second, the parietal old/new effect is sensitive to variables thought to affect recollection more than familiarity such as depth of processing (Rugg, Allan & Birch, 2000; Rugg *et al*., 1998; Paller, Kutas & McIsaac, 1995; Pallar & Kutas, 1992). Third, when participants are asked to introspectively differentiate words specifically 'remembered' from those merely 'known' to be old, larger parietal old/new effects are associated with 'remembering' than 'knowing' (Düzel *et al*., 1997; Rugg, Schoerscheidt & Mark, 1998; Smith, 1993; but also see Spencer, Vila Abad & Donchin, 2000).

With particular reference to local context and behavioural congruency effects, Tsivilis *et al.* (2001) used ERPs during a recognition memory test for previously studied visual objects. At test, studied objects were presented along with either their original context (landscape scenes), with a different context or with a new context. Unstudied objects were paired with either a studied or a new context. Results indicated ERP memory effects related to the amount of task-relevant features at test. There was a greater parietal old/new effect when item-context pairings were maintained between study and test phases, than when the pairings were changed. Hannula, Federmeier and Cohen (2006) used ERPs to investigate relational memory effects, which is similar to local context memory. The study phase involved learning face – scene pairs; at test, a scene was presented and followed by a matching, a familiar but mismatching, or a novel face. The researchers were interested in the different activity that may be elicited by the face as a function of whether it matched the preceding scene. Relational memory effects were evident as early as 270–350 ms (P3) after face onset. ERPs to faces viewed in a reinstated context were more positive – going than ERPs to either studied faces paired with a different context or novel displays.

There have been few functional neuroimaging studies, however, on episodic retrieval that specifically required the processing of relations among the multiple components involved in episodes. According to Tsukiura *et al.* (2002), this relational retrieval process must be more complicated than simple recognition such as old/new judgement. Reed and Squire (1997) claimed that impaired recognition memory is a robust feature of human amnesia following damage to MTL structures. In addition, many neuroimaging studies have shown that MTL structures are activated during the process of recognition of previously-learned components (for reviews, see Lepage *et al*., 1998; Schacter & Wagner, 1999). Although both the relational retrieval process and the simple recognition process can be

thought of as retrieval in the context of memory processes, it is possible that there may be some differences between these two retrieval processes.

The current study employed a high density 128-channel ERP array in order to investigate scalp waveform componentry and electrical dipole sources associated with *implicit* local context memory. The high density array allows for the use of Brain Electrical Source Analysis (BESA, MEGIS Software GmbH, Grafelfing, Germany) of the scalp recorded ERPs elicited during the study. BESA enabled the identification of mathematically feasible neural generators of the scalp potentials to be estimated. Context memory was examined in normal participants using a standard visual paired-associate task (see Chapters 2 & 3). The unique aspect of this study involved the presentation of a local contextual background with each pair. In doing so, every time a stimulus pair was presented during learning, a distinct background (colourful landscape) was also presented. Participants were given *no* explicit instructions to memorize these background pictures. During the test phase, participants were shown a probe stimulus (a single stimulus on a contextual background), which was followed by a full pair. The participants were required to judge if the two stimuli had been learned during the study phase (true-pair) or if the stimuli were recombined (false) pairs. Each pair continued to be presented along with a colourful background; however, half of the pairs were presented on a congruent background and the other half on an incongruent background.

In line with previous research within the area (see Chapter 1), it was predicted that upon encoding of the stimulus pairs, participants would implicitly associate each pair with a contextual background. Behaviourally, based on the findings emanating from Chapter 3, it was predicted that local context would exerted an effect on true-pair recognition in particular, given the finding of a performance decrement in response to the incongruent context. Therefore, it was hypothesized that accuracy would decrease in the incongruent condition as

opposed to the congruent condition. Further, it was expected than recognition for true- and false- pairs (i.e., stimulus type) would be affected to a greater extent than local contextual incongruity. In line with previous literature in the area, it was expected that reaction time (RT) would increase in incongruent conditions (note however that non-significance differences in RT were found in the corresponding Experiment 1 of Chapter 3 irrespective of context or stimulus pairing). In recording electrophysiological data, we expected to find amplitude and/or latency differences in waveforms associated with the congruent and incongruent conditions and the true and false-pair conditions. Finally, we hypothesized that correctly recognized true-pairs in the congruent context may elicit a stronger electrophysiological response in and around medial temporal and frontal regions than the true-pairs in an incongruent context.

4.2 Method

4.2.1 Participants

The participants in this study comprised 25 undergraduate university students aged between 18-43 years (mean age= 24.4±6.91yrs) years, recruited from the NUI Maynooth campus, who volunteered to take part in a general memory study. The EEG data of 5 participants were removed due to excessive EEG/EOG artifacts or head movement. Of the remaining 20 participants, 12 were male and 17 were right-handed. English was the primary language of all participants, and all reported normal or corrected-to-normal vision. All participants were free from psychoactive medications for at least 4 weeks prior to experimentation. Participants currently using prescription medication that may have affected cognitive processes were excluded from taking part in the study. Participants were also instructed not to consume alcohol or other recreational drugs within the 24 hours preceding the study. Participants gave written informed consent (Appendix 17) prior to taking part in the experiment in a manner approved by the 1964 Declaration of Helsinki and were informed of their rights under the Freedom of Information act. Furthermore, the experiment was conducted in accordance with the ethical standards set forth by the APA and the World Medical Association and was approved by the National University of Ireland Maynooth Ethics Board.

4.2.2 Stimuli

The task used for this study was a standard visual paired-associate task (VPA; see Chapters 2 & 3) which was created using the E-Prime experimental presentation program. Identical to Experiment 1 in Chapter 3, the task incorporated eight pairs of stimuli, as well as eight local contextual backgrounds. Each stimulus pair was presented in front of a distinct background.

The eight stimulus pairs and their associated backgrounds are shown in Figure 3.1 in Chapter 3. The pairs of stimuli to be learned comprised 16 non-verbalisable achromatic visual figures obtained from a graphic design website. The backgrounds were eight distinct landscape scenes; four were taken from the sample pictures provided with all Microsoft computer packages, whereas the other four were obtained from a landscape website. The experiment took place in the Department of Psychology at the National University of Ireland, Maynooth on a Dell Personal Computer with Pentium 4 processors (3.00GHz CPU) and standard LCD monitor and computer.

4.2.3 Procedure

4.2.3.1 Behavioural Paradigm & Analyses

Study Block

The task consisted of a study block containing 48 trials, followed by a test block containing 128 trials. The study block involved presenting the eight study pairs six times each in a pseudorandom order (objects were presented randomly in a run of 8 and this was repeated 6 times), such that consecutive presentations of the same object did not coincide. During this study block, each stimulus pair was presented for 3500ms with a 750ms inter-trial interval consisting of a fixation-cross. Participants were required to learn which stimuli formed a stimulus pair and to remember these pairs for the test phase. No explicit instructions were given regarding the learning of the contextual backgrounds. Refer to Figure 4.1 above for complete set of VPA pairs and corresponding backgrounds presented during the study block.

Test Block

During the test block, a probe stimulus was first presented for 1000ms in order to examine whether the paired associates were encoded in an implicit manner with the context as a

complete trace or whether each element was associated with disparate parts of the scene in a separate manner. A probe stimulus consisted of one half of a stimulus pair and a contextual background. The probe stimuli was positioned in either the right or left – hand side of the screen, consistent with where it had been positioned during the study phase. This was followed by a full pair [the same probe and background along with the second stimulus], which remained on screen until the participant responded. The full pairs can be referred to as the test pairs given that participants were required to judge if the pair had been seen during the study phase (in which case it would be a true-pair) or if it was not seen during the study phase (false-pair; please refer to Figure 3.2 Chapter 3). The false-pairs consisted of the same stimuli shown in the study phase, however the pairs were rearranged. No feedback was provided for any of the trials throughout the experiment. Therefore, each trial consisted of a probe stimulus, immediately followed by the test pair. Prior to the onset of the next trial, a fixation cross appeared for 750 ms in an effort to reduce participants' eye-movements prior to the next trial.

To test for implicit local context effects on memory, the backgrounds were manipulated during the test phase. There were four different test conditions, each comprising 32 trials. Each of the 16 stimuli learned in the study phase were presented twice each as probes. The four test conditions were derived by manipulating the background wherein the probe was presented and by following the probe with either a true or false-pair. True-pairs (one of the eight pairs learned during the study phase) were either presented along with their original background (congruent context condition) or they were presented on one of the seven incorrect backgrounds (incongruent context condition). The same applies to the false-pairs. Thus the test pairs contained four conditions: true-congruent; true-incongruent; false-congruent and false-incongruent (refer to Figure 3.3 Chapter 3). Presentation of these conditions was randomized and this random order was the synonymous for all participants.

During the test phase, both accuracy and reaction times were recorded. A correct response was elicited when participants pressed the left mouse button, with their index finger, when a true-pair was presented and the right mouse button, with their middle finger, when a false-pair was presented, regardless of the contextual background. Reaction times were measured as the interval between presentation of the stimulus and the response and were recorded for both correct and incorrect trials. Failure to respond was classed as incorrect. E-Prime logged reaction times and accuracy data for each participant and sent triggers to another computer to enable stimulus presentations (stimulus conditions) and responses (correct/incorrect) to be logged in real time for the EEG recording.

4.2.4 Statistics for Behavioural Data

Similar to Experiment 1 in Chapter 3, the experiment employed a 2x2 repeated-measures factorial design, i.e., two within group independent variables were manipulated. The first was context, operationalised at two levels: 'congruent' context and 'incongruent' context, and the second was stimulus type, also operationalised at two levels: true-pairs and false-pairs. This design allowed for the measurement of four different conditions: true-congruent (TC) condition, true-incongruent (TI) condition, false-congruent (FC) condition and false-incongruent (FI) condition. The scores were obtained across these conditions from the same participant. The allocation of participants to the experimental groups was performed in an ad hoc sampling manner. The behavioral part of this experiment measured accuracy and reaction time (RT) across all trials for all participants, as automatically recorded by E-Prime. RT data is presented in terms of milliseconds. A two-way repeated measures ANOVA was conducted in order to identify the main effect of stimulus type and context and any interaction effect that may occur. Bonferroni-corrected paired t-tests were also carried out to further investigate these effects. A star-based system for significance representing p-values of * $p<0.05$, **

$p<0.01$, and *** $p<0.001$, respectively, was used throughout. The symbol ± was employed throughout to denote deviation from the mean. Percentage accuracy values are presented for accuracy, and reaction time data is presented in the order of milliseconds. Bonferroni-corrected *p*-values are presented only once in cases where similar *p*-values were adjusted. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

4.2.5 Electrophysiological Recording and Analyses

See Chapter 2 for electrophysiological participant preparation procedure. EEG data were collected from 128 tin electrodes over the surface of the scalp, utilizing the extended version of the International 10-20 system for electrode placement. Impedance was reduced to <10mΩ. The reference electrode was located on the naison at the tip of the nose and 4 electrodes were positioned around the eyes to record blinking. Two electrodes were placed at the external canthi of the eyes to record horizontal movements, and one on the inferior and superior ridges of the orbit of the left eye to record vertical movements. Blinks were averaged off-line and a blink reduction algorithm was applied to the data off-line with BESA. The voltage differences between the 128-channel electrodes and the reference electrode were extracted as electrical waveforms, which were then amplified using a band-pass of 0.16-100Hz and a gain of 1000. The conversion rate was 2000 Hz per channel and the range was 150mV. Recordings were notch filtered off-line at 50Hz. EEG data were digitized at a sampling rate of 500Hz, and were averaged offline using BESA software. Epochs that exceeded the maximum amplitude of 50mV were discarded from the analysis.

Stimulus-locked average ERPs (see Chapter 2) were created by averaging the EEG using stimulus presentation as the trigger. ERPs time-locked to the onset of the stimulus presentations were computed for each subject at all scalp sites with epochs of -100ms to

1200ms. Nine conditional ERPs were created based on possible combinations of stimulus presentation; the study phase, the four probes- true-congruent, true-incongruent, false-congruent, false-incongruent, and the four tests pairs- true-congruent, true-incongruent, false-congruent, and false-incongruent. Since there were very few incorrect responses, ERP analysis was restricted to those trials wherein participants gave the correct response. Component structure was defined in an *a priori* manner with no prior knowledge of the pattern of effects the data may present. An overall grand-mean waveform was generated for each electrode by collapsing across all conditions. Visual inspection was used to identify the major components of interest in an a priori manner and BESA was used to conduct selected waveform analyses. The area under the curve (AUC) and/or latency for certain components were recorded and repeated-measures ANOVAs were used to compare conditions. Bonferroni-corrected paired t-tests were employed to examine paired comparisons and elucidate results from the ANOVAs.

4.2.6 Brain Electrical Source Analysis

Refer to Chapter 2 for a detailed account of the source analysis procedure employed. Individual component modeling was used here to generate the possible neural generators of certain components of interest. Single dipoles were added to each model until the solution presented became implausible, in this way, we searched for the minimum residual variance (RV). MRI slices were also generated in BESA and will be included in the results; however it is important to note that the modeled dipoles represent an oversimplification of the activity in the brain areas and they should not be referred to as exact generators but considered to represent centers of gravity of the observed activity (Molholm *et al*, 2004; Sehatpour *et al*., 2006).

Source models were estimated for the time windows, in which the P1, N2 and P3 of the test stimuli waveforms reached peak values. For the P1 component, sources were obtained for the true-congruent, true-incongruent, false-congruent and false-incongruent conditions. For the N2 component, sources were obtained for the true-congruent and false-congruent conditions, and finally, for the P3 component, dipoles were generated for the true-congruent and true-incongruent conditions. For each waveform, the time-dependent RV was computed for the model. Parameters were optimized for individual data at the time point at which the minimum RV was computed, within the predetermined latency window. Data with an RV of greater than 15% were excluded from further analysis, as well as those participants with anatomically implausible solutions.

Anatomical loci and Brodmann's areas were estimated using a Talairach Daemon software application (© The Research Imaging Centre, UTHSCSA, Texas; see Chapter 2). Finally, source waveforms were plotted and generic MRI slices were generated in BESA.

4.2.7 Statistics for Electrophysiological Data

Independent Variables for the electrophysiological paradigm contained 6 independent variables: the study phase, probe-congruent, probe-incongruent and four test conditions. The Dependent Variable was measured using amplitude and latency. An overall grand mean waveform for each condition at each electrode was obtained and visual inspection identified the latency windows and electrode sites of interest. Certain electrode sites were chosen (due to enhanced activity in this area) and AUC and/or latency data for each condition were recorded from this electrode. The data was entered into SPSS (Version 13 for Windows) for statistical analysis. 2x2 repeated measures ANOVA's and paired t-tests were carried out. Bonferroni-corrections were applied where necessary. A star-based system for significance representing p-values of * $p<0.05$, ** $p<0.01$, and *** $p<0.001$, respectively, was used

throughout. The symbol ± was employed throughout to denote deviation from the mean. ‘SEM’ refers to standard error mean value where present. Percentage accuracy values are presented for accuracy, and reaction time data are presented in the order of milliseconds. Bonferroni-corrected *p*-values are presented only once in cases where similar *p*-values were adjusted. Error bars, where present, show standard error of the mean, which is in turn denoted by ‘SEM’.

4.3 Results

4.3.1 Behavioural Results

Participants whose data were withdrawn from EEG analysis were also removed from behavioural analysis. As can be seen from Table 4.1 and Figure 4.1, mean accuracy scores were generally higher for false rather than true stimulus pairs. Faster response times were observed for correct responses compared to incorrect responses, with incongruent recombined contexts eliciting the fastest response times. Interestingly, the true-pair incongruent context demonstrated the quickest response time. Furthermore, regarding incorrect responses, the slowest response times were observed for the false-pairs in both context-congruent and context-incongruent conditions, with the true-pairs eliciting the fastest response times. The quickest response time was achieved in the true-pair context-incongruent condition. Interestingly, for true-pairs mean accuracy was higher for the congruent condition compared to the incongruent condition; however, for false-pairs, the opposite was true.

Table 4.1: Mean percentage accuracy scores and reaction times (in msec) for each condition during the test phase across correct and incorrect response. Standard deviations are shown in brackets.

Stimulus Type	**Mean Accuracy**	**RT (Correct Responses)**	**RT (Incorrect Responses)**
True-Congruent	80.15 (14.56)	962.94 (286.35)	1143.51 (348.18)
True-Incongruent	74.17 (20.41)	870.75 (326.16)	1153.25 (343.55)
False-Congruent	86.56 (13.79)	964.70 (293.64)	1204.36 (434.90)
False-Incongruent	88.75 (13.31)	967.13 (324.63)	1306.34 (647.58)

4.3.1.1 Accuracy

A 2x2 repeated measures ANOVA was used to explore the impact of stimulus type (i.e., true and false) and context (i.e., congruent and incongruent) on participants' accuracy within group. There was a significant main effect for stimulus type (Wilks' Lambda=.464, F(1,18)= 20.797, p<.0005; η_p^2 =.536). No significant main effect was obtained for context (Wilks' Lambda= .908, F(1,18)= 1.819, p=.194, η_p^2 =.092), although, as expected, accuracy was higher in both the true (80.15±14.56) and false congruent (86.56±13.79) conditions compared to the true incongruent condition (74.17±20.41). Further, there was a significant interaction effect between stimulus type and context (Wilks' Lambda= .776, F(1,18)= 5.182, p=.035, η_p^2 =.224). Interestingly, for true-pairs, mean percentage accuracy was higher in the congruent condition compared to the incongruent condition, whereas the opposite pattern was found for false-pairs, with percentage accuracy higher in the incongruent condition compared to the congruent condition. This significant trend suggests that participants employed the congruent context to enhance the association between true-pairs, and conversely, the incongruent context to facilitate recognition of false-pairs.

A series of subsequently conducted paired samples t-tests revealed a statistically significant increase in percentage accuracy from the true-congruent condition (80.15±14.56) to both the false-congruent condition (86.56±13.79; *t*(19)= -2.344, *p*=.030: Bonferroni-corrected, *p*=.018) and the false-incongruent condition (88.75±13.31; *t*(19)= -4.472, *p*<0.005: Bonferroni-corrected, *p*=.03). Further statistically significant increases in percentage accuracy were observed from the true-incongruent condition (74.17±20.41) to both the false-congruent condition (87.82±12.92; *t*(18)= -3.569, *p*=.002: Bonferroni-corrected, *p*=.012) and the false-incongruent condition (88.56±13.79; *t*(18)= -4.410, *p*<0.005: Bonferroni-corrected, *p*=.03). These significant differences are shown in Figure 4.1 below.

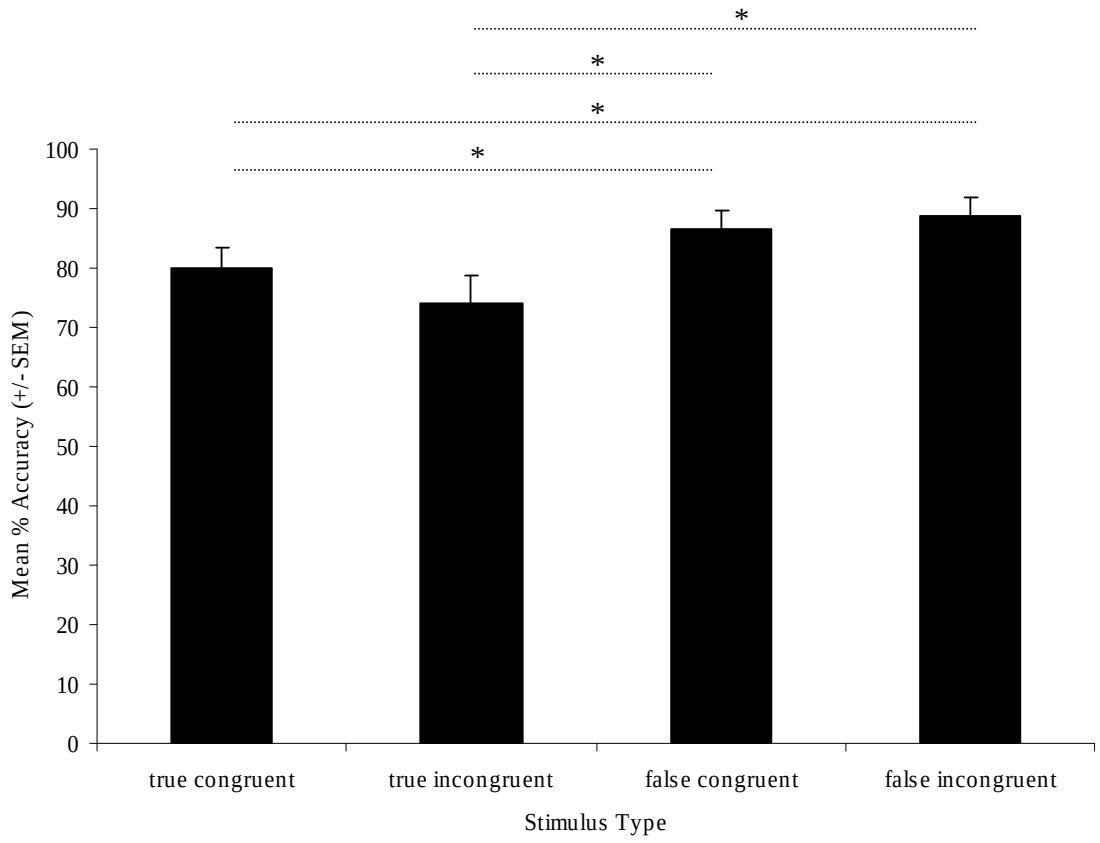


Figure 4.1: Mean percentage accuracy across stimulus type (+/- SEM) incorporating significant differences. Bonferroni-corrected *p*-values are shown: all *p*-values depicted are at the * $p<0.05$ level.

4.3.1.2 Reaction Time

The RT data for the four conditions were separated into correct responses and incorrect responses (see Table 4.1). For *correct* responses (Figure 4.2), the condition with the slowest RT was the false-incongruent condition (967.13±325.63), whereas the quickest RT was obtained in the true-incongruent condition (870.75±326.16). For *incorrect* responses (Figure 4.3), similar to that obtained for correct response the condition with the slowest RT was the false-incongruent condition (1306.34±647.58), whereas, unlike that obtained for correct responses, the quickest RT was obtained in the true-congruent condition (1143.51±348.18).

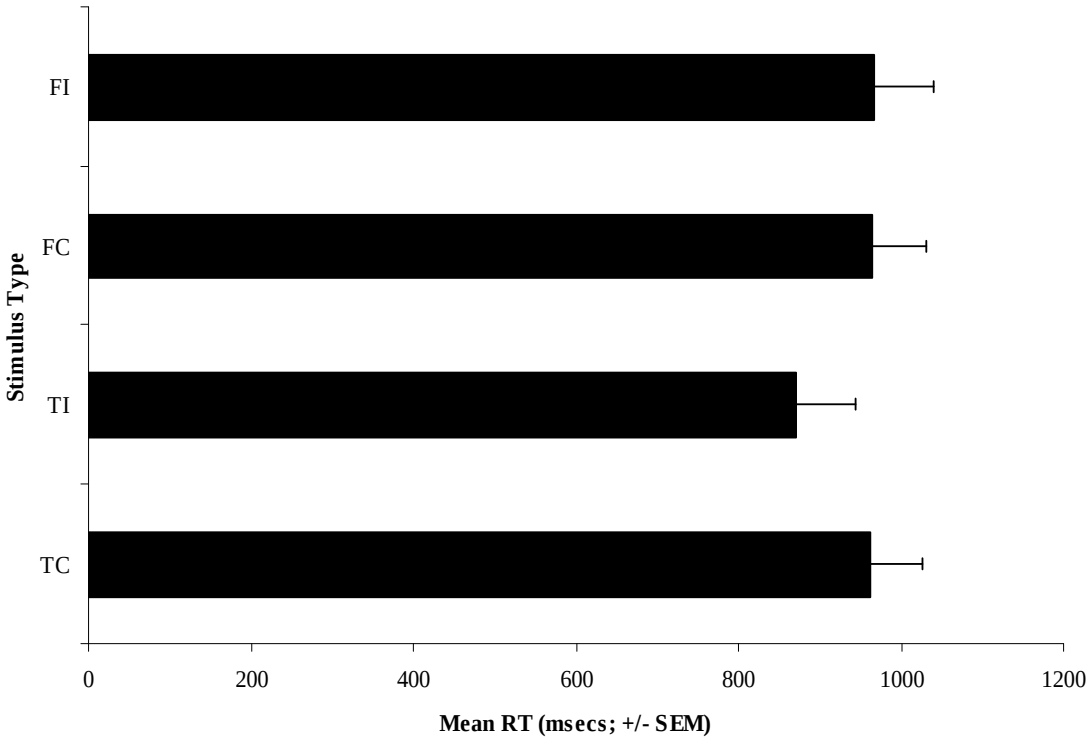


Figure 4.2: Mean RT across stimulus type (+/- SEM) for correct responses.

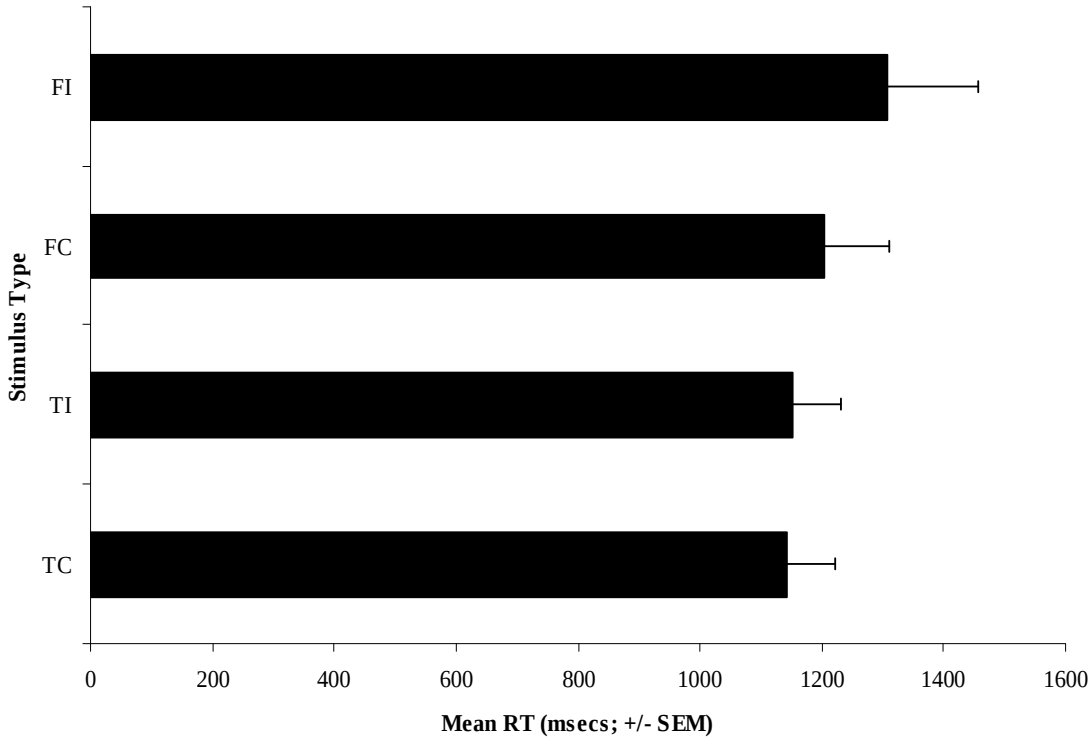


Figure 4.3: Mean RT across stimulus type (+/- SEM) for incorrect responses.

A 2x2 repeated measures ANOVA for RT of correct responses revealed no significant main effect for stimulus type (Wilks' Lambda= .931, F(1,19)= 1.402, p=.251, η_p^2 =.069) or context (Wilks' Lambda= .949, F(1,19)= 1.028, p=.323, η_p^2 =.051). Furthermore, no significant interaction effect (Wilks' Lambda= .895, F(1,19)= 2.221, *p*=.153, η_p^2 =.105) was obtained. The same analysis was undertaken for the RTs procured for incorrect responses. Again, no statistically significant differences were elicited regarding the main effect of stimulus type (Wilks' Lambda= .912, F(1,12)= 1.162, *p*=.302, η_p^2 =.088), or context (Wilks' Lambda= .950, F(1,12)= .629, *p*=.443, η_p^2 =.050). Also, no significant interaction effect (Wilks' Lambda= .968, F(1,12)= .391, *p*=.544, η_p^2 =.032) was observed.

4.3.2 ERP Analysis

An overall grand-mean waveform was created for each electrode by collapsing data across each condition. Correct responses only were included for analysis, given there were too few incorrect responses to generate an ERP. Visual inspection allowed for the identification of certain components of interest. We first discuss the main ERP components identified, followed by a comparison of area under the curve (AUC) and/or peak latency of identified components across the different conditions.

4.3.2.1 Visual analysis and component morphology

Study and probe conditions:

An overall grand-mean waveform for each condition was generated using BESA, across all 128 electrode sites. Visual inspection of the waveforms for study and probe conditions (used to ascertain whether the paired associates were encoded in an implicit manner with the context as a complete trace or whether each element was associated with disparate parts of the scene in a separate manner), maximal at electrode Pz (see Figure 4.4 below), indicated that the study condition showed a P100 component, occurring during a latency window of 100-200ms, followed by a short negativity and a large positive component occurring approximately 200-350ms, which was interpreted as indicative of an early P300 component. The probe-congruent conditions showed a slight positive wave occurring from approximately 100-180ms, followed by a short negativity and large P300 component occurring from approximately 280-400ms. Similarly, the probe-incongruent conditions showed a positive P100 component occurring from approximately 120-200ms, followed by a negative N200 component from approximately 150-220ms, and a large positive P300 component occurring from approximately 300-400ms.

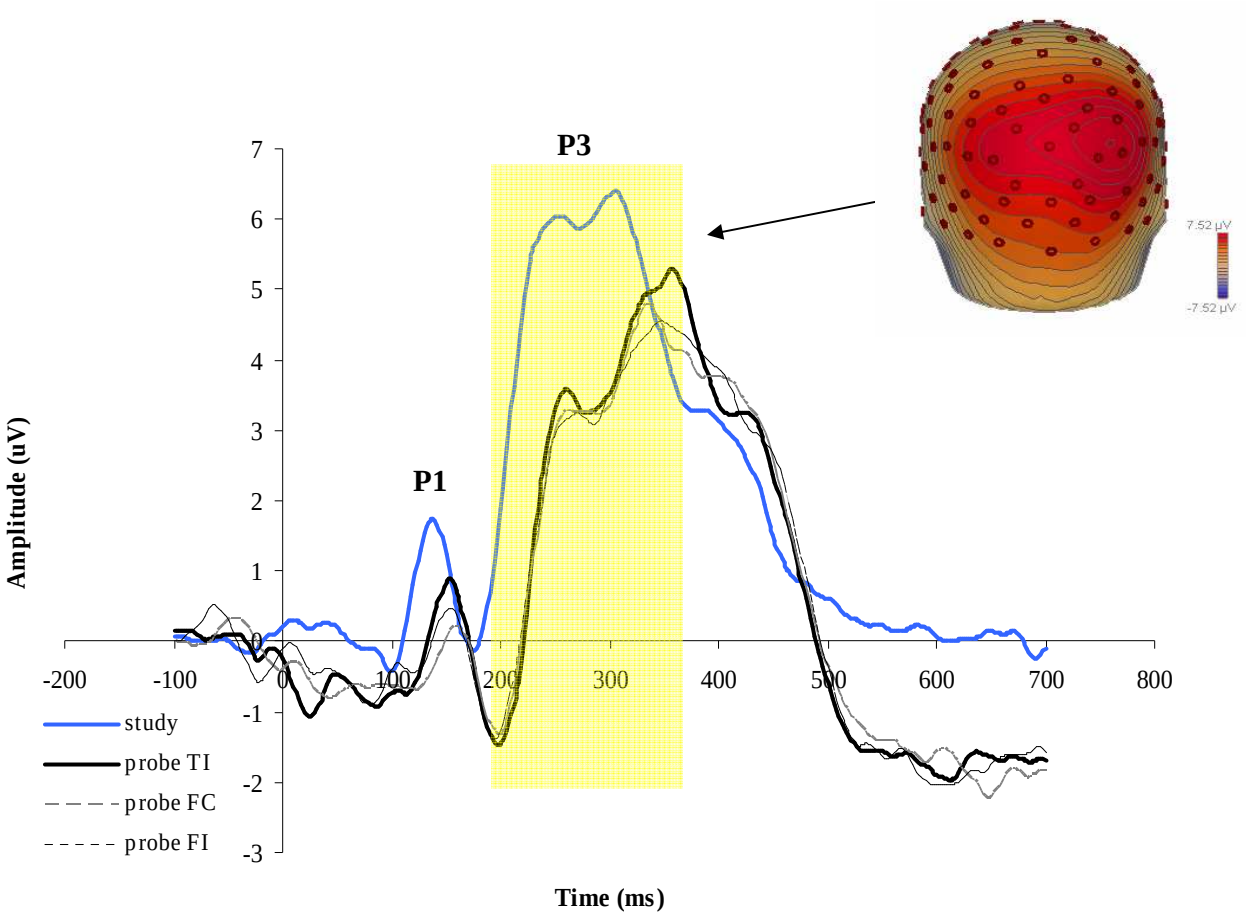


Figure 4.4: ERP waveforms and topographical map (see top right; posterior view) for study and probe conditions at electrode Pz showing P1 and P3 components and clear amplitude differences. *Only* probe-conditions with significant AUC differences from the study condition at the $p<0.05$ * level are shown within the turquoise shaded area (hence lack of true-congruent condition data).

An early **P300** was identified within a latency window of 200-350ms (see Figure 4.4 above) for the **study** and **probe-congruent** and **probe-incongruent** conditions. A series of paired t-tests compared the area under the curve (AUC) for this positive component across the study and probe-congruent conditions, as well as study and probe-incongruent conditions, at the $p<0.05$ level. The AUC for the study condition (842.36±432.09) was significantly higher than that obtained for the false-congruent condition (621.68±323.40; $t(19)= -3.433$, $p=.003$: Bonferroni-corrected, $p=.012$), the true-incongruent condition (628.11±308.75; $t(19)=-3.299$,

p=.004: Bonferroni-corrected, *p*=.016) and the false-incongruent condition (601.87±328.28; *t*(19)=-4.004, *p*=.001: Bonferroni-corrected, *p*=.004).

Probe conditions:

The probe conditions (both congruent and incongruent) showed P100, N200 and P300 components at the right parietal electrode P4. More specifically, there was a positivity evident within the 120-200ms window (i.e., P100 component), together with a negative component measured from approximately 170-250ms (i.e., N200 component), followed by a P300 component from 300-400ms. Figure 4.5 depicts the waveforms generated by the probe-congruent and probe-incongruent conditions.

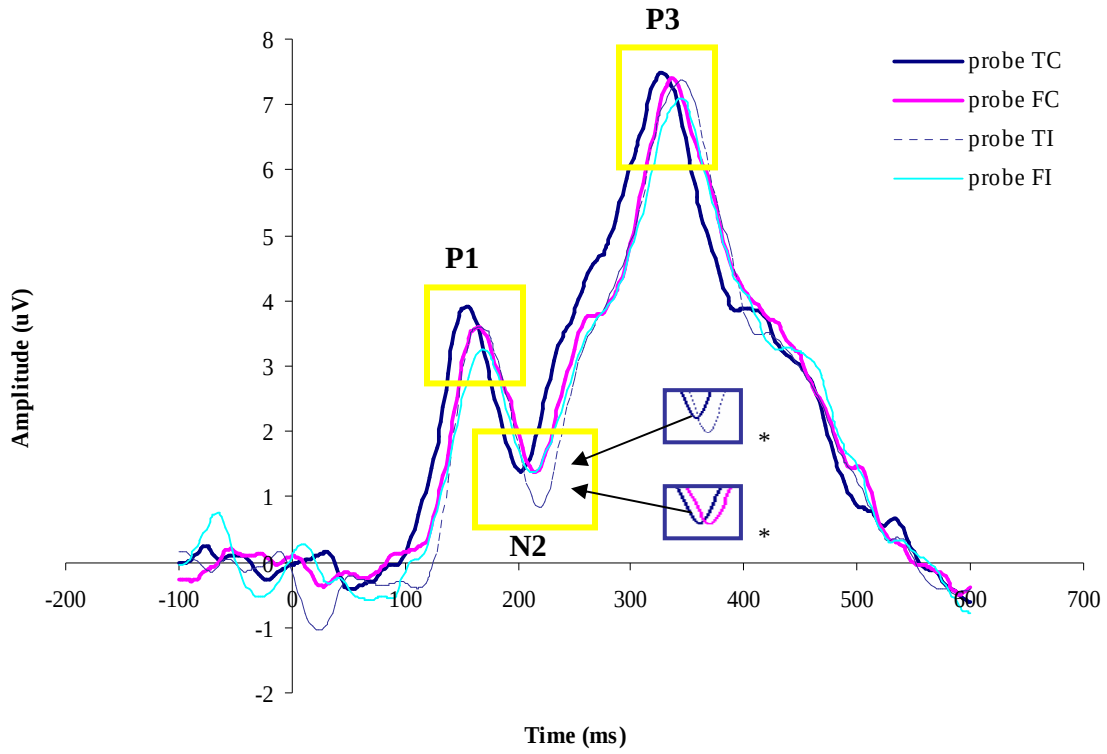


Figure 4.5: ERP waveforms for probe-congruent and probe-incongruent conditions at electrode P4 showing P1, N2 and P3 components and clear amplitude differences. Yellow boxes represent AUC and latency differences between the probe conditions. The purple boxes represent significant latency differences for the N200 component between true-congruent and true-incongruent/false-congruent probe conditions. Only Bonferroni-corrected *p*-values are shown.

For the P100 component, a paired samples t-test revealed a significantly higher AUC for the true-incongruent probe condition (262.51±187.80) than the false-incongruent probe condition (202.98±152.84; $t(19)= 2.083$, $p=0.05$). However, this proved non-significant when subjected to Bonferroni-correction (i.e., $p=0.30$). Further, no significant latency differences were found for the P100 component. For the N200 component, paired t-tests revealed significant latency shifts, with the true-congruent probe condition (204.70±19.35) peaking approximately 14ms earlier than the true-incongruent probe condition (218.60±19.67; $t(19)= -4.617$, $p<0.005$: Bonferroni-corrected, $p=0.03$), and approximately 12ms earlier than the false-congruent probe condition (216.50±20.03; $t(19)= -3.742$, $p=.001$: Bonferroni-corrected,

p=0.006). No AUC differences however were found. The P300 component was finally subjected to the same t-test comparisons; however no significant AUC difference was observed at the $p<0.05$ level. However, a significant latency shift was evident, with the true-congruent probe condition (334.60±30.35) peaking approximately 16ms before the false-incongruent probe condition (351.10±24.52; $t(19)= -2.642$, $p=.016$). This was however proved non-significant following Bonferroni-correction (i.e., $p=0.09$).

Test conditions:

Finally, the test conditions were subjected to component analysis. *All* four conditions elicited a P1-N2-P3 complex. Electrode P4, in particular, was used to identify the P100 and N200 components, occurring during a latency window of 100-200ms and 150-250ms, respectively (Figure 4.6). The P300 component was assessed at electrode CPz for time latency windows of 300-480ms and 480-800ms (Figure 4.7). These components were subsequently subjected to area under the curve (AUC) and latency difference comparison across the four test conditions (i.e., true-congruent, true-incongruent, false-congruent and false-incongruent). Figure 4.7 incorporates a topographical comparison of early and late aspects of the P3 component.

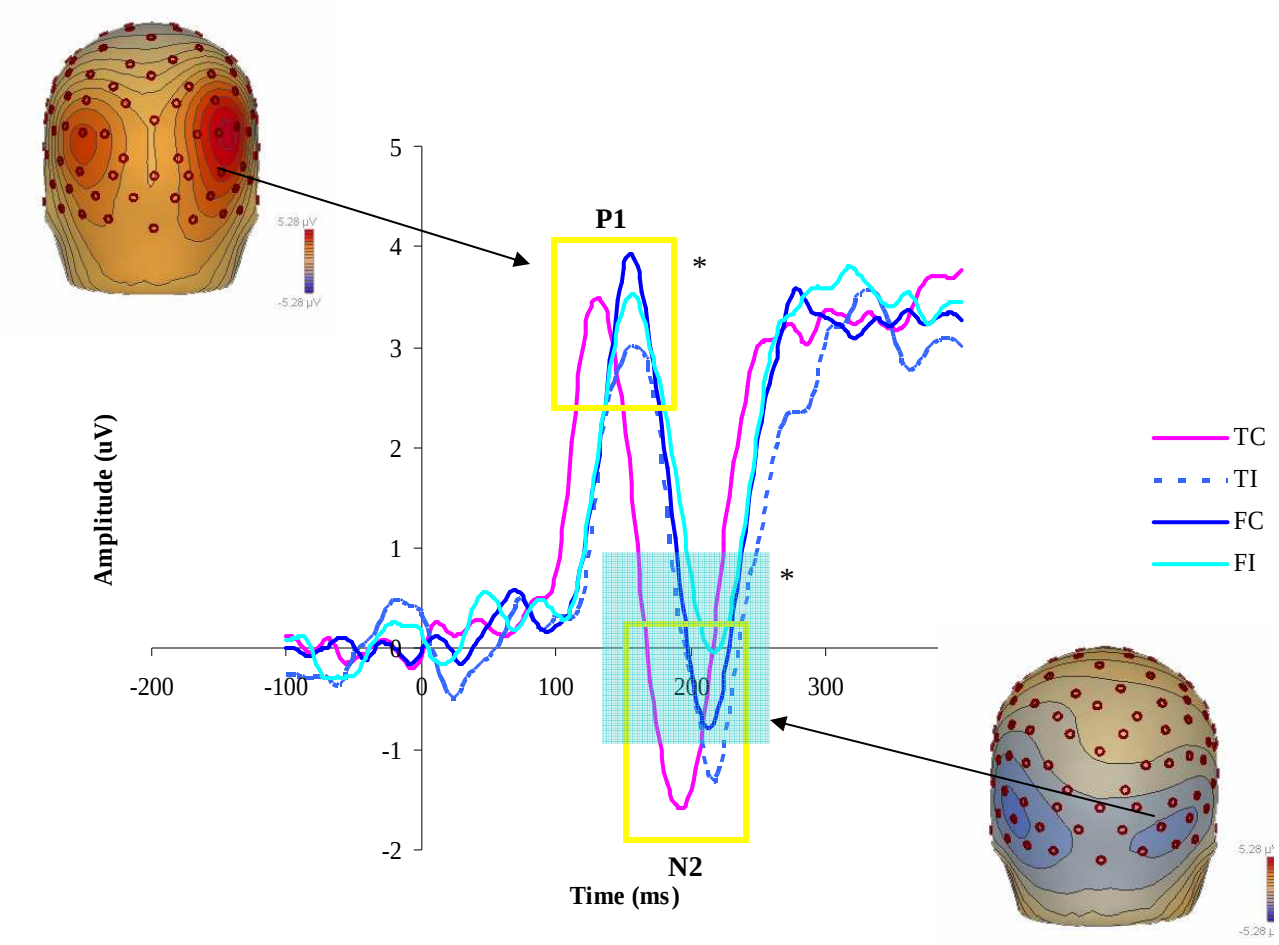


Figure 4.6: ERP waveforms across test conditions at electrode P4 showing P1 and N2 components, together with clear latency differences. Topographical map for P1 component shown in top left of figure (posterior view). Topographical map for N2 component shown in bottom right of figure (posterior view). Yellow boxes depict significant latency differences. Only Bonferroni-corrected *p*-values are shown. Shaded turquoise area represents significant N2 component differences between true-congruent and false-congruent/false-incongruent test conditions

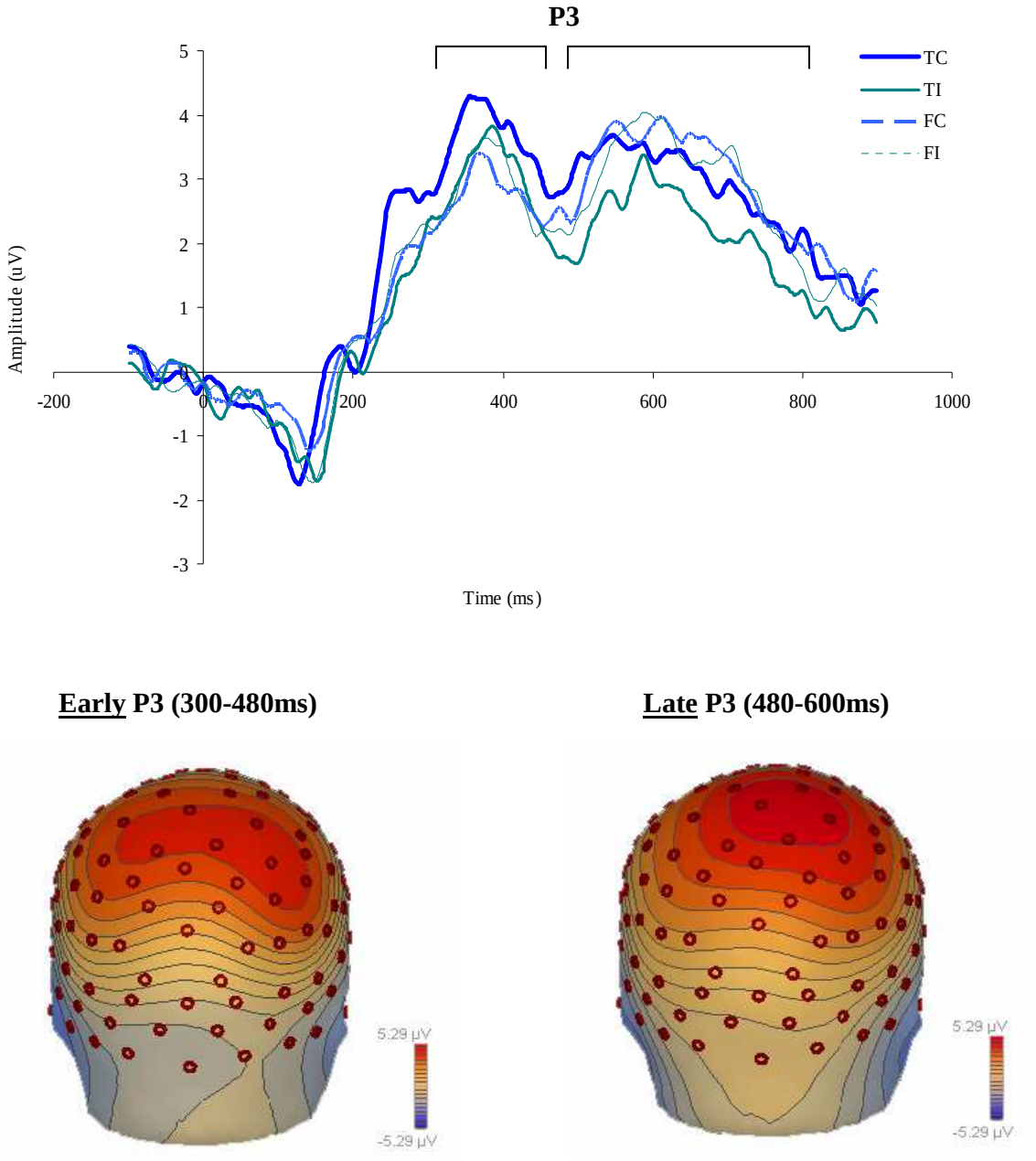


Figure 4.7: **(a)** *Top*: ERP waveforms across test conditions at electrode CPz showing a large P3 component, together with clear latency differences. An early P3 was analyzed from 300-480ms and a late P3 component was analyzed from 480-800ms. **(b)** *Bottom*: Topographical comparison of early (300-480ms) and late (480-800ms) aspects of the P3 component (posterior view).

P100 AUC: A 2x2 repeated measures ANOVA was conducted to compare AUC for the P100 component (100-200ms; see Table 4.6 above) for stimulus type (2 levels: true and false-pairs) and context (2 levels: congruent and incongruent context). Results revealed a

non-significant difference at the $p<0.05$ level, between the four test conditions. Thus, there was no significant main effect obtained for stimulus type (Wilks' Lambda= .950, F(1,19)= 1.006, p=.328, η_p^2 =.050), or context (Wilks' Lambda= .962, F(1,19)= .746, p= .398, η_p^2 =.038). The interaction effect was also non-significant at the $p>0.05$ level (Wilks' Lambda= .976, F(1,19)= .471, p=.501, η_p^2 =.024).

P100 Latency: The same 2x2 repeated measure ANOVA was carried out to ascertain latency differences in the P100 component across test condition. There was a statistically significant main effect for stimulus type (Wilks' Lambda= .232, F(1,19)= 62.996, $p<0.005$, η_p^2 =.768), together with a significant main effect for context (Wilks' Lambda= .407, F(1,19)= 27.731, $p<0.004$. η_p^2 =.593). An interaction effect was also observed at the $p<0.05$ level (Wilks' Lambda= .459, F(1,19)= 22.352, $p<0.005$, η_p^2 =.541). Figure 4.6 shows that each of the four conditions peaked at approximately 100ms; however, the true-congruent condition peaked first, followed by the false-congruent condition, and the false-incongruent condition peaked slightly later. A longer latency was evident for the incongruent conditions as opposed to the congruent conditions. This effect was more pronounced for true-pairs than false-pairs. Paired samples t-tests were subsequently conducted to ascertain differences between conditions, revealing that the true-congruent condition (132.40±11.67) peaked approximately 25 ms earlier than the false-congruent condition (157.10±15.70; $t(19)$= -8.617, $p<0.005$: Bonferroni-corrected, p=0.03), approximately 30ms earlier than the true-incongruent condition (160.20±17.10; $t(19)$= -8.185, $p<0.005$: Bonferroni-corrected, p=0.03) and approximately 30ms earlier than the false-incongruent condition (161.30±16.21; $t(19)$= -8.406, $p<0.005$: Bonferroni-corrected, p=0.03). Therefore, for the true-congruent condition, local context appears to affect the P100 latency, with the true-congruent condition peaking significantly prior to *all* other conditions.

N200 AUC: Subsequently, the N200 component (150-250ms) was analyzed across all test conditions. A 2x2 repeated measures ANOVA was conducted to compare area under the curve for this N200 component for stimulus type (2 levels: true and false-pairs) and context (2 levels: congruent and incongruent context). Results revealed a non-significant difference at the $p<0.05$ level, between the four test conditions. Thus, there was no significant main effect obtained for stimulus type (Wilks' Lambda= .850, F(1,19)= 3.354, p=.083, η_p^2 =.150), or context (Wilks' Lambda= .993, F(1,19)= .137, p= .716, η_p^2 =.007). The interaction effect was also non-significant at the $p<0.05$ level (Wilks' Lambda= .981, F(1,19)= .365, p=.553, η_p^2 =.019).

N200 Latency: The same 2x2 repeated measure ANOVA was carried out to ascertain latency differences in the N200 component across test condition. A statistically significant interaction effect was found at the $p<0.05$ level (Wilks' Lambda= .807, F(1,19)= 4.557, p=.046, η_p^2 =.193). Further, a statistically significant main effect for stimulus type was also found (Wilks' Lambda= .604, F(1,19)= 12.443, p=.002, η_p^2 =.396). However, there was no main effect for context (Wilks' Lambda= .841, F(1,19)= 3.583, p= .074, η_p^2 =.159) at the $p>0.05$ level. To further investigate these effects, paired t-tests were conducted, which revealed that the true-congruent condition (191.90±17.04) occurred approximately 20ms faster than the false-congruent condition (214.20±13.48; $t(19)$= -5.875, $p<0.005$: Bonferroni-corrected, p=0.03), approximately 21ms faster than the false-incongruent condition (213.30±17.76; $t(19)$=-4.930, $p<0.005$: Bonferroni-corrected, p=0.03) and approximately 14ms quicker than the true-incongruent condition (206.30±20.87; $t(19)$= -2.417, p=.026). However, the difference between the true-congruent and true-incongruent conditions was found to be non-significant upon Bonferroni-adjustment at p=0.156). The aforementioned differences are highlighted in Figure 4.6 above.

P300 AUC: The P300 waveform was compared across the four test conditions at electrode CPz (see Figure 4.7) from 300-480ms and 480-800ms, respectively. A 2x2 repeated measures ANOVA was conducted to compare area under the curve for this P300 component for stimulus type (2 levels: true and false-pairs) and context (2 levels: congruent and incongruent context) from 300-480ms. Results revealed non-significant main effects for both stimulus type (Wilks' Lambda= .848, F(1,19)= 3.416, p=.080, η_p^2 =.152) and context (Wilks' Lambda= .944, F(1,19)= 1.128, p=.301, η_p^2 =.056), and no interaction effect was found (Wilks' Lambda= .958, F(1,19)= .833, p=.373, η_p^2 =.042). Comparing AUC differences from 480-800ms (Figure 4.7), results revealed a significant main effect for context (Wilks' Lambda= .669, F(1,19)= 9.385, p=.006, η_p^2 =.331). However, no significant main effect was found for stimulus type (Wilks' Lambda= .894, F(1,19)= .2.242, p= .151, η_p^2 =.106), and no interaction effect was ascertained (Wilks' Lambda= .928, F(1,19)= 1.465, p=.241, η_p^2 =.072). Paired samples t-tests were conducted to assess these context effects, finding that the true-congruent condition (960.79±528.20) showed a significantly greater amplitude than the true-incongruent condition (748.71±438.09; t(19)=2.275, p=.035); and the true-incongruent condition (748.71±438.09) showed a significantly lower amplitude than that obtained in the false-congruent condition (1004.94±486.56; t(19)= -2.333, p=.031). However, Bonferroni-adjustments revealed that these differences were non-significant at p=0.21 and p=0.19, respectively.

P300 Latency: The same 2x2 repeated measure ANOVA was carried out to ascertain latency differences in the P300 component from 300-480ms. Results revealed non-significant effects for both context and interaction; however the main effect for stimulus type *approached* significance (Wilks' Lambda=.823, F(1,19)= 4.096, p=.057, η_p^2 =.177). In terms of the later latency (480-800ms), results revealed that the effects of stimulus type (Wilks'

Lambda=.948, F(1,19)= 1.042, p=.320, η_p^2 =.052) and context (Wilks' Lambda=.872, F(1,19)= 2.796, p= .111, η_p^2 =.128) were both non-significant at the p<0.05 level. The interaction effect was also non-significant (Wilks' Lambda=.992, F(1,19)= .162, p=.692, η_p^2 =.008). Paired samples t-tests, however, revealed that the true-congruent condition (603.30±75.52) peaked approximately 31ms faster than the false-incongruent condition (634.30±63.54; t(19)= -2.129, p=.047). However, such a difference is likely due to artifact given the aforementioned non-significant findings.

4.3.3 Dipole Source Analysis

Dipole analyses using BESA (Scherg, 1990; Scherg & Picton, 1991; see Chapter 2) were conducted on the grand-average ERPs to calculate spatial-temporal models for the structures involved in the generation of the observed surface potential distributions.

In order to examine neural generators of scalp potentials for the aforementioned data, components of interest isolated during the four test conditions were subjected to BESA dipole source analysis. The Residual Variance (RV) was <10% in most cases. Where this level of fit was not reached the models still retained a goodness-of-fit >80%, thereby indicating that the dipoles ascertained explain more than 80% of the electrical patterns recorded from the scalp

The dipole models generated to account for the patterns of data recorded in each of the test conditions are presented below in Table 4.2 for the P1 component, Table 4.3 for the N2 component and Table 4.4 for the P3 component. All Tables are superimposed with corresponding transverse MRI slices for anatomical reference. The P1 dipoles were reliably localised near the right middle temporal gyrus across *all* test conditions. The incongruent conditions both contained dipoles near the right frontal lobe and right parietally in the

precuneus. Similar dipoles were further found near the left cingulate gyrus for both congruent conditions. Dipoles were found near the left middle occipital gyrus for the true-congruent condition *only*, whereas a dipole was localised near the right fusiform gyrus for the false-congruent condition *only*. The N2 dipoles were reliably localised bilaterally in the occipital lobe, in the right middle temporal gyrus for the true-incongruent condition and in the left middle temporal gyrus for false conditions, as well as bilaterally in the medial frontal gyrus. Dipoles were localised in the left cingulate gyrus and right superior temporal gyrus for the true-congruent condition *only*. The P3 dipoles were reliably localised in the bilaterally middle temporal gyrus for all conditions except the false-incongruent condition, which showed dipoles bilaterally near the superior temporal gyrus. The same region bilaterally near the cuneus in the occipital lobe was isolated for all conditions, once again with the exception of the false-congruent condition. Specific only to the false-congruent condition, dipoles were localised in the right anterior cingulate gyrus.

Table 4.2: Dipoles generated for the P1 component from 100-200ms across all test conditions together with corresponding MRI slices showing each dipole anatomically.

Component; Epoch	Condition; Channel; RV	Dipole	TAL co-ordinates; x, y, z	BA	Structure
P100; 100-200ms	True-Congruent; 5.270%	1 2 3 4	-25.8, -93.8, 9.4 -6.0, 27.7, 29.2 30.5, -53.9, -18.4 39.6, -71.7, 27.1	18 32 - 39	L. Middle Occipital Gyrus L. Cingulate Gyrus R. Anterior Lobe; Culmen R. Middle Temporal Gyrus
	True-Inongruent;; 5.941%	1 2 3 4	39.7, -64.3, 21.2 -39.7, -64.3, 21.2 20.9, -78.6, 39.4 28.9, 35.7, -1.6	39 39 19 47	R. Middle Temporal Gyrus L. Middle Temporal Gyrus R. Parietal Lobe; Precuneus R. Inferior Frontal Gyrus
	False-Congruent; 5.401%	1 2 3 4	37.9, -75.8, 20.2 -37.9, -75.8, 20.2 41.2, -48.6, -7.3 -8.5, 32.2, 22.4	19 19 37 32	R. Middle Temporal Gyrus L. Middle Temporal Gyrus R. Fusiform Gyrus L. Anterior Cingulate
	False-Incongruent; 4.852%	1 2 3 4	38.7, -71.9, 18.4 -38.7, -71.9, 18.4 24.7, -68.1, 32.4 32.8, 51.7, -0.2	39 39 7 10	R. Middle Temporal Gyrus L. Middle Temporal Gyrus R. Parietal Lobe/Precuneus R. Middle Frontal Gyrus

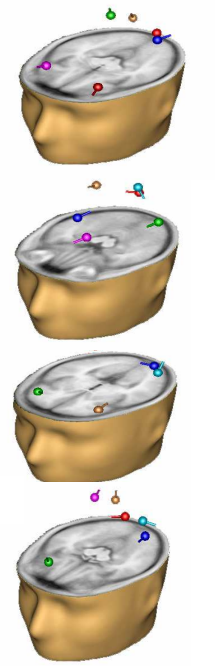


Table 4.3: Dipoles generated for the N2 component from 150-250ms across all test conditions.

Component; Epoch	Condition; Channel; RV	Dipole	TAL co-ordinates; x, y, z	BA	Structure
N200 (150-250ms)	True-Congruent; 8.517%	1 2 3 4 5	-5.3, -19.9, 41.9 23.7, -94.3, 12.1 -26.2, -96.4, 11.3 50.1, -53.7, 7.8 -27.0, 40.8, 0.7	24 18 18 39 -	L. Cingulate Gyrus R. Middle Occipital Gyrus L. Middle Occipital Gyrus R. Superior Temporal Gyrus -
	True-Incongruent; 8.354%	1 2 3 4 5	28.6, -99.6, 12.1 -28.6, -99.6, 12.1 49.5, -47.8, 0.9 -8.3, 26.3, 35.7 -64.6, -33.9, -2.2	18 18 22 6 21	R. Middle Occipital Gyrus L. Middle Occipital Gyrus R. Middle Temporal Gyrus L. Medial Frontal Gyrus L. Middle Temporal Gyrus
	False-Congruent; 10.391%	1 2 3 4 5	45.4, -59.4, 10.3 -45.4, -59.4, 10.3 -22.7, -88.6, -1.9 0.5, 37.3, 32.4 -55.6, 0.4, -14.6	39 39 17 9 21	R. Middle Temporal Gyrus L. Middle Temporal Gyrus L. Occipital Lobe/Lingual Gyı L. Medial Frontal Gyrus L. Middle Temporal Gyrus
	False-Incongruent; 14.730%	1 2 3 4 5	56.5, -47.5, -6.1 -56.5, -47.5, -6.1 3.2, 27.5, 37.4 29.8, -94.8, 14.9 -1.2, 34.2, 40.7	37 37 8 19 8	R. Middle Temporal Gyrus L. Middle Temporal Gyrus R. Medial Frontal Gyrus R. Middle Occipital Gyrus L. Medial Frontal Gyrus

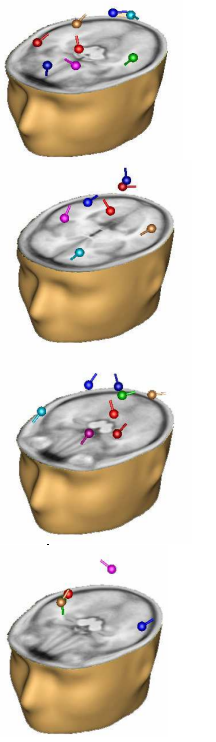
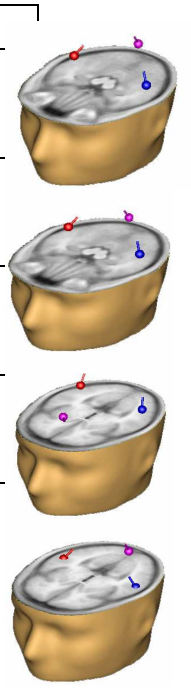


Table 4.4: Dipoles generated for the P3 component from 480-800ms across all test conditions.

Component; Epoch	**Condition; Channel; RV**	**Dipole**	**TAL co-ordinates; x, y, z**	**BA**	**Structure**
P300; 300-480ms	True-Congruent; 4.837%	1 2 3	53.8, -33.2, -3.3 -53.8, -33.2, -3.3 0.7, -84.1, 10.0	21 21 17	R. Middle Temporal Gyrus L. Middle Temporal Gyrus L. Occipital Lobe/Cuneus
	True-Incongruent;; 4.817%	1 2 3	52.4, -36.5, -2.4 -52.4, -36.5, -2.4 2.2, -82.7, 9.4	- - 17	R. Middle Temporal Gyrus L. Middle Temporal Gyrus R. Occipital Lobe/ Cuneus
	False-Congruent; 7.386%	1 2 3	48.8, -51.2, 10.9 -48.8, -51.2, 10.9 7.9, 30.2, 14.8	39 39 24	R. Superior Temporal Gyrus L. Superior Temporal Gyrus R. Anterior Cingulate Gyrus
	False-Incongruent; 5.190%	1 2 3	55.9, -34.1, -1.5 -55.9, -34.1, -1.5 -1.6, -86.2, 7.9	- - 17	R. Middle Temporal Gyrus L. Middle Temporal Gyrus L. Occipital Lobe/Cuneus



4.4 Discussion

The aim of this experiment was to utilize high-density ERPs in order to examine the processing components and corresponding source dipoles involved in an implicit local context memory test. Behavioural data revealed higher mean percentage accuracy for the false-pairs (similar to Chapter 3), more specifically in the false-incongruent condition than any other condition, with the lowest percentage accuracy evident in the true-incongruent condition. Reaction time data showed no significant differences between conditions thereby ruling out the possibility of a speed – accuracy trade-off. Concerning the electrophysiological data, there were significant amplitude differences between the study and probe conditions, with the study condition showing higher amplitude than that obtained for the false-congruent, true-incongruent and false-incongruent conditions. Regarding the probe conditions, there were significant latency shifts for the N2 component, with the true-congruent response occurring quicker than true-incongruent and false-congruent conditions. Comparing the four test conditions revealed statistically significant latency differences for the P1-N2 complex occurring maximally over parietal electrodes, with the true-congruent condition peaking earlier than all other conditions for both the P1 and N2 components. For the P3 component, the main effect for context was significant from 480-800ms, in terms of AUC. The main effect for stimulus type approached significance from 300-480ms, in terms of latency. Results indicate that implicit local context (i.e., scene backgrounds) interacted to affect learning of visual pairs at a relatively early stage in the information-processing stream, and that such scenes were processed as a unitary percept rather than as a set of linked elements.

Behavioural Performance Measures: The behavioural part of this study compared the four test conditions for mean percentage accuracy and reaction time (RT) differences. One interesting finding from the behavioural analysis was the fact that true-pairs presented in a congruent background showed greater mean percentage accuracy than true-pairs presented in an incongruent context. The opposite was true of the false-pairs, such that those presented in an incongruent context showed a greater mean accuracy than those in a congruent context. This significant trend suggests that participants may have implicitly associated the local contextual backgrounds with each stimulus pair so that when a true-pair was presented at test superimposed upon an incongruent background, accuracy was forfeit. Conversely, presentation of a false-pair in front of an incongruent background may have enhanced participants' confidence that this pair is false. Thus, perhaps future studies in this area could clarify this prediction by taking account of participant confidence levels at test.

There was a statistically significant accuracy difference between the true-incongruent and false-incongruent conditions; the lowest mean percentage accuracy occurred in the true-incongruent condition, whereas the highest percentage accuracy occurred in the false-incongruent condition. Given that an interaction effect was found to be statistically significant, together with a statistically significant main effect for stimulus type and a non-significant main effect for context, it is possible that the accuracy differences between conditions occurred mainly as a consequence of the type of stimulus presented, as well as possible implicit context effects on memory.

In relation to the current results, it is imperative to consider the circumstances in which local context is most likely to affect memory performance. Firstly, this study employed a recognition test and according to certain researchers (e.g., Jacoby, 1983), such tests have strong cues available to aid judgement, without the need to make use of contextual cues. This suggests that a free recall test may have found more prominent local context

effects. Moreover, the present study did *not* explicitly instruct the participants to learn the contextual backgrounds. Previous studies have manipulated modality of presentation and found strong local context effects on implicit memory tests (Jacoby & Dallas, 1981; Kirsner Milech, & Standon, 1983; Roediger & Blaxton, 1987; Schacter & Graf, 1989). However, modality of presentation is an intra-item context, whereas the current study employed an extra-item context in that the landscape backgrounds were external to the learning of the stimulus pairs. Mori and Graf (1996) report findings suggesting that extra-item (i.e., local) context will only exert an effect if the context gives some extra meaning to the target. In the current study, the relationship between the backgrounds and the pairs was arbitrary. In any case, the data warrant additional comparative studies taking the above considerations into account.

Event-related potentials and sources: The ERP data provided three comparisons of interest; firstly, the study versus probe-congruent waveforms was assessed for amplitude differences; this was followed by a comparison of the probe-congruent and probe-incongruent conditions. Finally, and most importantly, the four test condition waveforms were assessed for amplitude and latency differences.

Study versus probe-congruent conditions: It was decided that comparison of the study and probe-congruent conditions would be worthy of discussion, since the former involved the learning of stimulus-stimulus associations presented in front of distinct contextual backgrounds, and the latter involved presentation of a single stimulus (i.e., probe) in front of its congruent contextual background. It is presumed that the probe-congruent condition provides an opportunity for pattern completion in advance of the presentation of the full stimulus (test phase). The waveforms for both conditions elicited an early P3 component, maximal over right parietal areas. The parietal P3 component (P3b) is possibly

an index of the attentional resources allocated to the tasks. Greater parietal positivity in the interval between 400–1,100 ms has been reported during study for words that were subsequently recognized compared to those unrecognized – the 'DM' effect (Sanquist *et al*., 1980).

Significantly larger P3 amplitude for the study condition was found when compared with the false-congruent condition, together with both the true-incongruent and false-incongruent conditions. One interpretation of the P3 effect is that during the study phase there is more processing of relations between stimuli, as there are three visual elements: two geometric shapes on a landscape background. On the other hand, the probe condition has one less element to process. Furthermore, during the probe-congruent condition, the study phase has been completed and as a consequence there are less attentional resources being employed. According to the "context updating" hypothesis (Donchin, 1981), the P300 reflects the updating of working memory (i.e., updating one's representation of the current environment). However, researchers admit that such processes are sometimes not available to conscious awareness (Sommer *et al*., 1998; Donchin, & Coles, 1988). In terms of the current study, it is unlikely that all of the information contained in the study trials (i.e., stimulus pairs plus scenes) was available to conscious awareness and it could be argued that the local context was implicitly processed during the probe conditions, in order to influence subsequent responding. Such a possibility is supported by a recent finding by Lamy and colleagues (2009) that modulation of the amplitude of the P3 component of the ERP was widely spread across all scalp locations for subjective awareness, but was restricted to the parietal electrodes for unconscious perception. It is further possible, as found by Van Hoof (2005), that the greater P3 elicited during the study phase may index increased encoding intention over the probe conditions.

Probe-congruent versus probe-incongruent: Half of the probes were presented along with their associated contextual background (probe-congruent) and half were presented with a background incongruent to that of study (probe-incongruent). Regarding the P1-N2 complex (120-250ms), significant latency shifts were observed with the true-congruent probe condition peaking approximately 14ms earlier than the true-incongruent probe condition, and approximately 12ms earlier than the false-congruent probe condition. Given that the N2 is affected by cue validity (Mangun, 1995), it makes theoretical sense that the true-congruent condition peaked earlier than both the true-incongruent and false-congruent probes, given the similar cues provided. Thus, participants *expected* to see the cue provided by the true-congruent probe. The later onset of the other conditions may represent a deviation from a centrally maintained expectancy (Hoffman, 1990).

The main component however, identified during the probe conditions was the P3 (300-400 ms). There were no significant amplitude differences found between the probe-congruent and probe-incongruent conditions. Conversely, Hannula and colleagues (2006) found an amplitude increase in the P320 for faces seen in a reinstated context (match displays) compared to studied faces paired with a different context (re-pair displays) or novel displays. They postulate that this positive component is a relational memory effect which is sensitive to the greater processing occurring between the matched displays. This is consistent with Rugg and Donaldson's (1998) LPC - 'late positive component' whereby matched word pairs elicit greater parietal positivities than unmatched pairs. However, the current Experiment cannot be directly compared to that of Hannula *et al.* (2006). In that study, learning of face-scene relations was reinforced and the P320 relational effect was observed during the test phase. In light of this, it may be the case that the implicit local context in the current study will exert its effect during the successive test condition and given the brief presentation of the probe (i.e., 1 second), any effect of context is expected to be implicit.

Test conditions: For all test conditions a fast occurring positive followed by a negative peak was observed at electrode P4 (i.e., right parietal). This P1-N2 complex occurred at a latency of approximately 100-200 ms and 150-250 ms, respectively. This was followed by a large positivity approximately 300 ms after stimulus onset and continuing until approximately 600 ms (during *all* conditions). However, this component was more clearly identified at the mid-parietal electrode (CPz) compared to the right parietal electrode (Refer to Figures 4.6 & 4.7 for waveforms at electrode P4 and CPz, respectively).

P1-N2 complex: No significant amplitude differences between the four test conditions were found; however, with regard to the peak *latencies*, the four conditions diverged significantly. For the P1 component, there was a main effect for stimulus type, such that the true-pairs peaked significantly earlier than the false-pairs during the P1 component. There was also a main effect for context; that is, the congruent conditions peaked, on average, earlier than the incongruent conditions. This is a noteworthy finding for two reasons; firstly the difference is occurring very early after stimulus presentation (perhaps out of conscious awareness), and also, it implies an effect of local context on the latency of memory-related ERP components. It seems that the association of the context and stimulus pair occurs at a perceptual level, implicit and to some extent separate from later cognitive processing. The P1 for the true-congruent condition peaked at 132 ms, which was significantly earlier than the other three conditions. The false-congruent condition was the next to peak, followed by the true-incongruent and false-incongruent conditions. The last condition peaked nearly 30 ms later than the first.

The P1 is thought to be elicited by visual stimuli, and modulated by attention (Coull, 1998). This proposal fits well with the current study, as visual stimuli are presented some 100 ms prior to the positive peak. Such an early component is liable to involve neural generators in the visual areas of the occipital lobe. Consistent with this view, source dipoles for the test

conditions were found near the middle occipital gyrus (BA 18) for a latency of approximately 100-200ms. However, this dipole was localized in the true-congruent condition only. Dipoles were also located near bilateral temporal, right parietal, right frontal and left limbic lobes. Therefore, it is suggested that other processes, besides visual perception alone, were taking place during this P1 component.

A P1 component may reflect automatic, as opposed to controlled, processing. The possibility that priming paradigms elicit P1 components was suggested by Zhang *et al*. (1997), who found larger P1 amplitude to primed, as opposed to unprimed visual stimuli. A priming effect may account for the different P1 latencies observed in this study. Tsivilis and colleagues (2001) also found early occurring differences which, according to them, were due to the repetition of objects with their same context (landscape scenes) compared to those with new contexts. They reported findings from Brown and Xiang (1998) who recorded neurons in the anterior temporal cortex of the monkey that are sensitive to the repetition of complex visual stimuli, with the onset of such effects being less than 100 ms.

As already reviewed, the occipital lobe could only explain some of the P1 scalp distribution during the true-congruent test condition. The incongruent test conditions both contained dipoles near the right frontal lobe (true-incongruent; BA 10: false-incongruent; BA 47). Similar dipoles were also located bilaterally in the middle temporal lobes across test conditions (BA 39 & 19), right parietally near the precuneus for true-*in*congruent (BA 19) and false-*in*congruent (BA 7) conditions, and near the left cingulate gyrus for true-congruent and false-congruent conditions (BA 32). The right prefrontal cortex and superior parietal cortices have been consistently activated during memory retrieval studies (Fletcher *et al*., 1998). Furthermore, the frontal lobe has been shown to be important when "top - down" processing is needed (Miller & Cohen, 2001). The involvement of the parietal lobe at this early stage may reflect activation of the dorsal ("*where"*) visual stream. This pathway begins

at visual striate area (V1), through middle temporal and superior temporal, to the posterior parietal cortex (Desimone & Duncan, 1995). PET scans reveal the importance of the precuneus in spatial memory (Suchan *et al.*, 2002). It can be argued that spatial memory and memory for context are similar in some respects, given they both facilitate episodic memory recall (Tulving, 1983). Further, the anterior cingulate cortex is connected with the prefrontal cortex and parietal cortex as well as the motor system and the frontal eye fields, thereby rendering it a an integral region for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain.

The N2 element of the P1-N2 complex may reflect discrimination and classification (Coull, 1998). No statistically significant main or interaction effects of AUC for stimulus type or context were found across test conditions. However, as with the P1, a statistically significant interaction effect between stimulus type and context, together with a main effect for stimulus type, were found for N2 latency. However, there was no main effect for context. Collectively, these latency effects suggest that the local context of each stimulus pair presented during the study phase may have been encoded, such that a congruent or incongruent context at test affected the timing of cognitive processing. The latency differences during the test phase occurred only 190 ms after stimulus onset and so are likely to be relatively automatic and possibly implicit. Furthermore, the true-congruent condition peaked significantly earlier than all other conditions, insinuating that participants were both conscious of, and remembered, the previously presented true-pairs quicker than the other non-target conditions, during this component. Given the non-significant main effect for context, it is possible that the implicit context effects did not exert an effect during this period.

P300 component: A P300 component was identified in a latency window of 300-600 ms for *all* four test conditions, maximal over midline parietal areas (CPz; see Figure 4.7).

However, both early (300-480ms; P3a) and late (480-800ms; P3b) latencies for this component were assessed. Inferential statistics revealed no significant main effect for stimulus type or context, nor an interaction effect, with respect to amplitude differences for the earlier latency. However, in terms of the later latency, a significant main effect for context was identified. Prior to Bonferroni-correction, the true-congruent condition showed significantly greater amplitude than the true-incongruent condition, which in turn showed significantly lower amplitude than that obtained in the false-congruent condition. Thus, higher amplitudes were obtained across both congruent conditions when compared to the true-incongruent condition. Non-significant effects were found in terms of peak latency; however the main effect for stimulus type approached significance during the earlier latency (i.e., P3a). Regarding the later latency (i.e., P3b), the true-congruent condition peaked approximately 31ms faster than the false-incongruent condition. However, such a difference is likely due to artifact given the aforementioned non-significant findings.

The classic P3 identified in the literature is maximal over central-parietal midline electrodes (Nieuwenhuis, Aston-Jones & Cohen, 2005). The current study is in agreement with such findings, as the P3 was maximal at electrode CPz. The P3 amplitude is thought to be influenced by the probability of stimulus events and expectations about proceeding stimuli based on recently learned associations (Johnson, 1993). The finding of significantly higher amplitudes across both congruent conditions when compared to the true-incongruent condition for the later latency (i.e., P3b), is certainly in line with such findings. Further, the significant main effect found for context in terms of the later latency suggests that local context was exerting an effect at this juncture. It is well documented that the MTL structures predominantly generate the P3 component in both human (McCarthy *et al*., 1989; Smith *et al*., 1990) and animal studies (Paller *et al*., 1992). The present study reports dipole solutions for the P3b (480-800 ms) during the true-congruent, true-incongruent and false-congruent

conditions (see Table 4.4). Both 'true' conditions generated a three-dipole solution which explained over 95% of the variance in electrical activity for this time range. Similar dipoles were found near the left and right temporal lobes near the middle temporal gyrus (BA 21) and bilaterally near the cuneus of the occipital lobe (BA 17). The false-congruent condition generated a three-dipole solution which explained over 90% of the variance for this time range. Similar to the 'true' conditions, dipoles were located bilaterally near the temporal lobe. However, instead of the middle temporal gyrus, the superior temporal gyrus was localized. Further, the right limbic lobe, and more specifically, the anterior cingulate gyrus was also localized.

A dipole in the superior temporal gyrus (STG) is compatible with MRI research demonstrating a major role for STG sources in P300 generation (McCarley *et al*., 1993). The anterior cingulate cortex seems to be involved particularly when effort is required to carry out a task such as in early learning and problem solving (Allman *et al*., 2001), which makes sense in terms of the present findings wherein the false congruent condition elicited activation in this region. Thus, participants may be attempting to reconcile the false-pairs with the congruent local context. Interestingly, this region is associated with many functions that require *conscious* experience by the viewer. For example, higher anterior cingulate cortex activation levels were found for more emotionally aware female participants when shown short 'emotional' video clips (Lane *et al*., 1998). Better emotional awareness is associated with improved recognition of emotional cues or targets which is reflected by anterior cingluate activation. Taken together, the dipoles reflect bilateral temporal lobe activation, which is known to be involved in episodic memory processes and relational context binding (Fujii *et al*., 2000). This possibility is supported by the finding of a significant main effect for context regarding amplitude differences in the later P3 latency reported in the current study.

Furthermore, this finding is supported by previous ERP research on the Remember/Know and Old/New paradigms (Donaldson & Rugg, 1998). For example, Tsivilis and colleagues (2001) found greater parietal positivity, 300-500 ms post stimulus, when item-context pairings were maintained between study and test. They attributed this parietal effect to the greater contextual support each member of an intact pair gave each other. The finding of greater amplitudes in congruent conditions for the later latency period in the present study certainly provides support for such a contention.

Future research should consider comparing the current study with an original visual paired association task (i.e., without contextual backgrounds). In so doing, any processes involved in the implicit encoding of local context could be isolated. In addition, the introduction of new stimuli during the test phase on either a familiar or unfamiliar context would yield an interesting comparison. Waveform differences between these two conditions would suggest selective encoding of the contextual backgrounds. It may also be insightful to ask participants, after test completion, if they were influenced by the background scenes. If they reported ignoring the backgrounds, this would support the suggestion that local context can be implicitly encoded. Importantly, a potential confound inherent in the present task design should be addressed. That is, although the aim of incorporating a probe stimulus was to ascertain electrophysiologically whether the paired associates were encoded in an implicit manner with the context as a complete trace or whether each element was associated with disparate parts of the scene in a separate manner, it may be the case that at test the staggered presentation of the stimulus pairings (i.e., the presentation first of a single probe stimulus followed by the full pair) may have inadvertently yielded priming effects or commenced retrieval processes in advance of the presentation of the test-pair, thereby exerting significant implications for the performance and EEG data. Future studies should attempt to parse the behavioural and electrophysiological correlates of both employing a probe stimulus and

immediate presentation of the full pairs without exposure to a probe stimulus. Further, another potential task design limitation resides within the use of various permutations (i.e., true-incongruent, false-congruent, and false-incongruent) of false items not previously presented during the study block compared with only one permutation of true item (i.e., true-congruent) which was previously presented during the study block, thereby leading to substantially higher amounts of false as opposed to true items presented at test (i.e., 48 encoding items and 128 test items, most of them false) thereby potentially leading to substantial interference between items. It is suggested that future studies counterbalance true and false item pairings to a greater extent than conducted presently.

In conclusion, the waveform components generated for both the congruent and incongruent probe conditions differed significantly, and so it could be argued that local context failed to affect processing; however, only half of the stimulus pair was shown during the probe conditions, and it may well be the case that context will only have an effect on the full pair. Consistent with this proposal, context effects on the P1-N2 latency for the test conditions were evident. Results indicate a statistically significant latency shift between the test conditions demonstrating an effect of local context on the latency of memory related processing.

5

Chapter V

Behavioural and Electrophysiological differentiation of memory consolidation, reconsolidation and updating in human episodic memory

We wish to thank Orlaith Donnelly, Elizabeth Kehoe and Caroline Rawdon for assistance with data colleaction.

Abstract

Research has indicated that consolidation and reconsolidation employ similar mechanisms; both require protein synthesis and glutaminergic input, and both seem to be associated with the hippocampal formation. Despite this, other data argue that the two concepts are entirely separate and individual processes. Further, a number of contentious issues have been purported regarding the reconsolidation phenomenon. First, several studies assert that upon reactivation, an older memory trace does not become fragile to the same extent that a younger trace does, and that, over time, memory becomes increasingly insensitive to post-reactivation interference. Second, it has been suggested that although the process of retrieving a memory is necessary for linking new information with reactivated memories, the retrieval-induced reconsolidation process is not engaged in linking the new information with the reactivated memory. Here we report two experiments aimed at addressing these issues. A task was devised specifically to compare reconsolidation of an existing memory trace and the new consolidation of additional updated information. 128-channel EEG was recorded and source localisation was employed to identify neural generators associated with the paired-associate task. Experiment 1 compared the behavioural correlates (i.e., measures of recall and recognition memory) of consolidation- and reconsolidation-based processing of paired-associates, finding clear differentiation between both processes at both group and stimulus levels. Further, in accordance with the retrieval view of reconsolidation, this study differentiated consolidation and reconsolidation by showing that the distinction between the two processes was more evident in the case of free recall as opposed to recognition. Experiment 2 compared the electrophysiological correlates and neural generators of remote and newly-consolidated memory traces with reconsolidated traces, investigated indices of memory updating, and addressed the contentious issue concerning variations in the age of

memory traces by manipulating time between memory reactivation and testing. Behaviourally, it was found that probing episodic memory within hours of reactivation of the original trace renders pre-consolidated memories labile once again, as suggested by the reconsolidation hypothesis. Conversely, updating the memory or probing memory 24 hours following reactivation affects these newly-consolidated traces, as opposed to old/remote traces. Electrophysiologically, frontal and fronto-parietal modulations were identified for reconsolidated compared to both old and new memories. Dipoles were located bilaterally in and around the medial frontal gyrus, the bilateral temporal poles, bilaterally near the tempero-parietal junction and left frontally. Overall, we conclude that the similarity of component morphologies, accompanied by ERP amplitude differences, may imply a quantitative rather than qualitative difference in the nature of reconsolidation compared to consolidation processes.

5.1 General Introduction

Consolidation theory posits that memories are labile only during a time limited period following encoding, but as time passes, memories are consolidated and become resistant to change (e.g., McGaugh, 2000). The discovery of reactivation-induced reconsolidation challenged this view (e.g., Przybyslawski & Sara 1997; Sara, 2000; Nader 2003). In contrast to the consolidation account, reactivation is hypothesized to return memories to a labile state, wherein they can be manipulated. The evidence in favour of the Consolidation Theory is widespread both on a cellular and systems level (see Moore & Roche, 2007). Research indicates that consolidation and reconsolidation of memory employ similar mechanisms; *both* require protein synthesis and glutaminergic input, and *both* seem to be associated with the hippocampal formation (e.g., Nader *et al*., 2000; Debiec *et al*., 2002). Despite this, other data argue that the two concepts are entirely *separate* and individual processes (e.g., Lee *et al*., 2004; see Chapter 1 and Moore & Roche, 2007 for a more comprehensive account of findings). Much research has been carried out in an effort to determine whether reconsolidation is merely a recapitulation of consolidation or actually a distinct entity. Reconsolidation has thus far been mainly demonstrated in animal models using UCS-CS preparations (Nader *et al*., 2000; Debiec *et al*., 2002). In humans, reconsolidation has been observed in procedural memory (Walker *et al*., 2003), implicit memory in infants (Galluccio, 2005; Gallucio & Rovee-Collier, 2005), and most recently, in episodic memory and declarative memory (e.g., Hupbach, Gomez, Hardt, & Nadel, 2007; Forcato *et al*., 2007; see Moore & Roche, 2007, for a review).

Most pertinent to current concerns however, in 2007, two laboratories reported reconsolidation of human memories related to facts and episodes that are accessible to *conscious* recollection (Hupbach *et al*., 2007; Forcato *et al*., 2007). Hupbach and colleagues

(2007) demonstrated the reconsolidation phenomenon in *episodic* memory in humans. University students learned a list of objects on Day 1. On Day 2, they either received a reminder or not, and then learned a second list. Memory for List 1 was tested immediately on Day 2 (Experiment 2) or on Day 3 (Experiment 1). Although the reminder did not moderate the number of items recalled from List 1 on either day, participants who received a reminder incorrectly intermixed items from the second list when recalling List 1 on Day 3. Experiment 2 showed that this effect did not occur immediately and was therefore not time-dependent. The reminder did not affect memory for List 2 on Day 3 (Experiment 3). As such, modification occurred only for the original memory (i.e., List 1). This study demonstrates the integral role of reminders in the modification of episodic memory, that reconsolidation of episodic memory is time-dependent, and, contrary to previous reconsolidation findings, that reconsolidation is also a constructive process which supports the integration of new information into a memory trace.

Forcato and colleagues (2007) found that *declarative memory* can undergo reconsolidation. These researchers studied paired-associate learning (i.e. an association between a cue stimulus and the respective response stimulus) in human participants. Over three consecutive days, participants were required to learn two different lists of verbal syllable pairs (L1 and L2) on which they were tested on Day 3. The consolidation condition involved presentation of L2 five minutes after presentation of L1 on Day 1 followed by testing on Day 3, while the reconsolidation condition involved a similar procedure, the only difference being presentation of L2 on Day 2, five minutes after presentation of a reminder for L1. The researchers found that declarative memory for L1 was impaired in both conditions thereby demonstrating an impairment of both consolidation and reconsolidation of the associative memories as a direct result of the experimental procedure. Coupled with the recent demonstration of reconsolidation of episodic memory (Hupbach *et al*., 2007), these

findings further support the universality of the phenomenon thereby broaden the scope of the reconsolidation hypothesis in human-based research.

Despite the challenge posed by the Reconsolidation Hypothesis, proponents of Consolidation Theory have defended their position, questioning whether reconsolidation is in fact a veracious phenomenon. Alternative explanations for the return of consolidated memories to a fragile state have been proposed such as contextual cueing effects, variations in the age and source of memory traces as well as the effects of various drugs. These possibilities and other commonly held reservations concerning reconsolidation such as inconsistencies in research findings have been discussed in depth by Moore and Roche (2007). A central issue within the consolidation-reconsolidation debate is whether these are similar or distinct memory processes. Much research has been dedicated to this issue with the general view that if in its resolution, reconsolidation can be established as a unique process independent of consolidation, such findings would definitively validate the existence of reconsolidation as a legitimate memory process (see Chapter 1 for animal research in this area).

Ultimately, the current set of studies attempted to differentiate between Consolidation and Reconsolidation at both a behavioral and electrophysiological level. A task was devised specifically to compare reconsolidation of an existing memory trace and the new consolidation of additional updated information. An initial study block involved the presentation of 16 visual paired-associates. In a subsequent study block, half of the study pairs were combined with an additional stimulus to form a triplet, while the other eight pairs were not associated with a supplementary stimulus. In a final test-block, presented 24 hours later, paired versus non-paired stimuli were presented for yes/no recognition. The presentation of the original pair (i.e., reconsolidated memory) was contrasted with

presentation of the 'new' associates with either element of the original pair (i.e., newly consolidated memory).

5.1.1 Experiment 1: Behavioural

Measures of recognition and recall, two relative functions of declarative memory (Haist, Shimamura & Squire, 1992), acted as the behavioral correlates of consolidation and reconsolidation. Given that many paired-associate studies predominantly test only recognition memory (e.g., Forcato *et al*., 2007) the current study included a recall task to widen the scope of the investigation. Consolidation and reconsolidation were facilitated primarily at a stimulus level. Adopting a similar procedure to Forcato and colleagues (see above), we presently attempted to facilitate consolidation and reconsolidation at a group level through manipulation of the combination between study and test-blocks presented.

Behaviourally, there were three general research predictions. Firstly, it was predicted that differential recognition performance would be observed during the test-block between Reconsolidation and Consolidation trials. In addition, differences in both recall and recognition performance were predicted between the Reconsolidation and Consolidation groups. Finally, according to the retrieval model of reconsolidation wherein the distinction between reconsolidation and consolidation can be understood in terms of retrieval differences (Riccio *et al*., 2006), it followed that such a distinction should be easier to observe in a recall rather than recognition memory task given recall relies more strongly upon retrieval (Haist *et al*., 1992). Therefore, it was predicted that there would be greater between-group differences observed in the recall investigation.

5.1.2 Experiment 2: Electrophysiological

Electrophysiologically, we were specifically concerned with comparing the electrophysiological correlates and neural generators of remote and newly consolidated memory traces with reconsolidated traces, as well as investigating indices of updating an existing memory trace. It was conjectured that by using an 'old/new' protocol, indices related to both semantic and episodic processes could be used to ascertain differences or indeed similarities between both old and newly consolidated memory traces with reconsolidated traces. To our knowledge, no study to date has employed this protocol to differentiate consolidation from reconsolidation-based processes.

5.2 Method

5.2.1 Design and Participants

The sample comprised 30 undergraduate and postgraduate students recruited throughout the NUI Maynooth campus; 4 males and 26 females, ranging in age from 18 to 54, with a mean age of 23.57 (±9.22). Prior to participation in the experiment, participants signed an informed consent previously approved by both NUI Maynooth departmental and university-based Ethics Boards (see Appendix 18) and were informed of their rights under the Freedom of Information Act. English was the primary language of all participants and all participants reported normal or corrected-to-normal vision. All participants were asked to complete a Cognitive Failures Questionnaire (see Chapter 2) as a gross index of memory function and thus control measure to screen for any noteworthy memory impairments. Each participant was randomly assigned to one of three experimental groups as follows: Reconsolidation Group (n=10), Consolidation Group (n=10) and Control Group (n=10).

The experimental design incorporated two separate mixed factorial investigations. The first investigation was concerned with *Recognition Performance*. This involved two Independent Variables; Group (Three levels: Reconsolidation, Consolidation and Control) and Test-block Trial Type (Four Levels: Old Consolidation, New Consolidation, Reconsolidation and Distractor) together with two Dependent Variables – Accuracy and Mean Reaction Times which were noted using E-prime Version 2.0 E-Run studio recording software during the final test-block.

The second investigation involved the Dependent Variable *Recall Performance* together with two Independent Variables – Group (Three Levels: Reconsolidation, Consolidation and Control) and Task Type (Two Levels: Study or Test Recall). Findings

from both investigations were compared to ascertain any differences between Recall and Recognition performance.

5.2.2 Stimuli

All stimuli were presented using the E-Prime E-Run graphical interface software on an Intel Pentium 4 Processor (3.00GHz CPU) and displayed on an LCD monitor measuring 14.5 x 10.5cm. The general experimental task, employed in both behavioural (i.e., Experiment 1) and electrophysiological (i.e., Experiment 2) experiments, consisted of visual paired-associates, which differed according to study block. The task was created using the E-Prime E-Studio experimental presentation program. The stimuli consisted of black and white 1024 x 768 pixel bitmap images which were presented as visual paired-associates. During study and test-blocks, each paired-associate was presented on screen for a duration of 3500ms followed by a 1000ms presentation of a fixation point (see Figure 5.1). Participants also used a pen and A4 paper to complete free recall tasks.

For Study Block 1, which participants were exposed to on Day 1, 16 stimulus pairs, comprising everyday verbalisable objects, were presented during 64 trials (see Figure 5.1). Study Block 1 incorporated 8 ‘to be reconsolidated’ stimulus pairs, as well as 8 ‘to be consolidated’ stimulus pairs, each presented during 32 trials. On the following day, participants were presented with Study Block 2 (see Figures 5.2 and 5.3), wherein probe stimuli were employed to reactivate the memory trace. These probe stimuli were either followed by the addition of another stimulus (i.e., to form a stimulus ‘triplet’; Figure 5.2) which updated the original memory trace (thereby eliciting reconsolidation-based processing) or no new stimulus which alternately elicited consolidation-based processing (Figure 5.3). The Test-block, which took place 24 hours after the second study block, presented participants with either ‘old’ previously encountered stimuli or ‘new’ distractor stimuli to

which participants were newly exposed (see Figure 5.4). Regarding the 'old' stimuli, participants were shown reconsolidated, remote old consolidated and recently consolidated stimulus pairs. 32 distractor stimuli were composed of stimulus pairings presented in a similar manner to 'old' stimulus pairings. For the test-block, participants were shown randomized 'old/new' pairings during 128 trials (see Figure 5.4).

5.2.3 Procedure

5.2.3.1 General Experimental Protocol

Study Block 1

During the first study block participants were required to memorize the stimulus pairings presented;

"During this stage of the Experiment, you will be shown 16 pairs of stimuli. Each pair will be presented several times. Look carefully at the stimuli that appear and try to remember which stimuli form a pair. Press the spacebar to begin"

The study block comprised 8 'to be consolidated' and 8 'to be reconsolidated' stimulus pairs, each of which comprised 32 trials. In total, the study block consisted of 64 trials. The temporal sequence of the study block is depicted below in Figure 5.1. A fixation cross remained onscreen for 1000ms which was followed by the study stimulus pair which remained onscreen for 3500ms. Stimulus pairs were presented in black on a white background. All stimulus pairings were presented in a sequential manner such that numerous presentations of the same pairings did not coincide and all participants were exposed to the same pairings in a similar manner. At the end of the study block, the following instructions appeared and remained onscreen for 4000ms;

"That concludes the first part of the Experiment. Please follow the instructions for the next part."

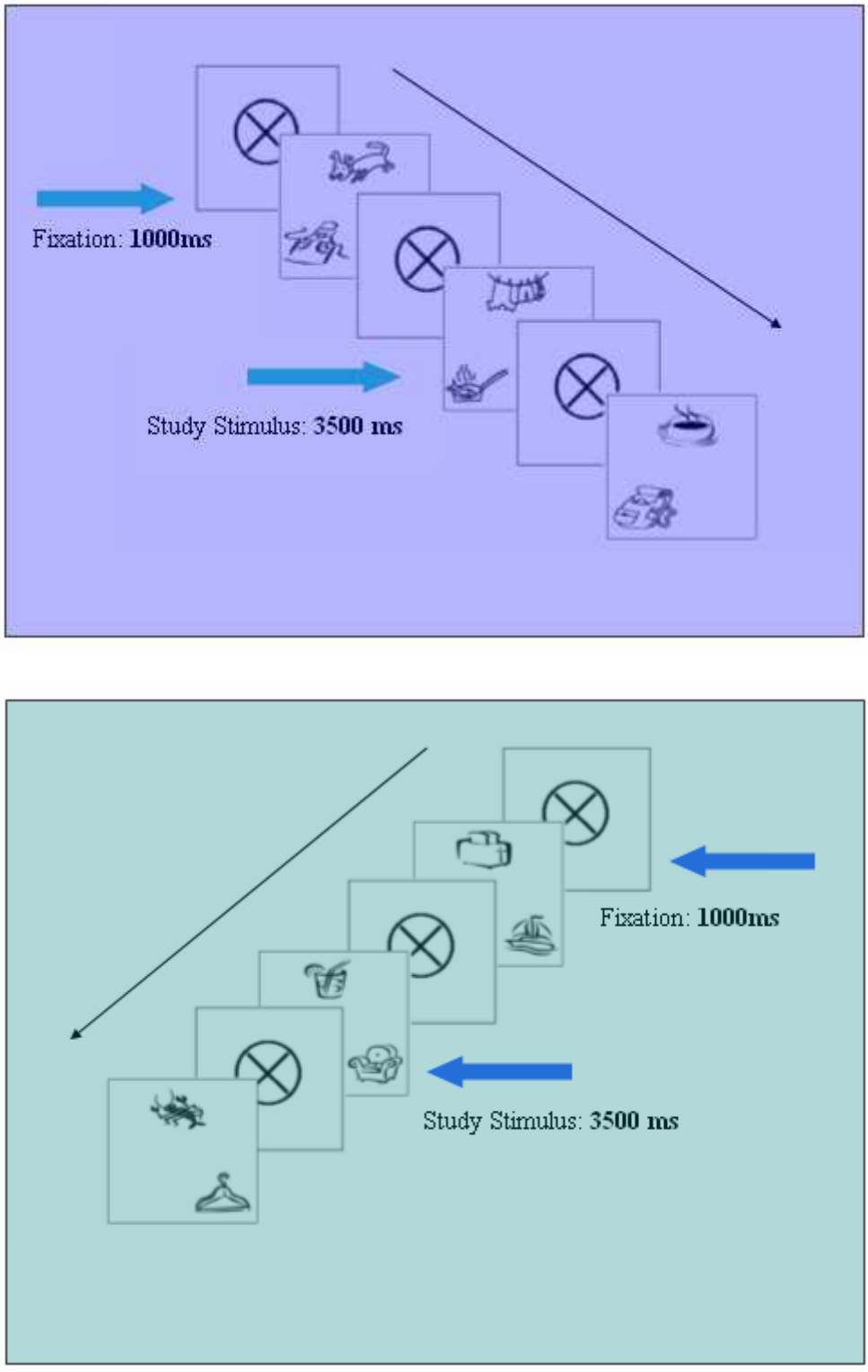


Figure 5.1: **Study Block 1**– "to be reconsolidated" (top purple shaded box; 8 stimulus pairs; 32 trials presented) and "to be consolidated" (bottom green shaded box; 8 stimulus pairs; 32 trials presented) stimulus pairs. 16 stimulus pairs; 64 trials presented during Study Block 1 in total.

Study Block 2

The second study block took place 24 hours following the first study block. During this study phase, 8 of the original pairs were presented again, first as a probe which acted to reactivate the memory trace for the stimulus pair, and subsequently with the addition of a third stimulus thereby rendering them 'triplets' (see Figure 5.2). The addition of a further stimulus acted to update the existing memory trace and elicit reconsolidation-based processing. The remaining 8 pairs were presented in their original state following the probe stimulus, in which no further updating of the stimulus pairing occurred. Participants were instructed as follows;

"In this part of the Experiment, you are going to see the same pairs of stimuli you studied yesterday. Sometimes when a pair appears, it will be followed by the addition of another stimulus, making the pair into a triplet. Sometimes, the pair will not have a new stimulus added. For both pairs and triplets, try to remember the stimuli that are presented together. Press the spacebar to begin"

The study block incorporated 64 trials; 32 of which were updated 'triplets' and 32 of which were 'to be consolidated' stimulus pairs. A fixation cross remained onscreen for 1000 ms, followed by the probe stimulus which remained onscreen for 3500 ms, and culminated with presentation of the stimulus pairing which remained onscreen for 3500 ms. This cycle was repeated for the 64 trials. Stimulus presentations were marked on the EEG recording for Experiment 2. Following stimulus presentation, the participants were informed that the study block was completed;

"That concludes this part of the Experiment. Now follow the instructions for the next part."

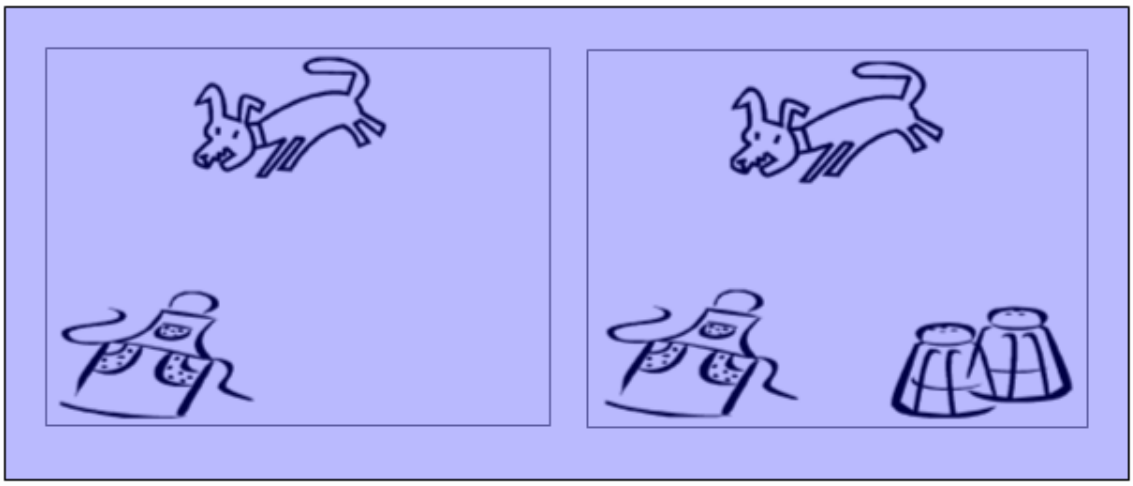


Figure 5.2: Study Block 2 updated stimuli- *Left:* Example of probe stimulus taken from the 'to be reconsolidated' stimuli previously presented to participants during Study Block 1 *Right:* Example of updated 'triplet' presented immediately after probe stimulus during Study Block 2.

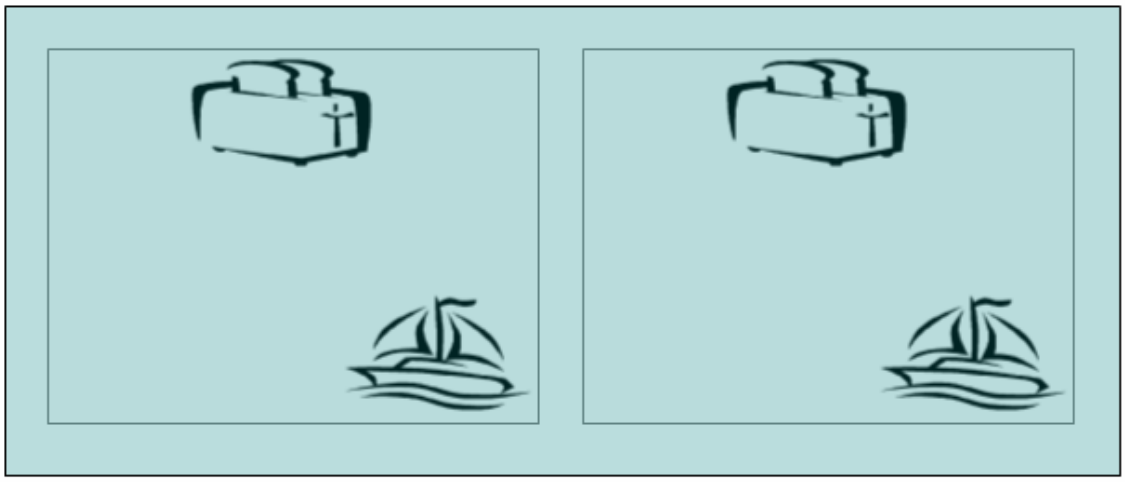


Figure 5.3: Study Block 2 non-updated stimuli- *Left:* Example of probe stimulus taken from the 'to be consolidated' stimuli previously presented to participants during Study Block 1 *Right:* Example of stimulus pairs presented in their original state with no further updating of the memory trace.

Test-block

Participants were presented with the Test-block either 1-2 hours (Experiment 2a) or 24 hours (Experiment 2b) after Study Block 2. The test-block was a recognition task which consisted of 128 pairs of stimuli (refer to Figure 5.4 overleaf). There were four different categories of stimulus pairings – old consolidated pairs (original pairs which had never become triplets), reconsolidated

pairs (original pairs presented during Study Block 1 which had become triplets during Study Block 2), newly consolidated pairs (one stimulus from an original pair paired with the associated triplet-creating stimulus) and novel distractor pairs. For each pair, participants were required to indicate whether or not they had seen it previously in any of the study blocks, using a button-press response. Participants were told to respond to previously studied or 'old' stimulus pairs that appeared during either of the two study blocks by pressing the left mouse button with their index finger. If a 'new' pair (i.e. not shown during either of the study phases) was presented, then the right mouse button should be pressed with their middle finger;

"In this part of the Experiment, you will see more pairs of stimuli. If the stimuli you see were paired together in any of the previous parts of the Experiment, press the LEFT mouse button with your index finger. If the stimuli have never been paired together, press the RIGHT mouse button with your middle finger. Press the spacebar to begin."

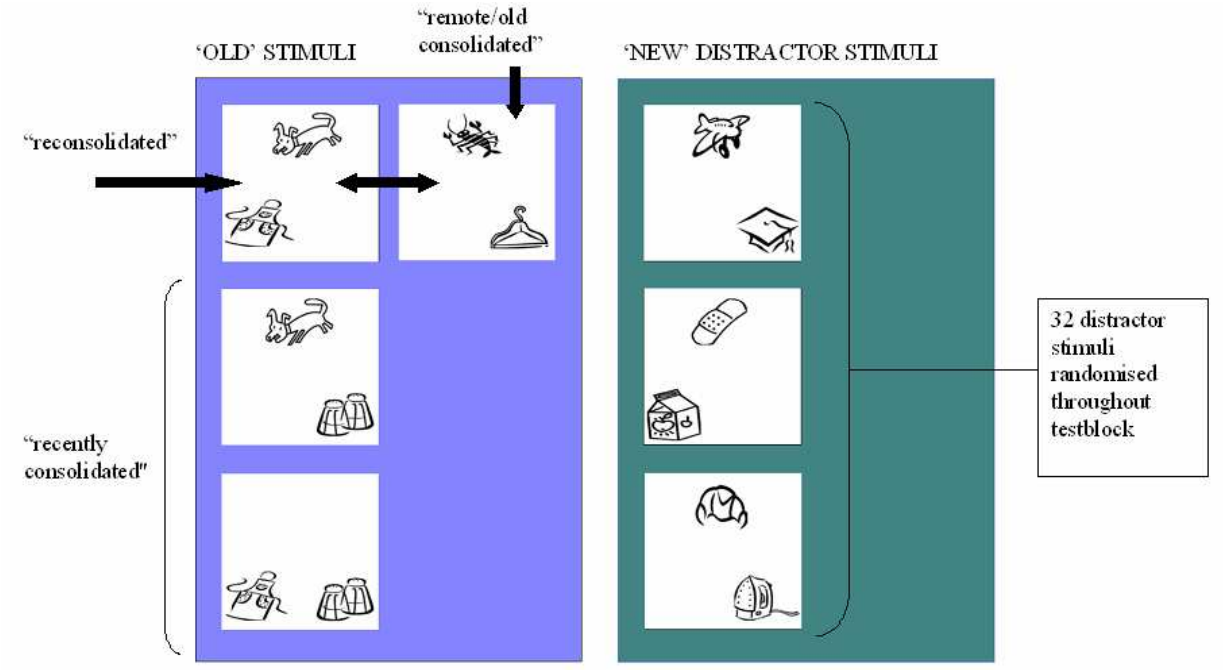


Figure 5.4: The test-block employed an old-new recognition paradigm. There were four different categories of stimulus pairings – old consolidated pairs (original pairs which had never become triplets), reconsolidated pairs (original pairs presented during Study Block 1 which had become triplets during Study Block 2), newly consolidated pairs (one stimulus from the original pair paired with the associated triplet-creating stimulus) and novel distractor pairs. For each pair, participants were required to indicate whether or not they had seen it previously in any of the study blocks, using a button-press response. They were required to press the LEFT mouse button if they had previously seen the stimulus pair presented and the RIGHT mouse button if they did not (128 trials).

Correct responses and reaction times were both recorded during the test phase of the experiment by E-prime. A correct response occurred if the participant pressed the left mouse button when an 'old' stimulus pair appeared and the right mouse button when a 'new' stimulus pair appeared. Pressing the opposite button than required or failure to respond resulted in an incorrect response. Reaction times were measured as the interval between presentation of the stimulus and the response, and were recorded for both correct and incorrect trials.

5.2.3.2 Experimental Protocol specific to Experiment 1

Participants completed one of the following combinations of tasks, depending upon the experimental group to which they were randomly assigned. Please refer to Figure 5.5 below for an overview of the experimental protocol employed across group. The free recall sheet employed by the Experimenter can be viewed in Appendix 21.

Group-specific procedures

Reconsolidation Group

Refer to Figure 5.5 for a comprehensive flow-chart detailing specific method across group (i.e., Consolidation, Reconsolidation and Control). On Day 1, participants in the Reconsolidation group were presented with Study Block 1. This consisted of 16 visual paired-associates which participants were asked to memorise. Eight of the stimulus pairs were to be reconsolidated (see Figure 5.1) while the remaining eight were to be consolidated (see Figure 5.1). There were 64 presentation trials with sequential selection of stimulus pairs.

Twenty-four hours later, participants returned and were first asked to perform a free recall task (i.e., study recall) wherein they were instructed to write down all the pairs that they could remember from Study Block 1. Immediately after this, they were presented with

Study Block 2. During this second study block, the “to be reconsolidated” pairs from Study Block 1 were presented again followed by the addition of a third stimulus (i.e., an update) making them into triplets (see Figure 5.2). The “to be consolidated” pairs were presented again in their original state (see Figure 5.3). Participants were required to memorise the pairs and triplets throughout this study block consisting of 64 trials in which stimulus pairs were selected sequentially.

Twenty-four hours hence, participants returned again and initially performed a second free recall task (i.e., test recall) where they were asked to note any pairs or triplets that they could remember from both study blocks. Immediately afterwards, they were presented with the test-block. The Test-block comprised 128 trials during which various stimulus pairs were presented onscreen. There were four different test-block trial types – 24 Remote/Old Consolidation trials (original pairs which had never become triplets), 24 Reconsolidation trials (original pairs from Study Block 1 which had become triplets in Study Block 2), 48 Recent/New Consolidation trials (one stimulus from the original pair paired with the associated update stimulus) and 32 Distractor trials (novel pairs) (see Figure 5.4). For each pair, participants were required to indicate whether or not they had seen it before in any of the study blocks, using a button-press response. They were required to press the left mouse button if they recognised the pair and the right mouse button if they did not.

Consolidation Group

On Day 1, participants in the Consolidation group were also presented with Study Block 1 (see Figure 5.1). Five minutes later, they were presented with the study recall task immediately followed by Study Block 2 (see Figures 5.2 and 5.3). Forty-eight hours later

they performed the Test Recall task and were then presented with the Test-block (see Figure 5.4).

Control Group

Participants assigned to the Control group were presented with Study Block 1 (see Figure 5.1) on Day 1. Forty-eight hours later, they were asked to perform the study recall task and were then immediately presented with the test-block (see Figure 5.4). These control participants were *never* exposed to either Study Block 2 or the test recall task. When their participation was complete, participants in all groups were thanked and given a full debriefing upon request.

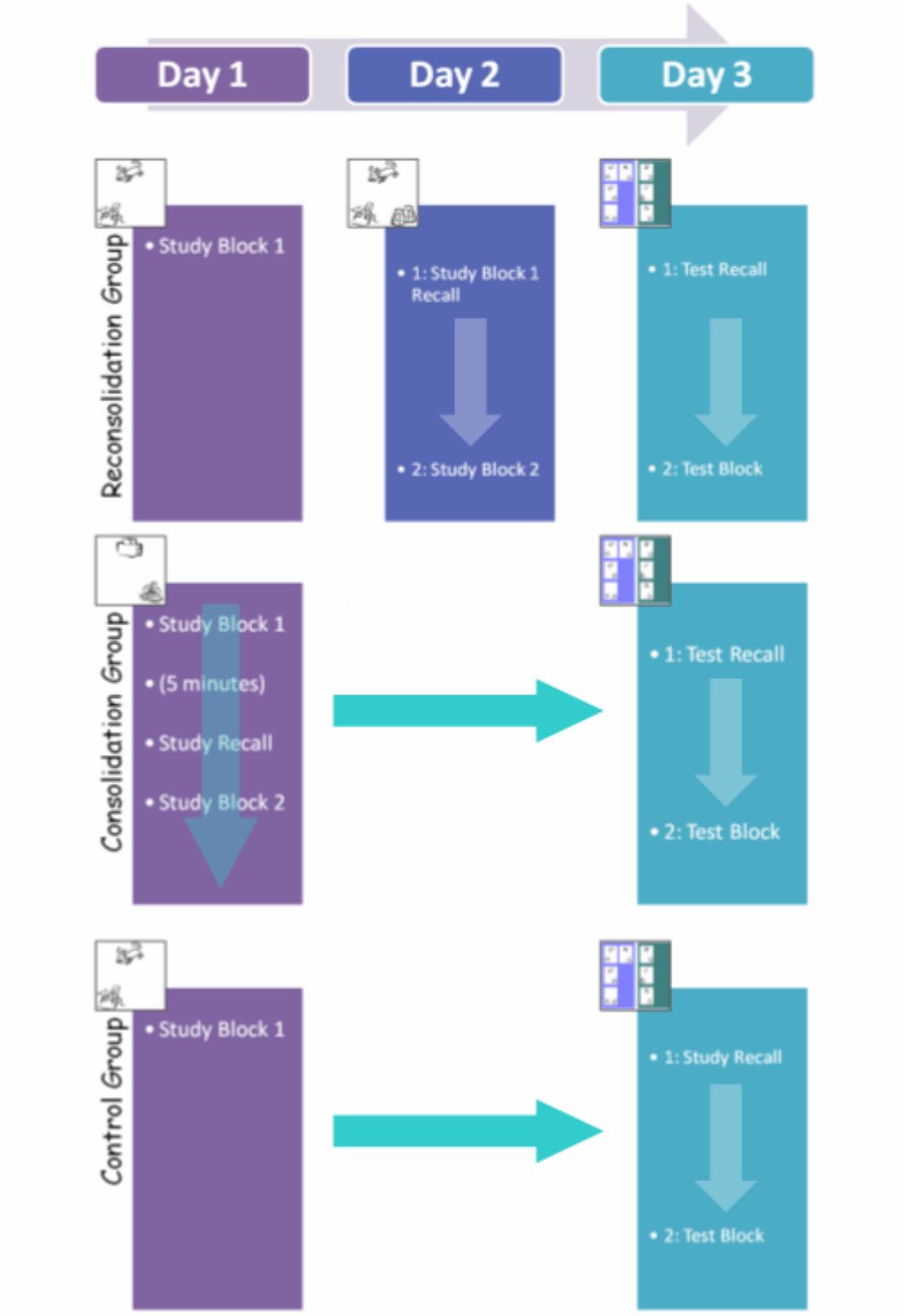


Figure 5.5: Flow chart depicting an overview of the Experimental protocol employed for Experiment 1.

5.2.4 Statistics

All statistical analysis of the collated data for Experiment 1 was conducted using the SPSS statistical package (Version 13 for Windows). Recognition performance was investigated across groups, as measured by response accuracy and reaction times (RTs) recorded during the test-block. Recall performance was also investigated across groups, as measured by scores obtained during the free recall tasks. A series of mixed factorial ANOVAs were conducted, with further Bonferroni-corrected paired samples t-tests where necessary. A star-based system for significance representing *p*-values of $p<0.05$ *, $p<0.01$ **, and $p<0.001$ ***, respectively, was employed throughout. The symbol ± was used throughout to represent standard deviation from the mean. Accuracy scores were presented in terms of percentage accuracy, while reaction times were presented in the order of milliseconds. Error bars show standard error of the mean, which is in turn denoted by 'SEM'.

5.3 Results

The data set was assessed for normality and none of the assumptions of analytical tests used were violated. The relationship between recurrent cognitive failures (as measured by the CFQ) and total accuracy was investigated using Pearson product-moment correlation coefficient. However, *no* statistically significant correlation was found [r= -.042, N=20, p= .859]. This infers that individual levels of cognitive failures did not affect either the Reconsolidation or Consolidation group participants' memory performance.

5.3.1 Recognition Performance

Recognition performance was investigated across groups as measured by response accuracy and RTs recorded during the test-block.

5.3.1.1 Accuracy

Initial analysis compared total accuracy scores for the Consolidation and Reconsolidation groups. While univariate analysis found no statistically significant differences [$F(1,18) = .689$, p=.417], a small difference between the two groups was found with slightly better performance in the Reconsolidation group (126.0±2.05) than in the Consolidation group (125.2±2.25; see Figure 5.6).

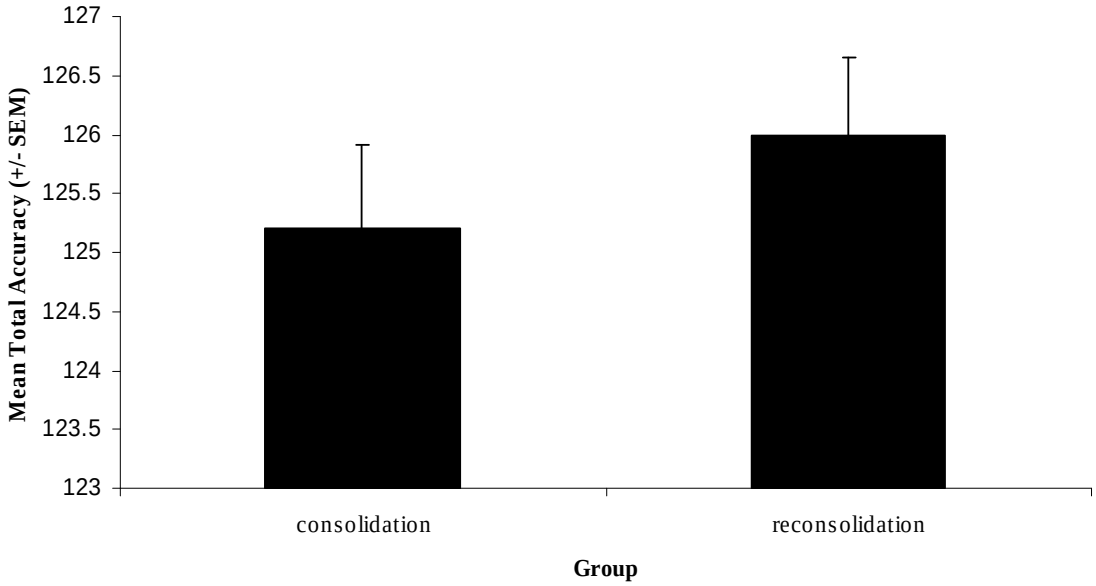


Figure 5.6: Mean Total Accuracy Scores across Reconsolidation and Consolidation Groups (Note: Error bars show standard error of the mean).

Individual accuracy across each trial type was also investigated. A mixed factorial AVOVA was initially conducted to ascertain the effects of Group (3 levels: Reconsolidation, Consolidation and Control) and Trial Type (4 levels: Old Consolidated, New Consolidated, Reconsolidated, and Distractor) on recognition accuracy (as measured by percentage of correct responses). While all three experimental groups were examined, only two trial types were included (i.e., Old Consolidated and Distractor), given that these were the only trial types whereby the Control group's responses were comparable to those of the Reconsolidation and Consolidation groups. The results of this ANOVA yielded a *large* main effect of Trial Type [$F(1,27)=14.077$, $p=.001$, $\eta_p^2 =.343$] and a *large* main effect of Group [$F(2,27)= 3.74$, $p= .037$, $\eta_p^2= .217$]. There was also a statistically significant interaction effect [$F(2,27)=4.275$, $p=.024$, $\eta_p^2 =.240$]. Thus, each of the main effects was modified by the other.

A second 2x4 mixed factorial ANOVA was subsequently conducted to investigate the impact of Group and Trial Type on recognition accuracy in the Reconsolidation and Consolidation groups *only*. All four trial types were included in this analysis (i.e., Reconsolidation, Old Consolidation, New Consolidation, and Distractor). While between-groups analysis found *no* significant main effect of Group [$F(1,18)=.159$, $p=.695$], some small differences between the two groups were found descriptively (see Figure 5.7). Notably, when responding to old consolidated paired-associates, participants in the Consolidation group (98.33±2.92) were slightly more accurate than those in the Reconsolidation group (97.08±4.42). For newly consolidated paired-associates, the Reconsolidation group (97.71±2.29) showed higher response accuracy compared to the Consolidation group (95.63±4.22). However, it must be stipulated that accuracy was very high generally.

Within-groups analysis found a statistically significant main effect of Trial Type [$F(3,16)=8.644$, $p=.001$] with a large effect size ($\eta_p^2=.618$). Further, subsequently conducted paired-sample t-tests found statistically significant differences between accuracy for Reconsolidation and New Consolidation trials, in both groups [Reconsolidation Group: $t(9)=-62.988$, $p=.0001$; Consolidation Group: $t(9)=-35.794$, $p=.0001$], with the Reconsolidation trial more accurate across both groups (see Figure 5.7). There was *no* significant interaction effect between Trial Type and Group [$F(3,16)=.862$, $p=.481$].

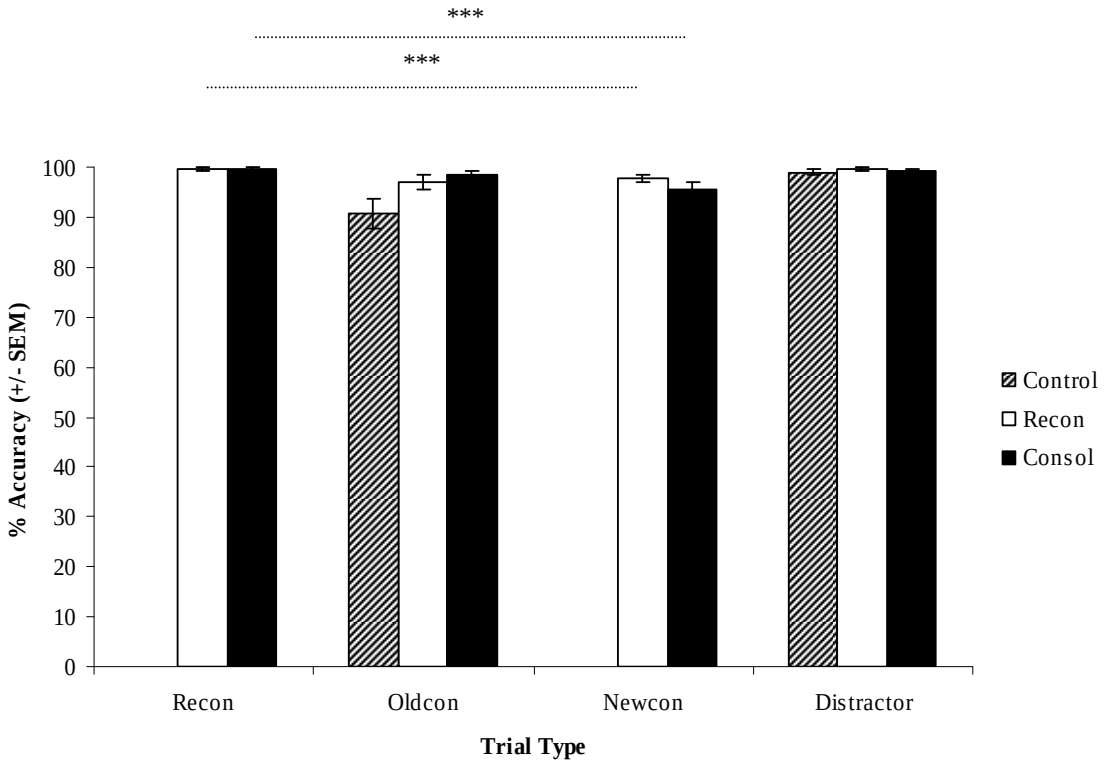


Figure 5.7: Mean percentage accuracy for Reconsolidation and Consolidation groups calculated across test-block trial type (+/- SEM).

5.3.1.2 Reaction Time

The second measure of recognition performance, reaction time (see Figure 5.8), was also investigated for each trial type. By means of a control comparison, a mixed factorial ANOVA was initially conducted to investigate the effects of Group (i.e., Reconsolidation, Consolidation, and Control) and Trial Type (i.e., Old Consolidated, New Consolidated, Reconsolidated, and Distractor). As before, the only data included for the Control group derived from the Old Consolidated and Distractor trials. Results showed *no* main effects of Trial Type [$F(1,27)=3.447$, $p=.074$] *or* Group [$F(2,27)=.642$, $p=.534$]. Further, *no* significant interaction effect was observed [$F(2,27)=1.569$, $p=.227$]. However, descriptive inspection of the means (Figure 5.8) did reveal some small differences between the groups. The Control group responded slowest out of the three groups for the Old Consolidated trials

(1112.59±182.63). In addition, mean RTs for the Control group in Distractor trials (981.76±183.1) were faster than the Consolidation group (1067.99±195.47) and fractionally slower than the Reconsolidation group (959.62±123.62).

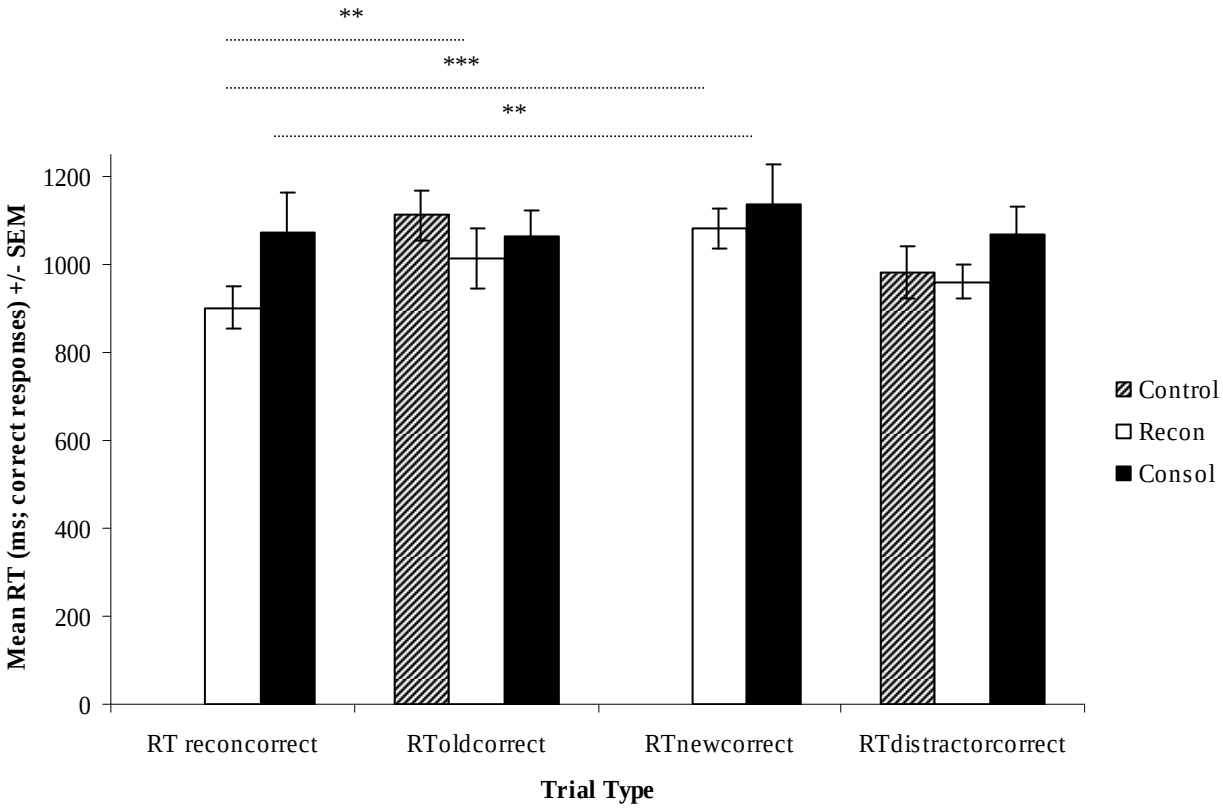


Figure 5.8: Mean reaction times for reconsolidation, consolidation and control groups across test-block trials (+/- SEM).

Another mixed factorial ANOVA then investigated RT data from the Reconsolidation and Consolidation groups *only*. While between-group analysis found *no* significant main effect of Group [F(1,18)=.979, *p*=.336], perusal of the means revealed slight differences between the two groups, with quicker RTs for the Reconsolidation group in every trial type (see Figure 5.8). Within-groups analysis showed a statistically significant main effect of Trial Type [F(3,16)=16.396, *p*=.0001] with a *large* effect size (multivariate η_p^2=.775). Paired samples t-tests subsequently revealed significant RT differences between Reconsolidation

and New Consolidation trials in *both* groups [Reconsolidation Group: $t(9)=7.00$, $p=.0001$; Consolidation Group: $t(9)=3.39$, $p=.008$], with Reconsolidation trials quicker than New Consolidation trials. Furthermore, significant differences were identified in the Reconsolidation Group between Reconsolidation and Old Consolidation trials [$t(9)=3.00$, $p=.015$; see Figure 5.8], once again with Reconsolidation trials showing quicker RTs. There was *no* significant interaction between the main effects [$F(3,16)=.572$, $p=.642$].

5.3.2 Recall Performance

Recall performance was also investigated across the groups, as measured by scores obtained during the free recall tasks. Scores for the study recall task across all three groups were compared initially. The Control groups' scores in the test recall task were included here given that this task was equivalent to the study recall task performed by the Reconsolidation and Consolidation groups. Univariate analysis revealed *no* significant differences between the three groups [$F(2,27)=.321$, $p=.728$]. However, inspection of the means revealed that the Control group (14.9±7.62) performed slightly better than the Reconsolidation group (13.9±7.84) and worse than the Consolidation group (16.3±4.03; see Figure 5.9).

A mixed factorial ANOVA was then performed in order to investigate the impact of Group and Task Type on performance in both recall tasks for the Consolidation and Reconsolidation groups only. There was a *large* main effect of Task Type [$F(1,18)= 87.99$, $p=.0001$, $\eta_p^2=.830$]. Paired-sample t-tests indicated a statistically significant difference between study recall and test recall performance within each group [Reconsolidation: $t(9)= -8.767$, $p =.0001$; Consolidation: $t(9)= -4.684$, $p =.0001$; see Figure 5.9], with test recall incurring significantly higher recall performance across group.

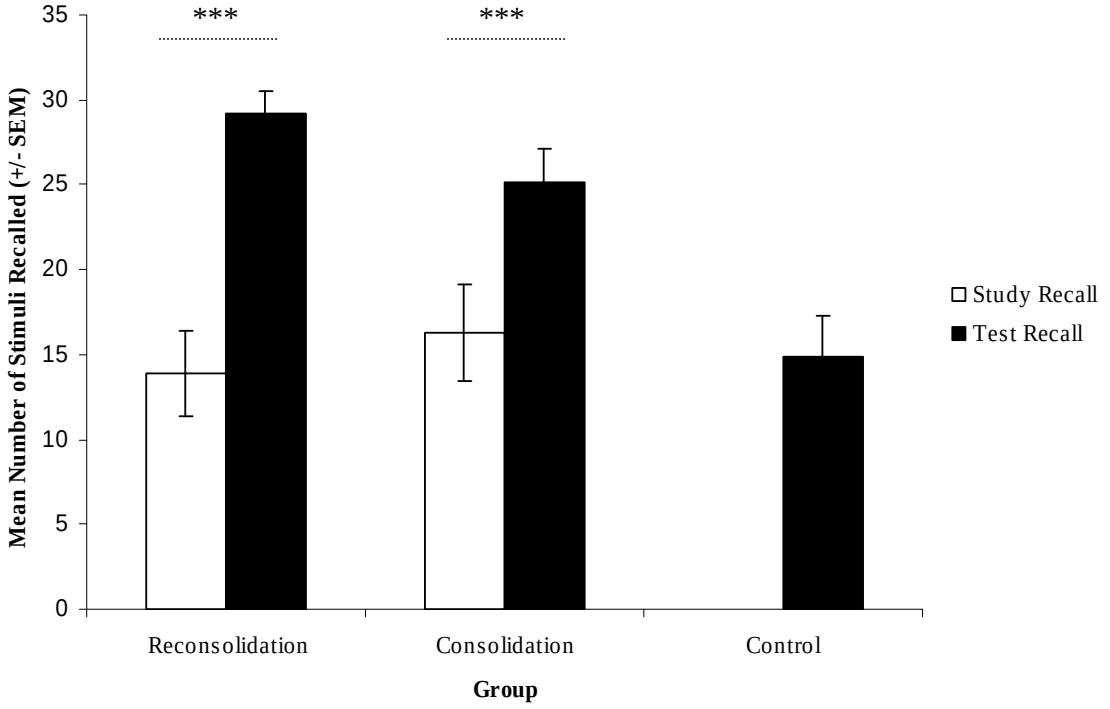


Figure 5.9: Mean recall performance for reconsolidation, consolidation and control groups in study and test recall tasks (+/- SEM).

While there was no statistically significant main effect of Group [F(1,18)= .08 *p*=.781], descriptive analysis revealed some differences in mean recall performance between the groups (see Figure 5.9). The Consolidation group accrued slightly better performance for the study recall task (16.3±4.03) in comparison with the Reconsolidation group (13.9±7.84). Mean performance scores for the test recall task also differed across the groups, with participants in the Reconsolidation group (29.2±8.99) performing in a superior manner than those in the Consolidation group (25.2±5.94). However, the results also revealed the presence of an interaction effect between Group and Recall Task type. This effect was found to be statistically significant [F(1, 18)= 6.154, *p*=.023] with a *large* effect size (η_p^2 =.255). Therefore, the main effect of Trial Type was modified by the effect of Group.

To summarize, the *Recognition* investigation found that within each group, the nature of the stimuli presented in each test-block trial affected participants' responses in

terms of accuracy and RT. Specifically, significant response accuracy and reaction time differences were observed in both Reconsolidation and Consolidation groups between Reconsolidation trials and New Consolidation trials. Furthermore, significant RT differences were observed in the Reconsolidation group between Reconsolidation trials and Old Consolidation trials. In these cases, the Reconsolidation trials were both faster and more accurate. However, the recognition investigation did not find any significant differences in performance between the groups.

The *Recall* investigation found that within each group, recall performance differed according to the recall task presented. While there were no significant differences between the groups, a significant interaction effect suggested that this effect of task type was influenced by each participant's experimental group.

5.4 Experiment 1: Discussion

Results indicate that the nature of the stimuli presented during each test-block trial affected participants' recognition performance in terms of accuracy *and* reaction time. Specifically, significant response accuracy and reaction time differences were observed in *both* Reconsolidation and Consolidation groups between Reconsolidation trials and New Consolidation trials. Further, significant reaction time differences were observed in the Reconsolidation Group between Reconsolidation trials and Old Consolidation trials. In these cases, the Reconsolidation trials were both faster and more accurate than both the New Consolidation and Old Consolidation trials. However, the recognition investigation did not find any significant differences in performance between the groups.

In terms of the recall investigation, it was found that within each group, recall performance differed according to the recall task presented. However, for the current study this effect was considered solely a by-product of the experimental procedure and was not included in the discussion given the recall tasks were not intended to facilitate reconsolidation and consolidation. The more relevant finding was that while there were no statistically significant differences between the groups, a significant interaction effect suggested that the effect of Task Type was modified by each participant's experimental group. Therefore, the group according to which participants were assigned exerted an effect upon recall performance.

In terms of differentiating between reconsolidation and consolidation processes, these results can be considered at several different levels. Firstly, at a stimulus level, Reconsolidation and Consolidation were facilitated by the specific combination of visual paired-associates presented in each of the study and test-block trials. Therefore the four test-

block trial types provided an index of the age and state of the various memories involved (i.e., reconsolidated, old consolidated, newly consolidated and distractor stimulus pairs).

Adopting a similar method to that of Forcato and colleagues (2007), the current study also attempted to facilitate Reconsolidation and Consolidation at a group level via the specific procedure performed by each participant according to their assigned experimental group. Notably in the current study, a twenty-four hour gap between study blocks 1 and 2 in the Reconsolidation group allowed for thorough consolidation of the original stimuli, thereby insuring that updating of stimuli during Study Block 2 both involved reactivation and initiated reconsolidation. When comparing recall performance in the Reconsolidation and Consolidation groups, it was found that a significant effect of recall task type was influenced by participants' experimental group. There were also slight (albeit non-significant) group differences suggesting that the Consolidation group performed better in the study recall task and that the Reconsolidation group performed better in the test recall task. These findings show that the specific procedure performed by each group exerted some influence upon participant's recall memory for the visual paired associates and therefore tentatively suggest that two distinct processes of reconsolidation and consolidation were facilitated by the experimental procedure.

The Recognition investigation failed to significantly distinguish between the Reconsolidation and Consolidation groups. These findings might therefore challenge previous studies supporting the distinct nature of these processes. However, differences were again observed between accuracy scores. These differences suggest that the failure to significantly distinguish between Reconsolidation and Consolidation at a group level could be a result of limitations of the current study rather than a lack of distinction between the two memory processes. As the current study used a relatively small sample, these differences might reach statistical significance in future studies conducted with larger samples.

Alternatively, alteration of the experimental procedure could perhaps diminish the interaction effect within the recall investigation and isolate the effect of group for closer examination.

In a broader sense, the current study further investigated Consolidation and Reconsolidation at a third level by comparing recall and recognition performance. It is generally agreed that recall is a more difficult cognitive task than recognition, involving more extensive reinstatement of the learning event and therefore a stronger retrieval effort (Haist *et al.*, 1992). According to the retrieval model of Reconsolidation, the distinction between Reconsolidation and Consolidation can be understood in terms of retrieval differences (Riccio *et al.*, 2006). It follows therefore that such a distinction should be easier to observe in a recall rather than recognition memory task given recall relies more strongly upon retrieval. In accordance with this view, the current findings have shown that while the recognition investigation failed to find any significant differences between the Reconsolidation and Consolidation groups, the recall investigation found that experimental group impacted upon the effect of trial type. These findings provide some indirect support for a retrieval view of reconsolidation.

In order to increase reliability and generalisability of results, a Control group was also included in the current study. The results showed that individual recognition accuracy for each test-block trial differed across the groups when the Control group was included in analyses. However, this effect was closely dependent upon trial type. While the recognition investigation did not find any significant group differences in term of reaction times and neither did the recall investigation differentiate between the three groups in terms of study recall scores, the data again revealed small differences in both cases. These differences might reach statistical significance in future larger scale studies.

However, the Control group performed a very different combination of tasks to that of the Reconsolidation and Consolidation groups. While specific procedural differences were

designed to enable this group to act as a control, it must be noted that some difficulties arose from inclusion of Control group data in the analysis. In the Recognition investigation, Control group responses were only comparable to those of Reconsolidation and Consolidation groups in Old Consolidation and Distractor trials. In addition, the Test Recall task performed by the Control group was the equivalent of the Study Recall task performed by the other two groups. Therefore, future studies might improve the value of the Control group making procedural alterations in order to increase the comparability of Control group responses.

The current study also had some general limitations, which must be taken into account when interpreting the results. Firstly, participants found the memory tasks quite easy with very high performance recorded for all participants especially in the recognition task, which could possibly account for the differential effects of group between Recall and Recognition investigations. Increasing the number of stimulus pairs presented in Study Block 1 or indeed presenting a list-learning procedure as previously conducted in the area (e.g., Hupbach *et al*., 2007) should increase task difficulty and participant errors, thereby rendering any differences in memory performance easier to observe. Secondly, Hupbach and colleagues (2007) have stressed the important role of a reminder for the reconsolidation of a consolidated memory. In the current study, the presentation of the reactivating probe stimulus prior to updating in Study Block 2 acted as a reminder during reconsolidation. However, in the Reconsolidation and Consolidation groups, presentation of Study Block 2 was immediately preceded by a task involving free recall of the original stimuli from Study Block 1. Therefore this recall task also acted as an additional reminder and could possibly have interfered with the reactivation and updating of the original memory. Future research should investigate this issue further. Finally, the reconsolidated items in the current study contained a greater load (i.e., three associated items) than the consolidated items (i.e., two items),

thereby potentially confounding the results obtained. It is suggested therefore, in line with previous research within the area (e.g., Hupbach *et al*., 2007; Forcato *et al*., 2007), perhaps incorporating word lists or object sets with equal loading across Consolidation and Reconsolidation groups may serve to increase task difficulty thereby demonstrating interference effects to a greater extent than allowed for presently, as well as counterbalancing the effects of consolidation versus reconsolidation which would elucidate more perspicaciously the relative effects of both forms of processing.

In conclusion, at a group level, the findings tentatively support the notion of distinct reconsolidation and consolidation processes. A clear differentiation between reconsolidation and consolidation processing was found at a stimulus level. At a group level, the experimental procedure, modeled upon Forcato *et al.* (2007) also facilitated a differentiation between reconsolidation and consolidation processing. In addition, differences in overall recall and recognition performance can be interpreted as support for a retrieval model of reconsolidation as proposed by Riccio *et al*. (2006).

Overall, these findings tentatively support the validity of reconsolidation as an actual memory process, independent of consolidation and therefore add to the growing body of research supporting the Reconsolidation Hypothesis. As the aim of the current study was simply to differentiate between reconsolidation and consolidation, the direction of differences were not of relevance to this investigation. In order to extend the scope of reconsolidation research, future studies might utilize similar procedures to investigate the specific effects of reconsolidation upon reactivated memories in an attempt to understand the specific mechanisms involved in, strengthening, weakening and even eradicating memories. For example, recent work regarding the psychopharmacological alteration of reactivated traumatic memories presents promising possibilities for future treatment of Post Traumatic

Stress Disorder (PTSD; Pitman & Delahanty, 2005). Experiment 2, which follows, seeks to explore the electrophysiological markers associated with the aforementioned effects.

5.5 Experiment 2: Introduction

Memory Consolidation has been defined on the basis of observations that a newly formed memory undergoes a transformation process, becoming stronger and more resilient over time until it is insensitive to disruption. In several species and memory systems, many molecular, anatomical and system-level investigations have contributed to the characterization of this transformation process. Insights into the anatomy of consolidation have been ascertained by testing the effects of functional inactivation or direct lesion of specific brain areas. Moreover, it has become evident that different brain regions are progressively engaged, thereby indicating that the consolidation process is sustained by spatial and temporal changes and occurs over an extended period (Bontempi *et al*., 1999; Frankland *et al*., 2004; Maviel *et al*., 2004). For example, in animals, the consolidation of many forms of memory is dependent upon hippocampal processing during the first few weeks but subsequently becomes hippocampus-independent (Anagnostaras *et al*., 1999). Furthermore, analyses of both human amnesic patients with anatomically defined cerebral injuries and animal models with ablations of specific brain regions indicate that graded retrograde amnesia, defined as a greater memory deficit for information acquired recently versus remotely, can occur for very old events (several years old in humans; Brown, 2002).

In *humans*, research on consolidation has focused on declarative memories and their temporary dependence upon structures located within the medial temporal lobe (MTL). These memories initially require the MTL and are thought to eventually be stored in neocortical circuits without a significant MTL contribution (McClelland *et al.*, 1995; Squire *et al*., 2004). Studies of hippocampus-dependent memory in animals have largely confirmed this postulation (see Moore & Roche, 2007 for a more comprehensive review). Further, remote

memory is often impaired by damage to the neocortex (Graham & Hodges, 1997; Squire *et al*., 2001; Bayley *et al*., 2003). This finding has suggested that neocortical areas serve as remote memory storage sites and that, although new memories are initially dependent on the MTL, they gradually become independent of this area as they are consolidated in neocortical circuits (Alvarez & Squire, 1994; Squire & Alvarez, 1995). Indeed, a series of recent experiments have demonstrated that specific regions of the neocortex and plastic mechanisms within these areas are integral for cortical memory consolidation (Bontempi *et al*., 1999; Frankland *et al.*, 2001; Takehara *et al.*, 2003; Cui *et al.*, 2004; Frankland *et al.*, 2004; Hayashi *et al*., 2004; Maviel *et al*., 2004).

Although both Consolidation and Reconsolidation appear to be associated with the hippocampal formation, several animal-based studies have demonstrated that *different* brain areas mediate these processes (for a more comprehensive account of animal-based findings, refer to Moore & Roche, 2007). Taubenfield and colleagues (2001) demonstrated that the hippocampus was required for consolidation but not for reconsolidation of an inhibitory avoidance memory. Similarly, Agnihotri and colleagues (2004) found a lack of protein synthesis-dependent reconsolidation in hippocampal place cells, which require protein synthesis for consolidation. Further, Lee and colleagues (2004) found that consolidation but not reconsolidation was impaired by blockade of BDNF expression in the hippocampus. Alternately, blocking hippocampal expression of zif268 impaired reconsolidation while consolidation was unaffected. Thus, in animals, independent cellular processes underpin hippocampal memory consolidation and reconsolidation.

Regarding frontally mediated activation, Nyberg and colleagues (1996), employing positron emission tomography (PET) in humans during encoding and retrieval of information, isolated distinct encoding and retrieval networks for episodic memory in accordance with the hemispheric encoding/retrieval asymmetry (HERA) model (Tulving *et*

al., 1994). According to this model, the left prefrontal cortex (PFC) is differentially more involved in retrieval of information from semantic memory, and in simultaneously *encoding novel aspects of the retrieved information into episodic memory* (i.e., updating), than is the right prefrontal cortex. The right prefrontal cortex, on the other hand, is differentially more involved in episodic memory retrieval than is the left prefrontal cortex. Further, in terms of animal research, in trace fear conditioning, the hippocampus and the medial prefrontal cortex (mPFC) are required for the consolidation of long-term memory. Several studies (e.g., Runyan & Dash, 2005; Blum *et al*., 2006) suggest that not all structures that participate in memory storage are involved in reconsolidation. Investigating whether the ventro-medial prefrontal cortex (vmPFC), which is known to be involved in the long-term storage and plasticity of memory as well as the discrimination of object familiarity, Akirav and Maroun (2006) demonstrated that the vmPFC is required for the consolidation of long-term visually-guided recognition memory in the rat, that this memory undergoes reconsolidation upon its reactivation, and that the vmPFC is also required for the reconsolidation process. Their data further suggested that protein synthesis and NMDA receptors are required for *both* consolidation and reconsolidation of recognition memory.

In contrast to the aforementioned research indicating their differences, numerous studies provide evidence that consolidation and reconsolidation are *similar* processes. Nader *et al.* (2000) and Debiec *et al.* (2002) both reported that, in the rat, *protein synthesis* is required in the amygdala for both consolidation and reconsolidation of cued fear conditioning, as well as in the hippocampus for both consolidation and reconsolidation of contextual fear conditioning. Furthermore, Sangha *et al.* (2003) demonstrated that in the pond snail *Lymnea stagnalis*, protein and RNA syntheses are required in the same cell for *both* consolidation and reconsolidation of a classical conditioning task. Similarities between the two tasks were also inferred by investigations into the requirement of *specific molecules*.

Kelly *et al.* (2003) showed that inhibition of the MAP kinase pathway by ICV injection of a specific inhibitor affects both consolidation and reconsolidation of an object recognition task. Koh & Bernstein (2003) demonstrated that the inhibition of protein kinase A in the amygdala affects both consolidation and reconsolidation of conditioned taste aversion. Child *et al.* (2003) found that inhibiting bond formation between cell-adhesion molecules blocks both processes in Pavlovian conditioning. Kida *et al.* (2002) noted that temporally-regulated knockout of the transcription factor CREB impairs both consolidation and reconsolidation of contextual fear conditioning. Finally, the knock-out of zif268 results in deficits in both consolidation and reconsolidation of an object recognition task (Bozon *et al.*, 2003).

Functional brain imaging studies have further shown that medial temporal, parietal and prefrontal cortices are involved in recognition memory of prior episodes (Rugg & Wilding, 2000; Rugg & Yonelinas, 2003). The functional role that these regions play in memory retrieval, however, is still debated. Specifically, it is unclear whether recollection, the retrieval of specific context-based information about a past experience, and familiarity, an acontextual sense that an event has been previously experienced (Tulving, 1985), are mediated by dissociated neural systems or separate strong (i.e., remote) memories from weak (i.e., recent) memories. Some studies suggest that separate cortical networks (Yonelinas *et al.*, 2005) and differential activation in the parietal cortex (Vilberg & Rugg, 2007) mediate these two distinct memory processes, whereas other studies suggest that recollection and familiarity reflect differences in the strength of a common memory trace (Donaldson, 1996; Dunn, 2004; Gonsalves *et al*., 2005; Squire *et al*., 2007; Wixted, 2007). Yago and Ishai (2006) found that activation elicited by new paintings in the parietal cortex was reduced with decreased similarity to old items, whereas in the hippocampus and precuneus, stronger responses were evoked by new, visually different paintings. Thus, recollection- and

familiarity-based memory decisions may reflect strong (i.e., remote) memories and weak (i.e., recent) memories, respectively.

A number of contentious issues have been purported regarding the reconsolidation phenomenon. First, the hypothesis that whenever a memory is retrieved or reactivated it again becomes labile and thereby "disruptable" (Nader *et al*., 2000; Sara, 2000) has been challenged. Several studies assert that the passage of time is a limiting factor for such post-retrieval vulnerability of memory (e.g., Milekic & Alberini, 2002). In this regard, Milekic and colleagues ultimately concluded that upon reactivation, an older memory trace does not become fragile to the same extent that a younger trace does, and that, over time, memory becomes increasingly stable and insensitive to the postreactivation interference. Thus, the reconsolidation phenomenon reflects a fragile state of a memory that has only been partially consolidated, thereby remaining within the remit of consolidation-, as opposed to *re*consolidation-based processing. Several studies have corroborated this position (e.g., Litvin & Anohkin, 2000; Eisenberg & Dudai, 2004; Suzuki *et al*., 2004).

Exploring such timing effects, Frankland and colleagues (2006) found that, in the dorsal hippocampus of mice, post-retrieval anisomycin disrupted subsequent expression of recent but not remote memory. Similar infusions into the anterior cingulate cortex had no effect on either recent or remote contextual fear memories, whereas systemically applied anisomycin blocked remote memory expression only when long re-exposure durations were used to retrieve the memory. The dissociation between the effects of systemically and centrally administered anisomycin on remote memory led the authors to conclude that memory stability is attributable, in part, to the distributed nature of remote contextual fear memory traces. In contrast, Nader and colleagues (2000) reported that *both* 2-day- and 2-week-old memories of cued-fear conditioning in rats were disrupted by post-retrieval bilateral injections of anisomycin into the amygdala. Further, adopting a similar contextual

fear conditioning task to Frankland and colleagues (2006), these researchers found that post-recall anisomycin injection into the dorsal hippocampi of rats disrupted a 45-day-old memory, a time wherein contextual memory is theoretically, according to classic consolidation theory, independent of the hippocampus.

A further contentious issue within this reconsolidation realm concerns the functional role of reconsolidation itself (see Chapter 1). It has been proposed that reconsolidation is a manifestation of a memory updating system which adapts the reactivated, already established memory trace to new circumstances (Sara, 2000; Dudai, 2004; Dudai & Eisenberg, 2004). According to Alberini (2007), although the process of retrieving a memory is necessary for linking new information with reactivated memories, the retrieval-induced reconsolidation process is not engaged in linking the new information with the reactivated memory. Rodriguez-Ortiz and colleagues (2005), investigated memory updating in rats, ultimately finding that the formation of new associations linked to a previously established memory requires protein synthesis. However, they did not ascertain whether it is the protein synthesis required for the reconsolidation of the old memory that is recruited to mediate the incorporation of new information. Therefore, as suggested by Alberini (2007), it is possible that this type of memory updating also recruits a consolidation-like process and not the reconsolidation of the original memory. Indeed, consistent with this assertion, the study by Rodriguez-Ortiz *et al*. demonstrated that the old and new memories were dissociable processes because, while the old memory could be rendered insensitive to disruption (i.e., consolidated), the incorporation of the new information (i.e., updating) remained sensitive to disruption.

In the current study, we used high-density ERPs to investigate the electrophysiological correlates and neural generators of remote and newly consolidated memory traces versus reconsolidated traces. By utilizing an “Old/New” effect protocol,

indices related to both semantic and episodic processes could be used to ascertain differences or indeed similarities between both old and newly consolidated memory traces with reconsolidated traces. To our knowledge, no study to date has employed this protocol to differentiate consolidation from reconsolidation-based processes. We also elaborate indices related to both updating an existing memory trace and explore the timing effects involved in episodic trace reactivation of old and newly consolidated traces.

Specifically, 128-channel EEG was recorded for four different memory trace stimulus types (i.e., Old Consolidated, New Consolidated, Reconsolidated and Distractor) in a specifically designed updating task and BESA source localization was employed to identify neural generators associated with the task processing. It was predicted that greater activity would be identified over posterior scalp, as well as a reduction in component amplitude, for remote consolidated items when compared to both newly consolidated and previously unstudied foil items. A late positive parietal effect was expected in terms of reconsolidation-based processing with increased amplitude for old as opposed to new items. A frontal effect was further hypothesized which may represent an index of updating the existing memory trace (i.e., reconsolidation), with increased amplitude predicted for old as opposed to newer traces.

5.6 Method

5.5.1 Participants

The present study comprised 30 undergraduate and postgraduate students (age range= 18-46 yrs, mean= 24.83±6.75) who volunteered to take part in a study on memory. 18 participants took part in Experiment 2a (age range= 19-38 yrs, mean= 24.61 ±4.24). Following data screening, one participant's data were rejected due to excessive EEG/EOG artefacts. Of the remaining 17 participants, 10 were female and all were right-handed (age range= 19-38 yrs, mean= 24.70±4.35). For Experiment 2b, a total of 12 volunteers participated (age range= 18-46 yrs, mean= 25.17±9.59). Again, one participant's data were removed from analysis due to excessive EEG/EOG artifacts or head movements. Of the remaining 11 participants, 9 were female and 8 were right-handed (age range= 18-46 yrs, mean= 25.45±10.0). English was the primary language of all participants and all reported normal or corrected-to-normal vision. All participants were asked to complete a Cognitive Failures Questionnaire (Broadbent *et al*., 1982; see Appendix 2) as a control measure. Participants were further self-reported free from psychiatric or serious memory problems. The experiment conformed to the 1964 Declaration of Helsinki and was approved by the local NUI Maynooth ethics committee. Participants provided written consent (Appendix 4) prior to taking part in the study and were informed of their rights under the Freedom of Information Act. The experiment was conducted in accordance with the Code of Ethics of the World Medical Association as well as the ethical standards of the APA.

5.5.2 Stimuli

Stimuli similar to those discussed for Experiment 1, with the exception that the test-block took place either 1-2 hours (Experiment 2a) or 24 hours (Experiment 2b) after the second study block. Dissimilar to Experiment 1, one group of participants employed who were tested across all trial types (i.e., Old Consolidated, New Consolidated, Reconsolidated, Distractor), due to EEG recording constraints. Instead, time between reactivation of the original trace (i.e., Study Block 2) and memory testing was varied by either 1-2 hours or 24 hours thereby accounting for recent and remote memory traces.

5.5.3 Materials

See Method section for Experiment 1.

5.5.4 Procedure

Study Block 1

See Method section for Experiment 1.

Study Block 2

See Method section for Experiment 1.

Test-block

The test-block was identical to that employed for Experiment 1, with the exception that it was presented either immediately (i.e., 1-2 hours; Experiment 2a) or 24 hours (i.e., Experiment 2b) *after* Study Block 2.

Recording of Responses

Correct responses and reaction times were both recorded during the test phase of the experiment. A correct response occurred if the participant pressed the left mouse button when an 'old' stimulus pair appeared and the right mouse button when a 'new' stimulus pair appeared. Pressing the opposite button than required or failure to respond resulted in an incorrect response. Reaction times were measured as the interval between presentation of the stimulus and the response, and were recorded for both correct and incorrect trials. E-prime logged accuracy and RT data for each participant and sent triggers to the EEG acquisition PC to allow stimulus presentations and responses to be logged in real time on the continuous EEG recording.

5.5.5 Electrophysiological Recording

The electrophysiological recording was performed at the Department of Psychology, NUI Maynooth. Participants were seated in a cubicle (150cm x 180cm) half a meter from the computer monitor and had access to a mouse for response. Refer to Chapter 2 for a detailed account of electrophysiological set-up and recording procedures. Stimulus-locked average ERPs[5] were obtained by averaging the EEG using stimulus presentation as the starting trigger, and continuing for an epoch of 1500ms post-stimulus. Participant EEG was used to create four separate conditional ERPs based on different trial types: Reconsolidated, New Consolidated, Old Consolidated and Distractor. For measurements of mean amplitude and area under the curve (AUC), the naison electrode was used for reference. Blinks were averaged off-line and a blink reduction algorithm was applied to the data.

[5] The term "stimulus-locked" is used here to describe averaging binned by stimulus. Averages based on stimulus triggers are referred to as Stimulus Triggered Averages (STA).

5.5.6 Data Analysis

5.5.5.1 Behavioural data analysis

Response accuracy was calculated automatically by E-Prime and manually collated into accuracy totals for each response (correct, incorrect) and condition (old consolidated, new consolidated, and reconsolidated). All latencies were calculated automatically by E-Prime and grouped as described above. Accuracy scores were presented in terms of percentage accuracy, while reaction times were presented in the order of milliseconds. A series of one-way repeated measures ANOVAs was conducted to compare accuracy scores and RT data across trial type (i.e., Reconsolidated, Old Consolidated, New Consolidated, and Distractor), with further paired t-tests conducted where appropriate. A series of 2x4 mixed factorial ANOVAs was subsequently conducted to compare accuracy scores and RT data across experimental group (i.e., Experiment 2a and Experiment 2b) and trial type using Greenhouse Geisser corrections wherever appropriate. A star-based system for significance representing *p*-values of $p<0.05$ *, $p<0.01$ **, and $p<0.001$ ***, respectively, was employed throughout. The symbol ± was used throughout to represent standard deviation from the mean. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

5.5.5.2 Electrophysiological Data Analysis

An overall grand-mean waveform was generated for each of the electrodes by collapsing across participants for each of the four conditional ERPs (i.e., Old Consolidated, New Consolidated, Reconsolidated and Distractor). From this, amplitude differences between conditions were identified at selected electrode sites through a visual analysis of the scalp data and using BESA. From this initial inspection, possible comparisons were generated and were tested for statistical significance. Only scalp sites selected after a visual analysis of the

data were included in the inferential statistics. Bonferroni-corrected paired samples t-tests were conducted on Mean Amplitude and Area under the Curve (AUC) measurements to assess latency and amplitude differences between reconsolidated and old/newly consolidated trial types. Source analysis was subsequently conducted for trial types which indicated significant amplitude differences. A star-based system for significance representing *p*-values of $p<0.05$ *, $p<0.01$ **, and $p<0.001$ ***, respectively, was employed throughout. The symbol ± was used throughout to represent standard deviation from the mean. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

5.5.5.3 Source Analysis

Refer to Chapter 2 for a detailed account of source analysis technique employed.

5.7 Results

5.7.1 Control Measures

All Participants completed a Cognitive Failures Questionnaire in order to screen for possible confounding lapses in everyday memory between the groups (Experiment 2a (n=15); mean CFQ score= 37.67+/-12.0, Experiment 2b (n=11); mean CFQ score= 47.73+/-14.09). The results yielded no significant differences between the groups across experiments in terms of cognitive failures and everyday memory.

5.7.2 Experiment 2a (1-2 hrs between Study Block 2 and Test Block; n=15)

5.7.2.1 Accuracy

Figure 5.10 shows percentage accuracy across trial types. Initial inspection of the data indicates that the Reconsolidation stimuli elicited the highest accuracy scores. The lowest accuracy scores were obtained for the Old Consolidated stimuli. The New Consolidated trial type yielded the second lowest scores, with the Distractor trial type yielding the second highest after the Reconsolidated stimuli. A one-way repeated measures ANOVA was conducted to compare accuracy scores across trial types (i.e., Reconsolidated, Old Consolidated, New Consolidated, and Distractor). A non-significant effect for accuracy was observed (Wilks' Lambda = .618, $F(3, 12)= 2.473$, $p= .112$, $\eta_p^2 = .382$).

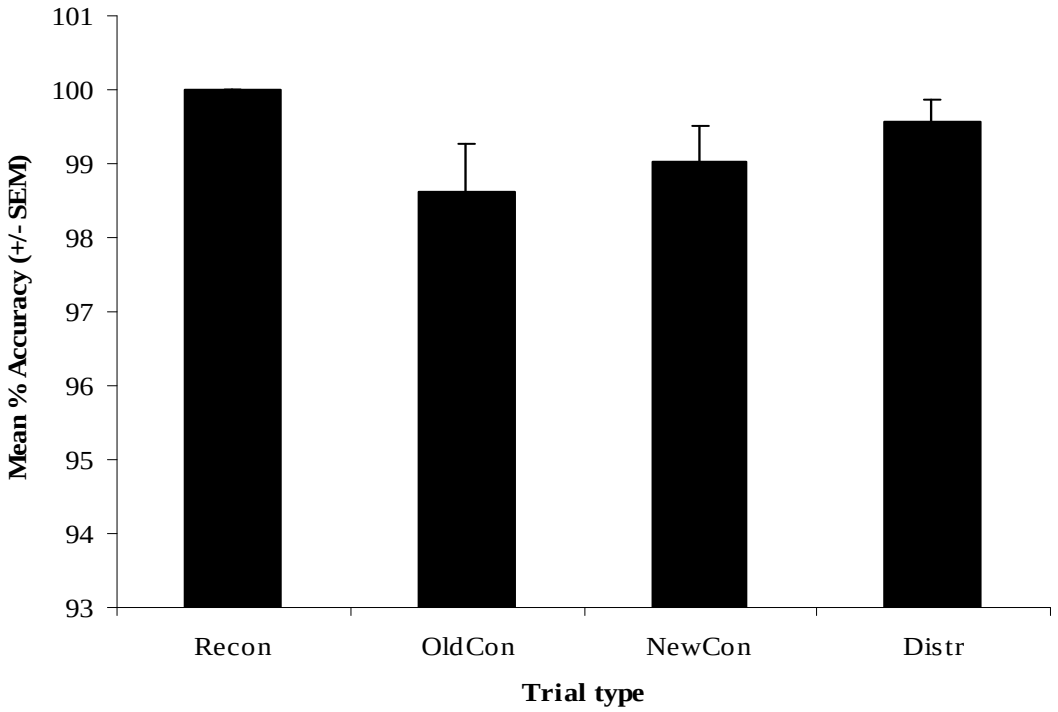


Figure 5.10: Mean percentage accuracy scores across trial type (+/- SEM) for Experiment 2a (n=15).

5.7.2.2 Reaction Time

In terms of RT, only correct responses were subjected to analysis, given the high level of accuracy achieved across trial type. Cursory inspection of RT data obtained (see Figure 5.11) infers that quickest RTs occurred for Old Consolidated stimuli, with slowest RTs occurring for New Consolidated stimuli. Such a result is not in line with predictions made by the accuracy data obtained in this group wherein the Old Consolidated trial type was the least accurate. Alternately, the New Consolidated stimuli yielded the slowest mean RT. Again, this RT data is not in line with accuracy data wherein the New Consolidated condition performed second poorest. Both Reconsolidation and Distractor trial types performed similarly RT wise, neither performing fastest nor slowest. Interestingly, these trial types performed more accurately than *both* Old Consolidated and New Consolidated trial types.

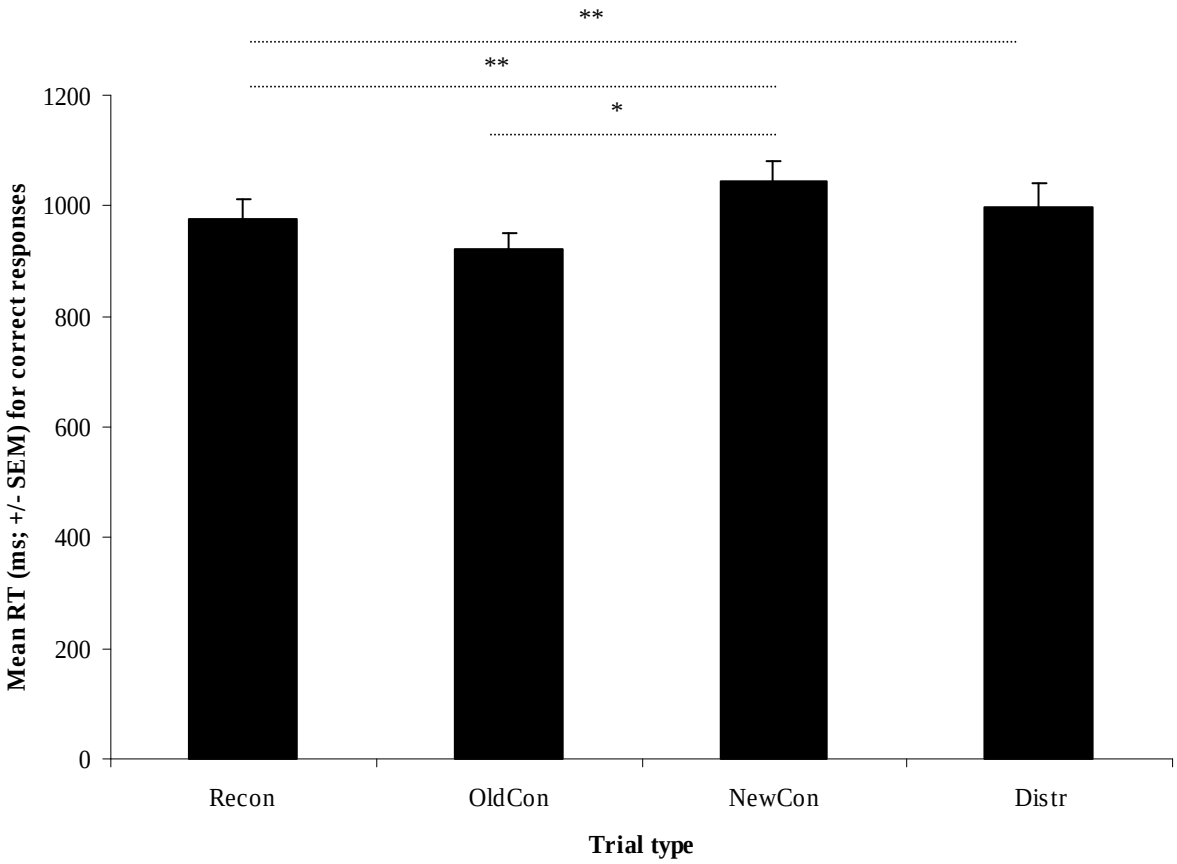


Figure 5.11: Mean RT (msec) for correct responses across trial type (+/- SEM). Only Bonferroni-corrected *p*-values are shown.

A one-way repeated measures ANOVA was conducted to compare RTs across trial types. A significant effect for RT was obtained (Wilks' Lambda =.135, $F(3,12)= 25.704$, $p<.001$, $\eta_p^2= .865$). Paired t-tests further analysed these within-group differences. There was a statistically significant increase in RT from Old Consolidated stimuli (921.84±116.92) to New Consolidated stimuli (1043.82±142.82), $t(14)= -3.693$, $p=.002$: Bonferroni-adjusted $p=.012$. Further, a significant increase in RT was identified from Reconsolidated stimuli (868.87±169.08) to New Consolidated stimuli (1043.82±142.82), $t(14)= 8.819$, $p<0.001$: Bonferroni adjusted $p=.006$). The η^2 statistic (0.8) indicated a large effect size. Finally, a statistically significant increase in RT was found from the Reconsolidation condition

(868.87±169.08) to the Distractor condition (997.22±167.20), $t(14)= 5.273$, $p<0.001$: Bonferroni-adjusted $p=.006$). The η^2 statistic (0.7) indicated a moderate to large effect size.

5.7.2.3 Electrophysiological Results

Visual Analysis

Modulations of frontal positivity and posterior negativity between reconsolidated stimuli old consolidated stimuli were evident at channels F9, FP2, F8 and P6, respectively (see Figure 5.12). Similar modulations were observed between reconsolidated stimuli and new consolidated stimuli at the same electrode sites. Thus, across comparisons between reconsolidated and both old and new comparisons, modulations were identified left frontally at channel F9, parietally at channel P6, fronto-parietally at channel FP2, and right frontally at channel F8.

Amplitude Comparison

Paired t-tests were used to compare reconsolidated and old consolidated stimuli across channels F9, FP2, F8 and P6, at the $p<0.05$ level. A significant mean amplitude difference was found for channel F9 from 848-1500 ms [$t(14)= -2.250$, $p=.041$], with old consolidated stimuli eliciting greater amplitude. Further, a significant AUC difference was found for channel FP2 for the later latency of 822-1132 ms [$t(14)=-2.131$, $p=.051$], with reconsolidated stimuli eliciting greater amplitude. Comparing reconsolidated and new consolidated stimuli across the same channels, significant AUC differences were found for channel P6 for *both* latencies isolated; 100-216ms [$t(14)= 4.849$, $p<0.005$: Bonferroni-adjusted; $p=.01$], 406-542ms [$t(14)= 2.943$, $p=.011$: Bonferroni-adjusted; $p=.02$], with reconsolidated stimuli

eliciting greater amplitude across both latencies. See Figure 5.12 below for waveform differences between reconsolidated and both old and newly consolidated stimuli.

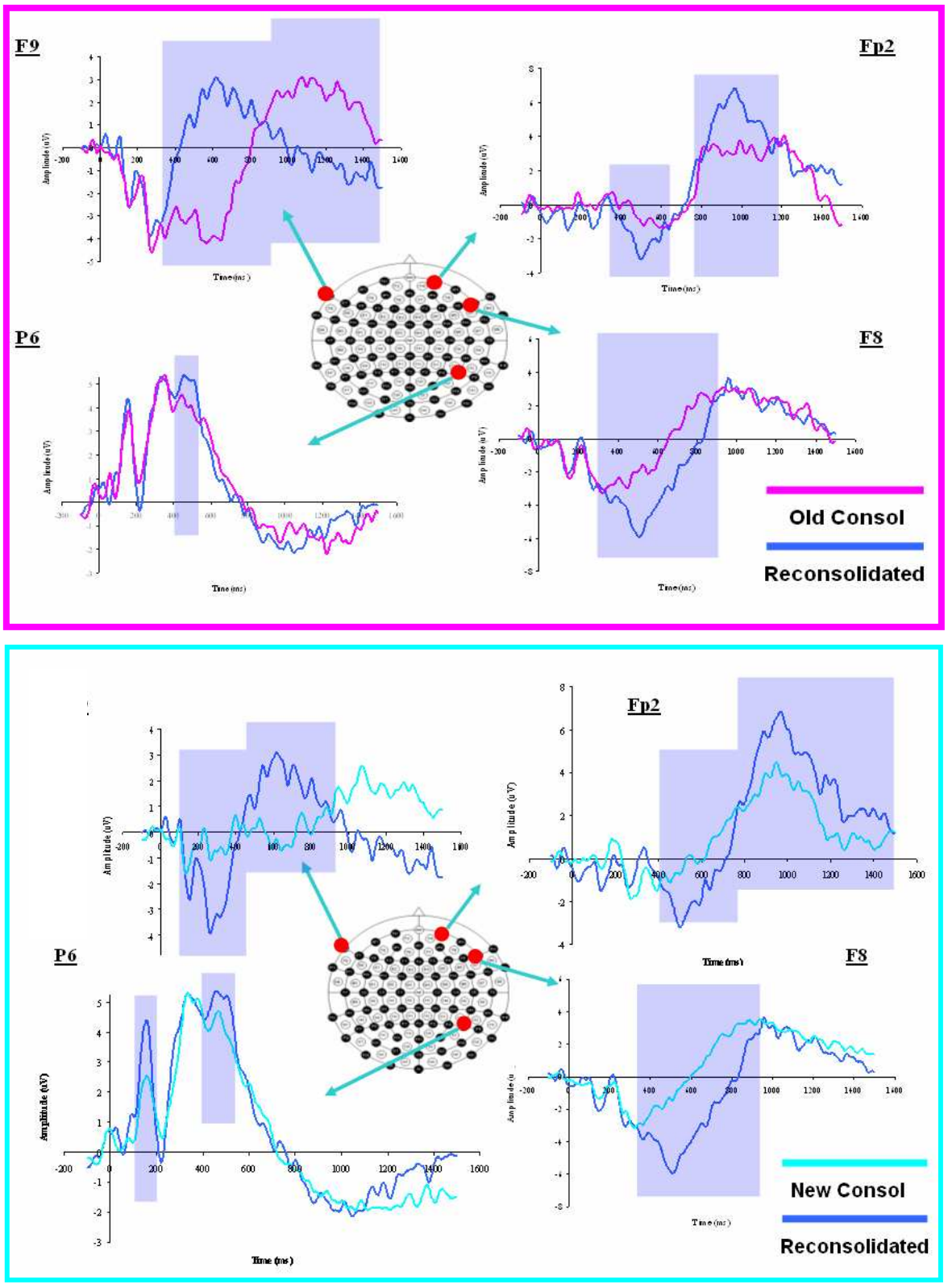


Figure 5.12: **(a)** Waveform differences between **reconsolidated** (blue lines) and **old consolidated** (pink lines) trial types at channels F9 (320-828ms; 858-1500ms), FP2 (344-606ms), F8 (344-876ms) and P6 (452-534ms). **(b)** Waveform differences between **reconsolidated** and **new consolidated** trial types at channels F9 (200-400ms; 424-868ms; 894-1500ms), FP2 (424-760ms; 804-1482ms), F8 (334-958ms) and P6 (100-216ms; 406-542ms).

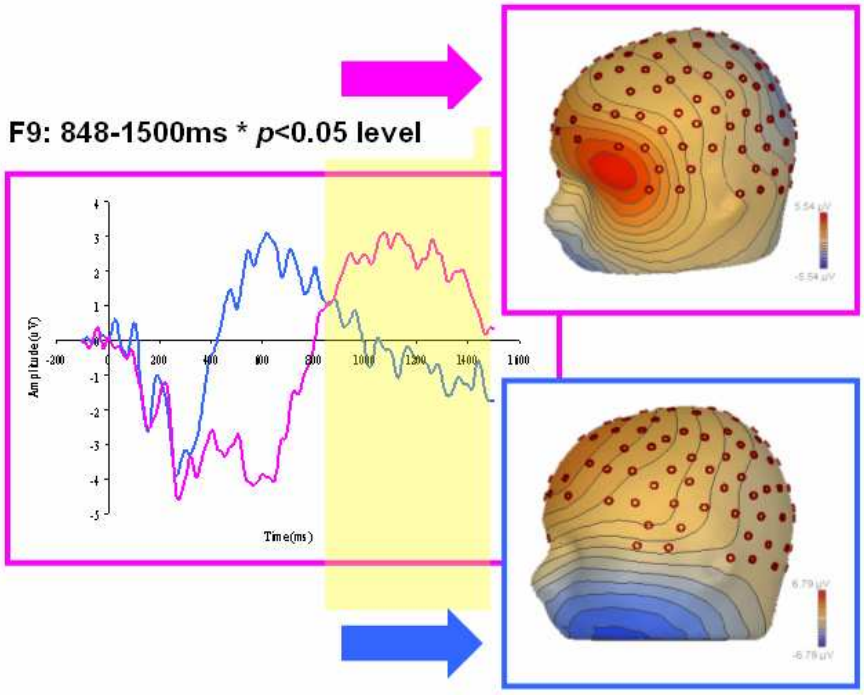


Figure 5.13: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel F9 from 848-1500ms for Experiment 2a shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Anterior left-side view).

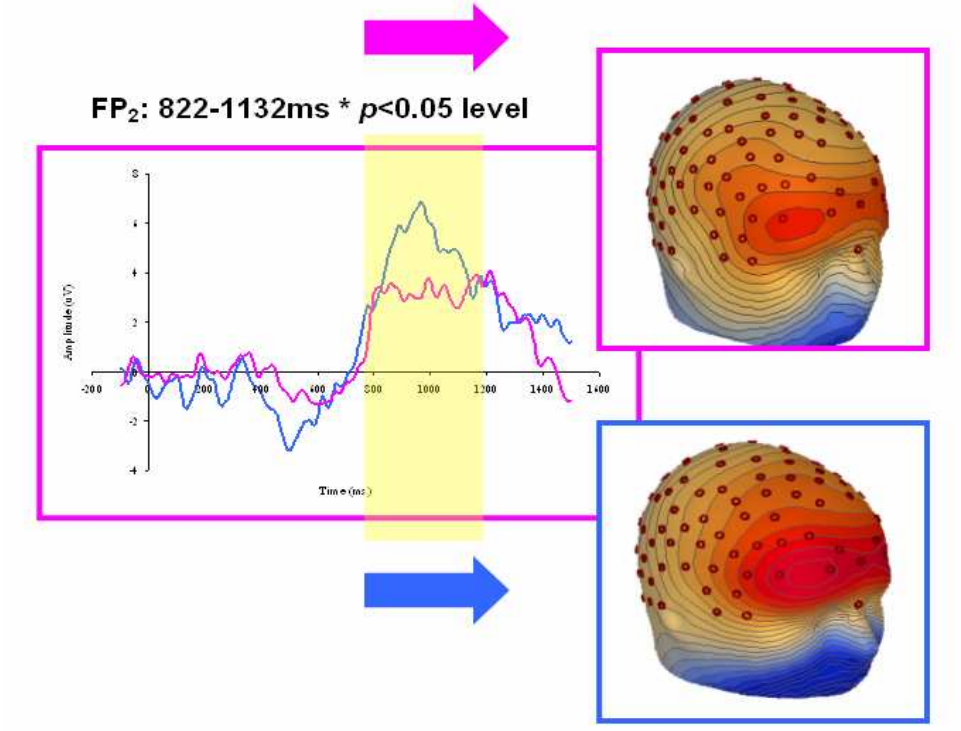


Figure 5.14: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel FP2 from 822-1132ms for Experiment 2a shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Anterior right-side view).

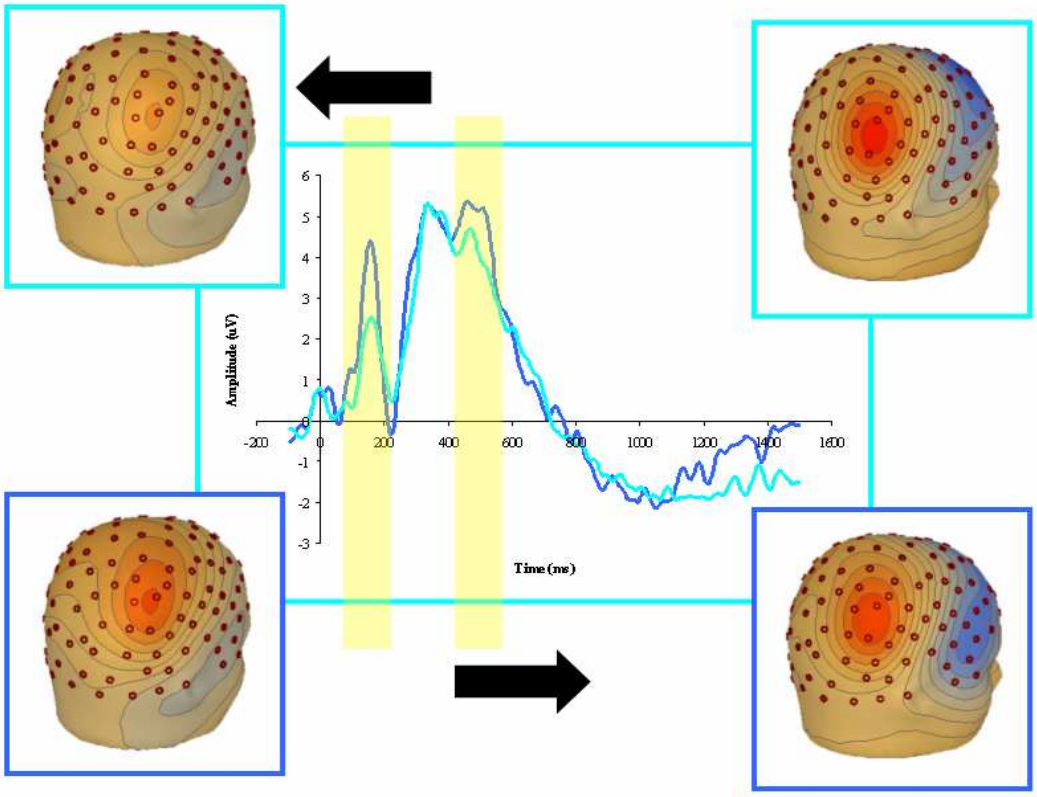


Figure 5.15: Significant waveform amplitude differences between **reconsolidated** and **new consolidated** stimuli at channel P6 from 100-216ms (left-hand side) and 406-542ms (right-hand side) for Experiment 2a shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **new consolidated** (top) stimuli during time frame of significant amplitude differences (Posterior right-side view).

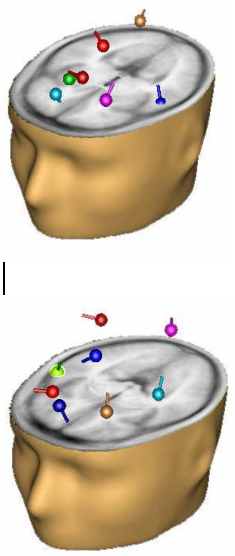
5.7.2.4 Dipole Source Analysis

Dipole source models were generated for reconsolidated and old consolidated conditions from 800-1130ms (see Table 5.2 for Residual Variances, dipoles, Talairach co-ordinates, Brodmann's Areas and approximate locations as provided by the Talairach daemon; Lancaster *et al*., 2000). All Tables are superimposed with corresponding transverse MRI slices for anatomical reference. A 7 dipole solution was generated for both reconsolidated and old consolidated conditions, with both solutions explaining >90% of the variance in electrical activity. Similar dipoles were located bilaterally near the medial frontal gyrus (reconsolidated: BA 9, old consolidated: BA 10) and left parietally near the precuneus (BA 7). Interestingly, dipoles were located left frontally in both conditions. However, the left middle frontal gyrus (BA 10) was localised for the reconsolidated stimuli whereas the left superior frontal gyrus (BA 6) was localised for the old consolidated stimuli. Further, the

temporal lobe was localised bilaterally across reconsolidated and old consolidated conditions (BA 21). However, the superior temporal gyrus was localised for reconsolidated stimuli whereas the middle temporal gyrus was localised for old consolidated stimuli. Dipoles were generated near the caudate and putamen for reconsolidated stimuli *only*, whereas dipoles were generated bilaterally in the frontal lobe near the inferior frontal gyrus (BA 47) and precentral gyrus (BA 6) for old consolidated stimuli *only*.

Table 5.2: Residual variances, Dipoles, Talairach co-ordinates, Brodmann's areas and approximate locations as provided by talairach daemon from 800-1130ms for reconsolidated and old consolidated stimuli.

Channel	**Condition; Epoch; RV**	**Dipole**	**TAL co-ordinates; x, y, z**	**BA**	**Structure**
FP2	Reconsolidated 800-1130ms RV= 6.230%	1	31.3, -37.7, 11.1	-	R. Caudate
		2	-54.0, -14.4, -2.3	21	L. Superior Temporal Gyrus
		3	26.6, 14.1, 4.1	-	R. Lentiform Nucleus-Putamen
		4	-35.4, 38.0, 17.7	10	L. Middle Frontal Gyrus
		5	-5.3, -44.3, 45.5	7	L. Parietal Lobe-Precuneus
		6	14.7, 46.4, 8.5	10	R. Medial Frontal Gyrus
		7	-11.4, 41.2, 31.7	9	L. Medial Frontal Gyrus
FP2	Old Consolidated 800-1130ms RV= 6.781%	1	40.2, 25.5, -0.4	47	R. Frontal Lobe; Inferior Frontal Gyrus
		2	-9.5, 29.4, 53.5	6	L. Frontal Lobe; Superior Frontal Gyrus
		3	60.8, -5.1, -3.9	21	R. Middle Temporal Gyrus
		4	-16.0, -61.1, 39.9	7	L. Parietal Lobe-Precuneus
		5	-33.4, 43.7, 16.4	10	L. Frontal Lobe; Middle Frontal Gyrus
		6	-50.7, -2.9, 18.4	6	L. Frontal Lobe- Precentral Gyrus
		7	4.5, 59.5, 15.0	10	R. Medial Frontal Gyrus

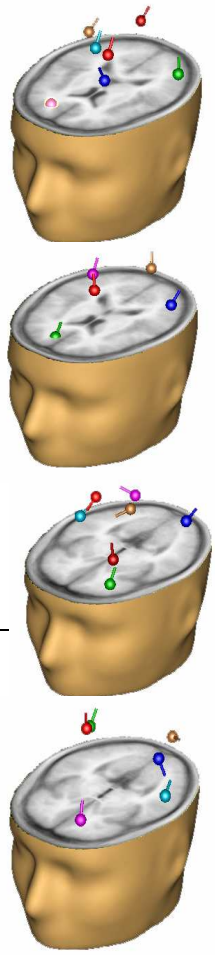


Dipole source models were further generated for reconsolidated and new consolidated conditions from 100-216 ms and 406-542 ms, respectively (see Table 5.3 for Residual Variances, dipoles, Talairach co-ordinates, Brodmann's Areas and approximate locations as provided by Talairach daemon). From 100-216ms, a 7-dipole solution was generated for the reconsolidated condition, with a residual variance (RV) of 5.685%. A 5-dipole solution was generated for the new consolidated condition, with a RV of 5.792%. Similar dipoles were

generated near the right medial frontal gyrus and right cingulate gyrus for both conditions. Dipoles were localised bilaterally in the parietal lobe near the supramarginal gyrus and precuneus (left: new consolidated, right: reconsolidated). Finally, dipoles were generated bilaterally near the superior temporal gyrus (left: reconsolidated, right: new consolidated). The reconsolidated stimuli also elicited a dipole near the left cingulate gyrus. From 406-542 ms, a 7-dipole solution was generated for the reconsolidated condition, with a RV of 5.611%. A 5-dipole solution was generated for the new consolidated condition, with a RV of 4.609%. Similar dipoles were generated left parietally near the inferior parietal lobule (BA 40). Right parietal dipoles were elicited for the reconsolidated stimuli *only* (BA 2, BA 43). Bilateral frontal dipoles were localised in the middle frontal gyrus (BA 6; left: reconsolidated, right: new consolidated). Bilateral frontal dipoles were localised, near the left inferior frontal gyrus (BA 4) for the reconsolidated stimuli and the right middle frontal gyrus (BA 6) for new consolidated stimuli. Dipoles were generated right occipitally near the precuneus (BA 31) and the caudate for reconsolidated stimuli only, whereas dipoles were generated bilaterally temporally near the superior temporal gyrus (left: BA 42, right: BA 39) and left anterior cingulate (BA 10) for new consolidated stimuli only.

Table 5.3: Residual variances, Dipoles, Talairach co-ordinates, Brodmann's areas and approximate locations as provided by talairach daemon from (a) 100-216 ms and (b) 406-542 ms for reconsolidated and new consolidated stimuli.

Channel	Condition; Epoch; RV	Dipole	TAL co-ordinates; x, y, z	BA	Structure
P6a	Reconsolidated 100-216ms RV= 5.685%	1 2 3 4 5 6 7	25.8, -45.3, 21.0 -3.8, -4.9, 23.3 -52.2, -56.7, 25.0 18.8, 46.6, 13.0 54.6, -51.7, 31.4 15.1, -14.1, 45.9 11.0, -76.3, 48.0	31 24 39 10 40 31 7	R. Cingulate Gyrus L. Cingulate Gyrus L. Superior Temporal Gyrus R. Medial Frontal Gyrus R. Parietal Lobe-Supramarginal Gyrus R. Cingulate Gyrus R. Parietal Lobe-Precuneus
P6a	New Consolidated 100-216ms RV= 5.792%	1 2 3 4 5	10.5, -12.4, 39.1 -51.4, -53.1, 28.2 9.6, 46.3, 14.5 48.5, -55.4, 23.6 -5.9, -78.1, 40.3	24 40 10 39 7	R. Cingulate Gyrus L. Parietal Lobe-Supramarginal Gyrus R. Medial Frontal Gyrus R. Superior Temporal Gyrus L. Parietal Lobe-Precuneus
P6b	Reconsolidated 406-542ms RV= 5.611%	1 2 3 4 5 6 7	41.1, -27.7, 35.5 -56.1, -48.4, 37.3 -35.6, 42.4, 4.8 26.9, -69.8, 23.8 -30.3, 5.5, 64.1 50.2, -14.8, 17.9 -11.8, 9.5, 6.8	2 40 4 31 6 43 -	R. Parietal Lobe L. Inferior Parietal Lobule L. Inferior Frontal Gyrus R. Occipital Lobe-Precuneus L. Middle Frontal Gyrus R. Parietal Lobe-Postcentral Gyrus L. Caudate Body
P6b	New Consolidated 406-542ms RV= 4.609%	1 2 3 4 5	17.7, -6.5, 58.3 -45.2, -38.9, 38.4 53.7, -54.6, 25.7 -19.5, 46.9, 8.0 -58.9, -32.3, 10.6	6 40 39 10 42	R. Middle Frontal Gyrus L. Inferior Parietal Lobule R. Superior Temporal Gyrus L. Anterior Cingulate L. Superior Temporal Gyrus



5.7.3 Experiment 2b (24 hrs between Study Block 2 and Test Block; n=11)

5.7.3.1 Accuracy

Figure 5.16 depicts percentage accuracy across trial types. Similar to results obtained for Experiment 2a, cursory inspection of the data indicates that the Reconsolidated and Distractor conditions both achieved similar highest accuracy scores, with the Reconsolidated stimuli showing a slightly higher advantage over the Distractor stimuli. Conversely, the lowest accuracy scores were obtained for the New Consolidated trial type, as opposed to the Old Consolidated trial type in Experiment 2a. Further, unlike results obtained in Experiment 2a, the Old Consolidated trial type yielded the second lowest scores. A one-way repeated measures ANOVA was conducted to compare accuracy scores across trial types. Again a non-significant effect for Accuracy was observed (Wilks Lambda = .647, F(3, 8)= 1.453, p= .298, η_p^2 = .353), at the p>0.05 level.

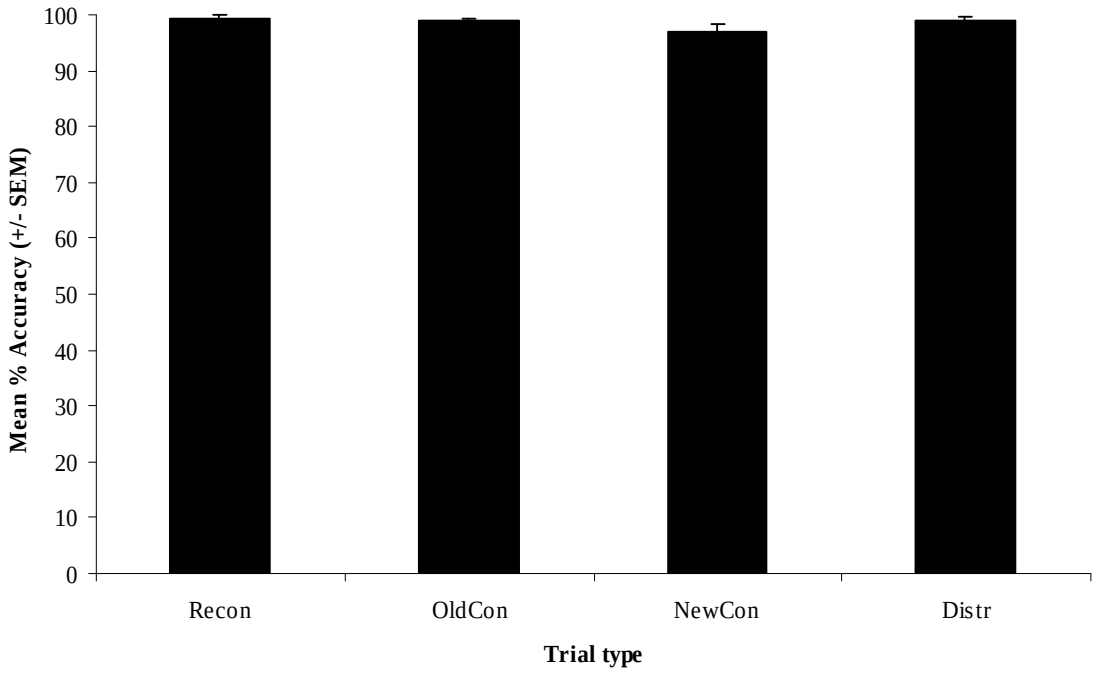


Figure 5.16: Mean percentage accuracy scores across trial type (+/- SEM) for Experiment 2b.

5.7.3.2 Reaction Time

Inspection of the RT data as Figure 5.17 infers that, unlike Experiment 2a, the quickest RT was achieved by presentations of Reconsolidated stimuli. Similar to Experiment 2a however, the slowest RT was obtained following presentation of New Consolidated stimuli, the second slowest RT was found after presentation of Distractor stimuli, and the second fastest RT was seen following presentation of Old Consolidated stimuli. RT results were in line with the accuracy data for all trial types. A one-way repeated measures ANOVA revealed a non-significant within-subjects effect for RT (Wilks' Lamba= .515, F(3, 8)= 2.516, p= .132, η_p^2 = .485), at the p>0.05 level.

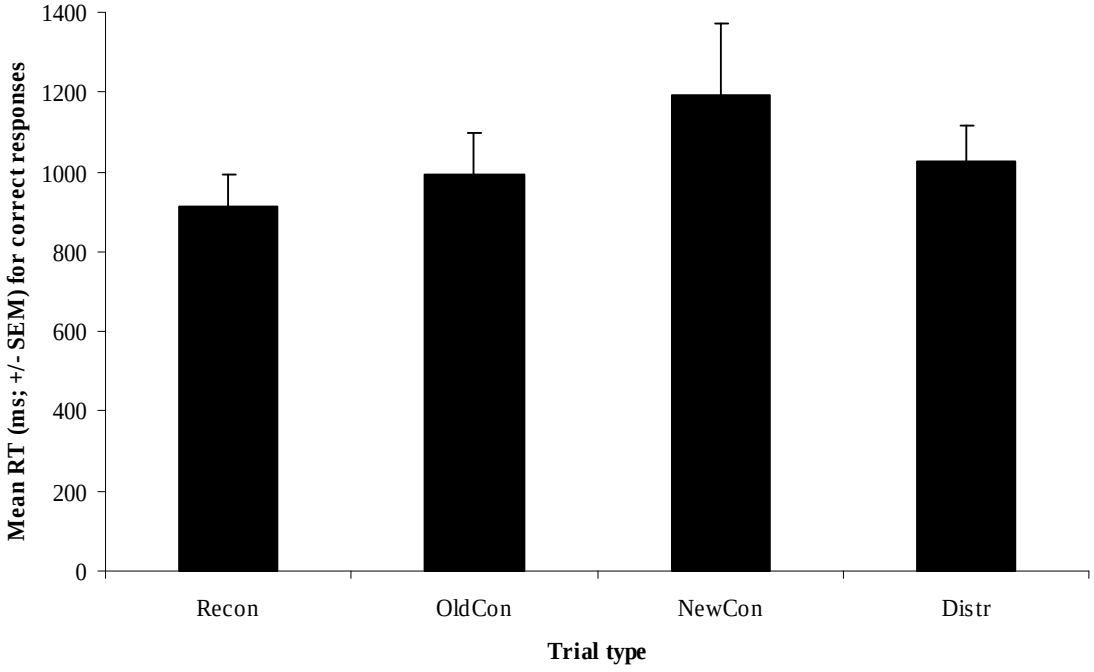


Figure 5.17: Mean RT (msec) for correct responses across trial type (+/- SEM) for Experiment 2b.

In terms of electrophysiological findings for Experiment 2b (i.e., 24 hour delay), only negligible differences, if any, were observed upon visual inspection of waveforms across trial type. Therefore, it was decided to group electrophysiological results emanating from both Experiments 2a and 2b, such that any differences between trial type regardless of

time lag between Study Block 1 and Study Block 2 could be ascertained to a greater extent given the larger sample size.

5.7.4 Combined data (Experiment 2a and Experiment 2b combined: n=26)

5.7.4.1 Accuracy

Descriptive results were broadly similar to those obtained for Experiments 2a and 2b in that the highest accuracy scores were obtained for the Reconsolidated and Distractor trial types, respectively. Further, as in Experiment 2b, the lowest accuracy scores were identified in the New Consolidated condition, while the Old Consolidated condition achieved the second lowest scores.

A 2x4 mixed factorial ANOVA was conducted to compare accuracy scores across Experimental Group (i.e., Experiment 2a or 2b) and Trial type. Using Greenhouse-Geisser correction (to account for variance in sample size across experiments), there was a significant main effect for accuracy [$F(2.47, 16.10)= 3.369$, $p= .032$, $\eta_p^2 =.123$. However, *no* interaction effect for Accuracy/Group was observed [$F(2.47, 7.21)= 1.509$, $p= .226$, $\eta_p^2 = .059$. Further, in terms of between-subjects effects, the main effect for Group did not reach statistical significance [$F(1, 14.259)= 1.446$, $p= .241$, $\eta_p^2 =.057$]. Bonferroni corrected t-tests were used to further analyse these within-group differences. As expected, accuracy elicited for the Reconsolidation stimuli (99.68±1.63) was significantly higher than that obtained for the New Consolidated stimuli (98.16±3.55; $t(25)= 2.977$, $p=.006$: Bonferroni-adjusted; $p=.036$). However the eta squared statistic (0.3) indicated a small effect size.

5.7.4.2 Reaction Time

Inspection of the RT data obtained for both Experiments 2a and 2b combined in Figure 5.18 suggests that, generally results were similar to those obtained for Experiment 2b; the quickest RT was achieved by the Reconsolidated stimuli, the slowest RT was obtained for the New Consolidated stimuli, the second slowest RT was found in the Distractor stimuli, and the second fastest RT was seen in the Old Consolidated stimuli. RT results were in line with the accuracy data for the Reconsolidated and New Consolidated stimuli.

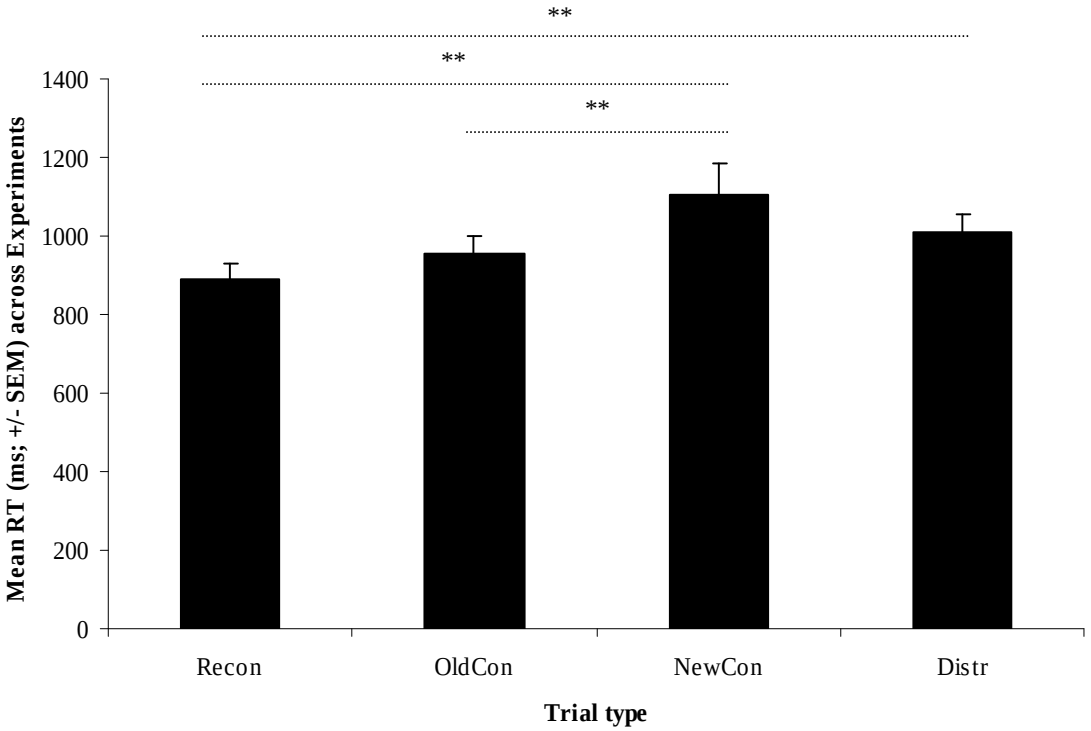


Figure 5.18: Mean RT (msec) for correct responses across trial type (+/- SEM) for Experiment 2a and 2b combined data. Only Bonferroni-corrected *p*-values are shown.

A 2x4 mixed between-within repeated measures ANOVA was conducted to compare RT scores across Experimental Group (i.e., Experiment 2a or Experiment 2b) and Trial type. There was a significant main effect for RT (Wilks' Lamba= .418, $F(3,22)= 10.204$, $p<0.001$, $\eta_p^2= .582$). However, *no* interaction effect between RT and Group was observed (Wilks'

Lambda = .964, p= .843, η_p^2 = .036). Further, in terms of between-subjects effects, the main effect for Group did not reach statistical significance [F(1, 24)= .564, p= .460, η_p^2 = .023]. Bonferroni corrected t-tests were used to further analyse these within-group differences. As expected, the mean RT for the Old Consolidated stimuli (952.63±236.31) was significantly faster than that obtained for the New Consolidated stimuli (1105.65±403.31; t(25)= -3.592, p=.001: Bonferroni-adjusted; p=.006). Further, the Reconsolidated stimuli elicited significantly faster response (888.06±210.29) than the Old Consolidated stimuli (952.63±236.31), t(25)=2.370, p=.026: Bonferroni-adjusted; p=.156; the New Consolidated stimuli (1105.65±403.31), t(25)=3.911, p=.001: Bonferroni-adjusted; p=.006, as well as the Distractor stimuli (1009.63±222.45), t(25)= 4.026, p<0.001: Bonferroni-adjusted; p=.006).

5.7.4.3 Electrophysiological Results

Visual Analysis

Modulations of frontal positivity and posterior negativity between reconsolidated stimuli old consolidated stimuli were evident at channels F9, FP2 and P6 (see Figure 5.19). Similar modulations were observed between reconsolidated stimuli and new consolidated stimuli at channels F9, F8 and P6 (see Figure 5.19). Thus, across comparisons between reconsolidated and both old and new comparisons, modulations were identified left frontally at channel F9, parietally at channel P6, fronto-parietally at channel FP2, and right frontally at channel F8.

Amplitude Comparison

Paired t-tests were used to compare reconsolidated and old consolidated stimuli across channels F9, FP2 and P6 for the specified latencies (see Figure 5.19) at the p<0.05 level. A significant mean amplitude difference was found at the F9 channel from 274-814ms [t(24)= -

2.301, *p*=.030], with reconsolidated stimuli eliciting greater amplitude. Further, a significant AUC difference was found at the FP2 channel from 848-1140 ms [*t*(25)= -2.189, *p*=.038], with reconsolidated stimuli eliciting greater amplitude. Comparing reconsolidated and new consolidated stimuli across channels F9, P6, and F8 (see Figure 5.19), significant AUC differences were found at the P6 channel from 100-220ms [*t*(25)= 2.705, *p*=.012], with reconsolidated stimuli eliciting greater amplitude, and at the F8 channel from 354-954 ms [*t*(25)= 2.129, *p*=.043], with reconsolidated stimuli eliciting greater negative amplitude.

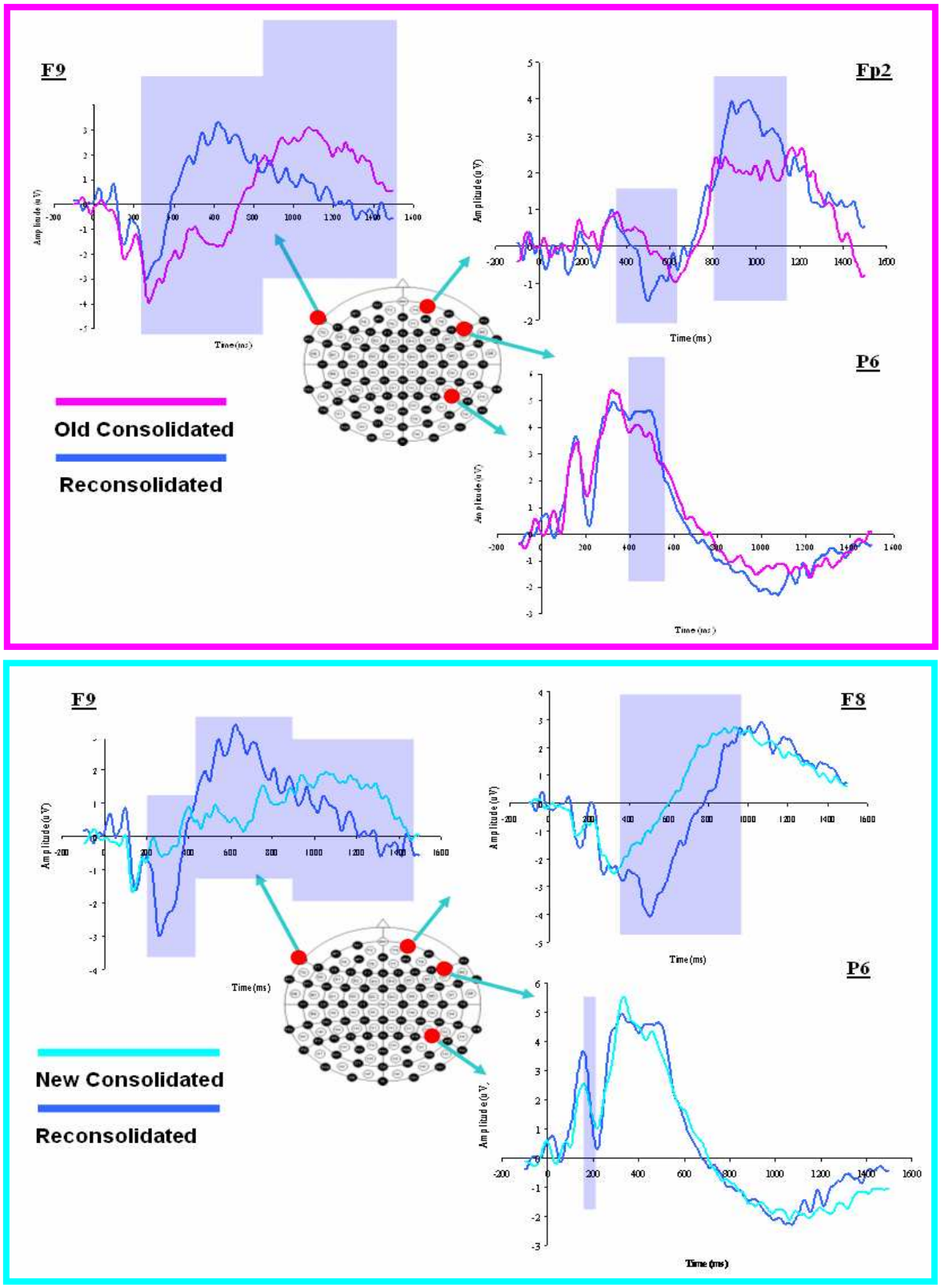


Figure 5.19: **(a)** Waveform differences between **reconsolidated** (blue lines) and **old consolidated** (pink lines) trial types at channels F9 (274-814ms; 858-1500ms), FP2 (400-600ms; 848-1140ms) and P6 (400-530ms). **(b)** Waveform differences between **reconsolidated** and **new consolidated** trial types at channels F9 (212-406ms; 400-800ms), F8 (354-954ms) and P6 (100-220ms).

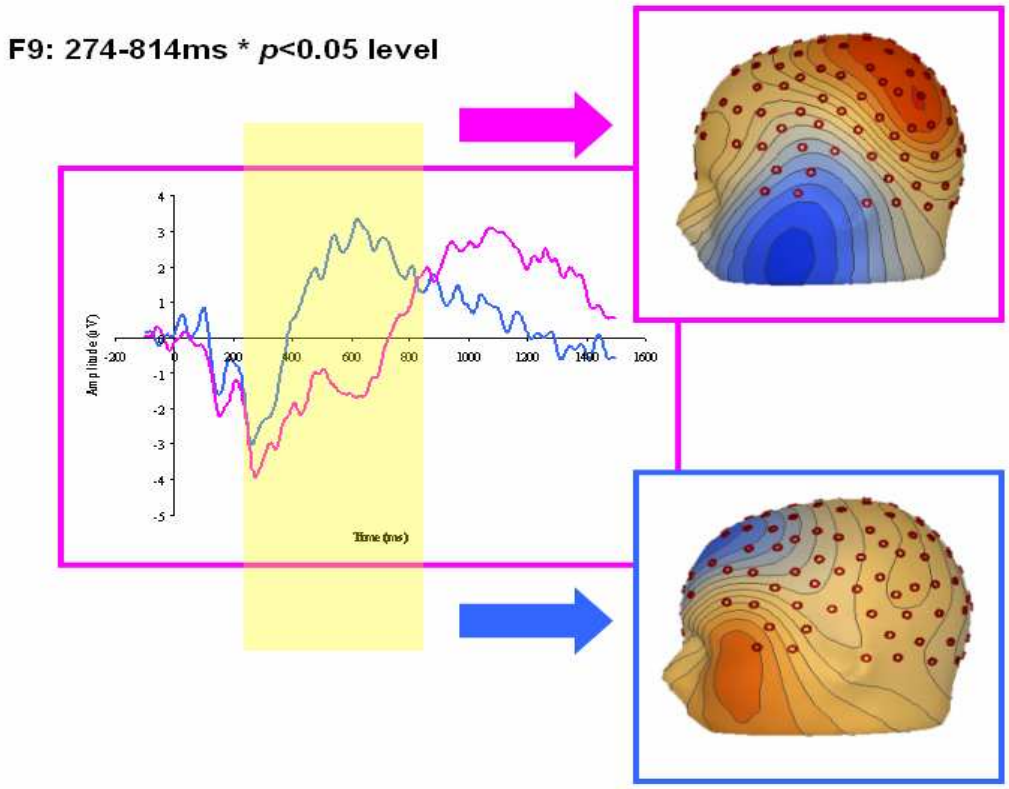


Figure 5.20: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel F9 from 274-814ms for Experimenta 2a and Experiment 2b combined data shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Left-side view).

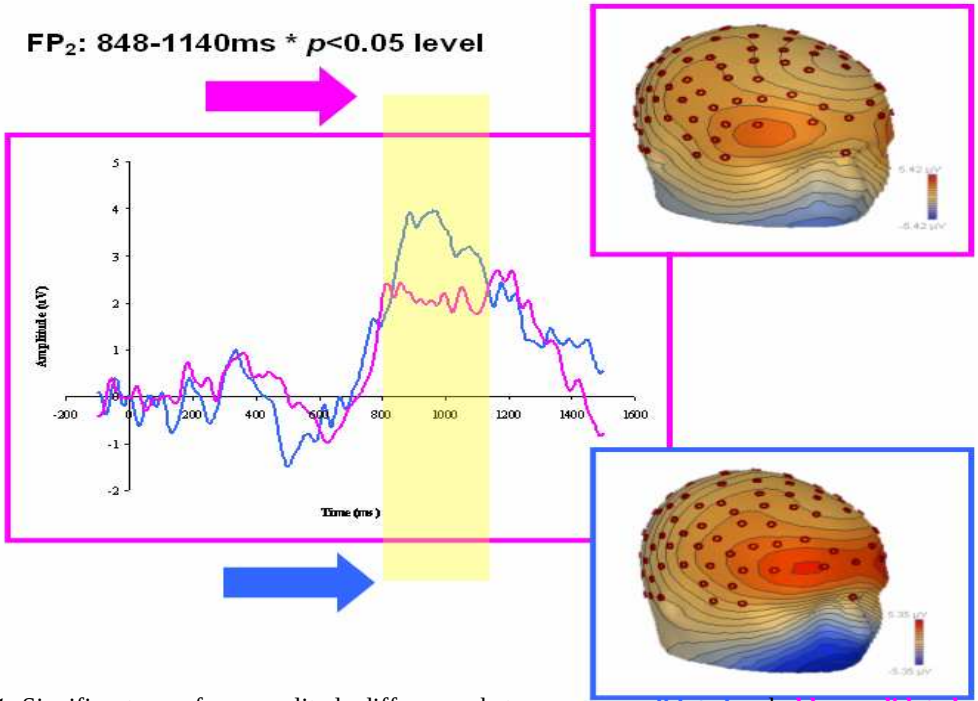


Figure 5.21: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel FP2 from 848-1140ms for Experimenta 2a and Experiment 2b combined data shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Anterior right-side view).

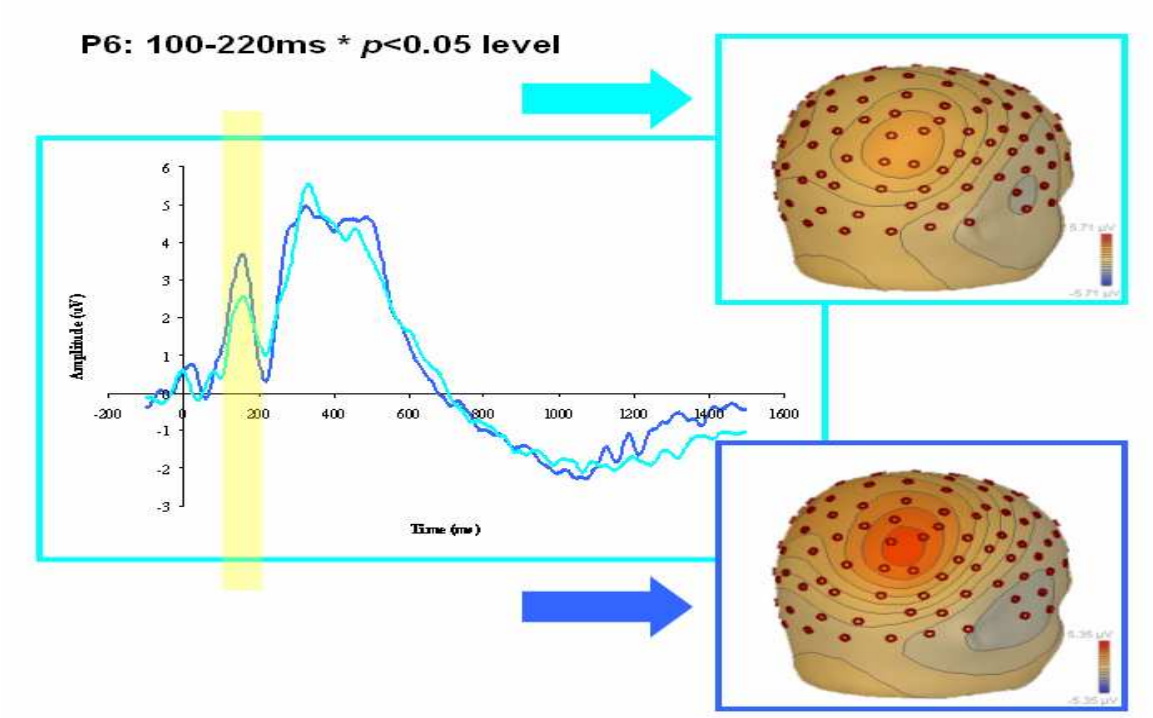


Figure 5.22: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel P6 from 100-220ms for Experimenta 2a and Experiment 2b combined data shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Posterior right-side view).

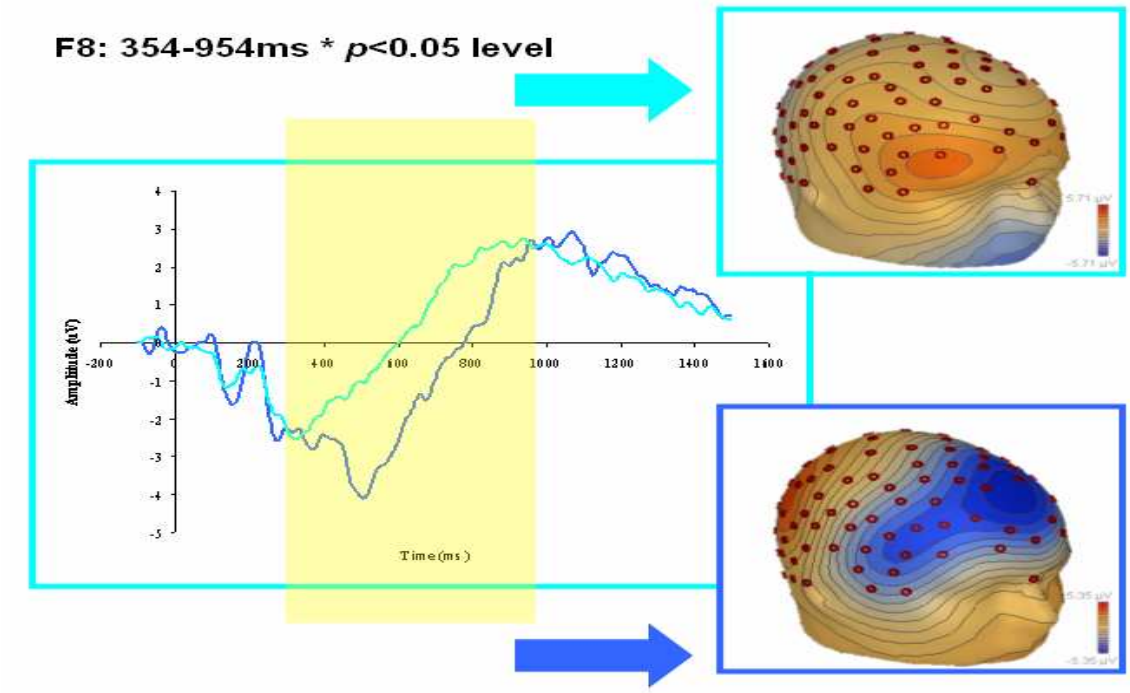


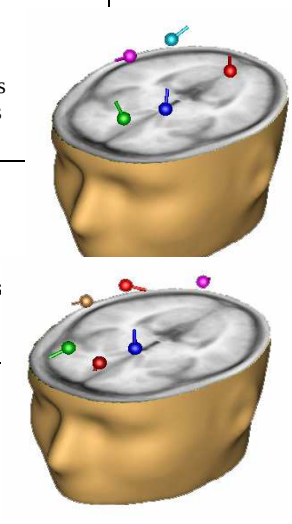
Figure 5.23: Significant waveform amplitude differences between **reconsolidated** and **old consolidated** stimuli at channel F8 from 354-954ms for Experimenta 2a and Experiment 2b combined data shown in yellow box. Topographical maps showing activity for **reconsolidated** (bottom) and **old consolidated** (top) stimuli during this time frame of significant amplitude differences (Right-side view).

5.7.4.4 Dipole Source Analysis

Dipole source models were generated from 848-1140ms for reconsolidated and old consolidated conditions (see Figure 5.4). A 6-dipole solution was generated for the reconsolidated stimuli, with an RV of 6.523%. A 6-dipole solution was generated for the old consolidated stimuli, with an RV of 6.651%. Similar dipoles were located left frontally (BA 9) near the superior frontal gyrus for reconsolidated stimuli, and near the middle frontal gyrus for old consolidated stimuli. Similarly, dipoles were generated right frontally for both conditions, again near the superior frontal gyrus (BA 6) for reconsolidated stimuli, and near the middle frontal gyrus (BA 10) for old consolidated stimuli. Similar dipoles were also generated near the right anterior cingulate gyrus (reconsolidated: BA 24, old consolidated: BA 32) for both conditions. Interestingly however, dipoles were generated near the right inferior (BA 20) and middle (BA 39) temporal gyri for reconsolidated stimuli *only*; as well as bilateral dipoles parietally near the precuneus of the left parietal lobe (BA 7) and the right inferior parietal lobule (BA 40) for old consolidated stimuli *only*.

Table 5.4: Residual variances, Dipoles, Talairach co-ordinates, Brodmann's areas and approximate locations as provided by talairach daemon from 848-1140 ms for reconsolidated and old consolidated stimuli.

Channel	Condition; Epoch; RV	Dipole	TAL co-ordinates; x, y, z	BA	Structure
FP2	Reconsolidated 848-1140ms RV= 6.523%	2 3 4 5 6	-34.1, 34.1, 29.8 8.1, 33.1, 4.9 7.6, 26.6, 59.9 53.1, -25.9, -15.7 40.5, -62.0, 23.5	9 24 6 20 39	L. Superior Frontal Gyrus R. Anterior Cingulate R. Superior Frontal Gyrus R. Inferior Temporal Gyrus R. Middle Temporal Gyrus
FP2	Old Consolidated 848-1140ms RV= 6.651%	1 2 3 4 6	46.9, -40.4, 27.7 -31.2, 41.9, 33.5 36.6, 38.2, 7.1 -13.3, -58.4, 45.4 3.5, 41.9, 6.9	40 9 10 7 32	R. Inferior Parietal Lobule L. Middle Frontal Gyrus R. Middle Frontal Gyrus L. Parietal Lobe-Precuneus R. Anterior Cingulate



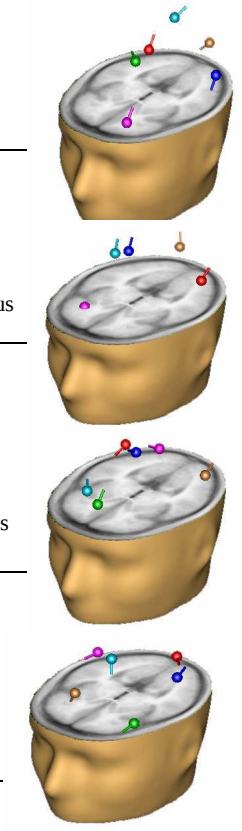
Dipole sources were further generated from 100-220 ms and 354-954 ms (Table 5.5), respectively for reconsolidated and new consolidated conditions. A 6-dipole solution, with an RV of 4.689%, was generated for the reconsolidated condition. A 5-dipole solution, with an RV of 4.078%, was generated for the new consolidated condition. Similar dipoles were located bilaterally near the precuneus of the parietal lobe (left: new consolidated, BA 7; right: reconsolidated, BA 31. A dipole was located also near the right superior parietal lobule (BA 22) for reconsolidated stimuli *only*. Similar dipoles were also generated bilaterally frontally, near the left superior frontal gyrus (BA 10) for reconsolidated stimuli, and near the right inferior frontal gyrus (BA 47) for new consolidated stimuli. Finally, similar dipoles were generated bilaterally near the superior temporal gyrus (BA 39) for both conditions (BA 22 for right superior temporal gyrus in the reconsolidated condition). The left caudate was also isolated for reconsolidated stimuli.

From 354-954 ms, 6-dipole solutions were generated for both reconsolidated and new consolidated conditions, with RVs of 4.870% and 5.749% respectively. Similar dipoles

were generated bilaterally near the inferior parietal lobule (BA 40) for both conditions (left: new consolidated, right: reconsolidated). Dipoles were located left frontally near the middle frontal gyrus (BA 10) for reconsolidated stimuli, and near the inferior frontal gyrus (BA 45) for new consolidated stimuli. Similarly, dipoles were generated left occipitally (BA 18) and near the right insula (BA 13) for both conditions. Dipoles were generated near the left superior temporal gyrus (BA 22) and left anterior cingulate gyrus (BA 24) for reconsolidated stimuli *only*. Conversely, dipoles were generated near the right medial frontal gyrus (BA 9) for new consolidated stimuli *only*.

Table 5.5: Residual variances, Dipoles, Talairach co-ordinates, Brodmann's areas and approximate locations as provided by Talairach Daemon from (a) 100-220ms and (b) 354-954 ms for reconsolidated and new consolidated stimuli.

Channel	**Condition; Epoch; RV**	**Dipole**	**TAL co-ordinates; x, y, z**	**BA**	**Structure**
P6	Reconsolidated 100-220ms RV= 4.689%	1 2 3 4 5 6	24.0, -44.1, 33.9 -6.3, 0.8, 20.5 -50.6, -60.3, 18.9 -23.0, 49.2, 4.2 34.0, -79.0, 47.0 54.1, -52.5, 16.9	31 - 39 10 7 22	R. Parietal Lobe-Precuneus L. Caudate L. Superior Temporal Gyrus L. Superior Frontal Gyrus R. Superior Parietal Lobule R. Superior Temporal Gyrus
	New Consolidated 100-220ms RV= 4.078%	1 2 3 4 5	-48.0, -57.6, 21.9 48.0, -57.6, 21.9 31.5, 30.5, -0.3 -8.4, -71.2, 42.0 26.7, -11.2, 47.7	39 39 47 7 6	L. Superior Temporal Gyrus R. Superior Temporal Gyrus R. Inferior Frontal Gyrus L. Parietal Lobe-Precuneus R. Frontal Lobe-Precentral Gyrus
F8	Reconsolidated 354-954ms RV= 4.870%	1 2 3 4 5 6	32.8, -41.1, 39.3 -50.8, -48.6, 16.5 -31.9, 44.8, 8.8 -4.8, 24.5, 20.8 55.7, -38.3, 16.0 -3.3, -90.0, -11.0	40 22 10 24 13 18	R. Inferior Parietal Lobule L. Superior Temporal Gyrus L. Middle Frontal Gyrus L. Anterior Cingulate R. Insula L. Occipital Lobe-Lingual Gyrus
F8	New Consolidated 354-954ms RV= 5.749%	1 2 3 4 5 6	-18.1, -77.8, 24.2 -46.1, -44.9, 24.3 -52.3, 29,7, 5.5 48.7, -34.6, 23.4 10.0, 46.4, 25.4 34.5, -39.1, 18.7	18 40 45 13 9 13	L. Occipital Lobe-Cuneus L. Inferior Parietal Lobule L. Inferior Frontal Gyrus R. Insula R. Medial Frontal Gyrus R. Insula



5.8 Discussion

The aim of the current study was to compare the electrophysiological correlates and neural generators of remote and newly consolidated memory traces with reconsolidated traces, as well as to isolate possible indices of updating an existing memory trace. It was hoped that through using the 'old/new' effect protocol, indices related to both semantic and episodic processes could be used to ascertain differences (or indeed similarities) between both old and newly consolidated memory traces with reconsolidated traces. Secondly, we attempted to address a highly contentious issue within the reconsolidation realm, that of the role of reconsolidation in the updating of information, in terms of declarative memory, which is an integral component of human mental flexibility.

Behaviourally, no significant effect for accuracy was found when participants were exposed to the test-block within a few hours of exposure to the second study block (Experiment 2a) or after 24 hours (Experiment 2b). However, the reconsolidated stimuli elicited greater response accuracy than both the old and newly consolidated stimuli in Experiments 2a and 2b, respectively. Thus, it appears that testing memory for episodic traces (i.e., probes) *within hours* of reactivation of the original memory trace (given 24 hours to consolidate) renders already consolidated traces labile once again, as suggested by the reconsolidation hypothesis. Conversely, testing memory for episodic traces 24 hours following reactivation and updating of the original memory trace affects these newly consolidated traces, as opposed to old consolidated traces. It was found that, combining both groups, the reconsolidated stimuli elicited greater response accuracy than *both* old and newly consolidated stimuli. In this case, it would appear that reactivation of episodic memory traces leads to instability of the trace resulting in disruption of old and new consolidated traces in favour of reconsolidated traces.

Nader and colleagues (2005) propose a reconsolidation process involving three steps: (1) Reactivation of the existing memory returning it to a labile state, (2) modification of the existing memory, and (3) reconsolidation of the modified memory over a period of time. Both Experiments 2a and 2b clearly demonstrated the first two steps (the reminder reactivated the original memory trace, and the presentation of the new triplet-forming stimulus modified the existing memory). These experiments also served to answer the question concerning whether the original memory was altered immediately or whether, as assumed by Nader (2003), memory modification involves a time-dependent reconsolidation process. In this case, we found that administering the memory test immediately following memory trace reactivation lead to destabilization of the original memory, whereas administering the memory test *24 hours after* trace reactivation lead to destabilization of the newly formed memory trace *only* (as opposed to the already consolidated/original memory trace). Thus, reactivation of an episodic memory trace exerts an *immediate* effect on memory for that trace. We herein demonstrate that the modification of episodic memories depends critically upon their preceding reactivation as suggested by the reconsolidation account. Similar to what has been found for Pavlovian conditioning (e.g., Nader *et al.*, 2000), instrumental conditioning (e.g., Wang *et al*., 2005), and human procedural memory (Walker *et al.*, 2003), reactivated episodic memories also undergo a time-dependent reconsolidation process: incorporation of *new* information did not occur immediately but was seen 24 hours after memory reactivation and subsequent presentation of new material.

In terms of reaction time, a significant effect for RT was found when participants were tested *immediately* following reactivation of old consolidated traces. A significantly slower RT was found for the new consolidated trial type when compared to the old consolidated trial type, thereby reinforcing the aforementioned possibility that incorporation of *new* information does not occur immediately but is instead evident 24 hours after memory

reactivation and subsequent presentation of new material. Furthermore, Takashima and colleagues (2007) also reported that stabilized associations for face-location stimulus pairs were retrieved faster than labile associations. Thus, memory stabilization is associated with faster access to stored traces. The increase in speed of access to old consolidated stimuli could also be attributable to the participants' repeated exposure to the identical memory cues as well as repeated rehearsal of the processes involved in search (Nadel *et al*., 2007). Additionally, the reconsolidated trial type elicited significantly quicker RTs than *both* new consolidated and distractor trial types, thereby providing further support for reconsolidation theory and lability in particular. No significant effect for RT was found when participants were tested 24 hours following exposure to Study Block 2. Combining data from both experiments, a significant main effect was found for RT. However, no main effect for group and no interaction effect between RT and group were observed. In this case, the old consolidated stimuli elicited a significantly faster RT than new consolidated stimuli. Further, the reconsolidated stimuli elicited faster RTs than *all* other trial types (i.e., old consolidated, new consolidated and distractor). Thus, there appears to be a form of trade-off between old consolidated and reconsolidated stimuli, with reconsolidated stimuli leading to quicker RTs than all other trial types. Overall, it appears that reconsolidated traces elicited a quicker RT than did non-reactivated distractor stimuli. Such a finding differs from previous findings that false, previously unseen, stimulus pairs elicit higher response accuracy and quicker RT than true, previously encountered stimulus pairs without a contextual background (see Chapter 3). Given this effect for RT was immediate and not elicited 24 hours after reactivation of the initial memory trace, it would appear that reactivation has led to interference of the original trace and allowed for structural reorganization of the trace.

However, a potential limitation of the experimental design concerns the fact that the reconsolidated items contained a greater load (i.e., three associated items) than the

consolidated items (i.e., two items), thereby potentially confounding observed effects. It is suggested that future studies within the realm should adopt methods similar to those employed by Hupbach *et al*. (2007) wherein counterbalanced lists of objects were employed across consolidation and reconsolidation groups (see Chapter 1 for greater detail) to test for episodic memory effects.

Electrophysiologically, modulation of the frontal positivity and posterior negativity between reconsolidated and old consolidated stimuli was evident left frontally, parietally, anterior frontally, and right frontally for Experiment 2a and the combined data set (i.e., Experiment 2a and 2b; with the exception of F8). Similar modulations were observed between reconsolidated stimuli and new consolidated stimuli at the same electrode sites for both Experiment 2a and combined data. Thus, for reconsolidated and both old and new comparisons, modulations were identified left frontally at channel F9, parietally at channel P6, fronto-parietally at channel FP2 at the left frontal pole, and right frontally at channel F8. ERP data accrued for Experiment 2b were not analysed herein due to similar morphology across trial types.

Interestingly, regarding frontally-mediated activation, according to the HERA model (Nyberg *et al*., 1996; see Introduction to Experiment 2), the left prefrontal cortex is differentially more involved in retrieval of information from semantic memory, and in simultaneously encoding novel aspects of the retrieved information into episodic memory, than is the right prefrontal cortex. The right prefrontal cortex, on the other hand, is differentially more involved in episodic memory retrieval than is the left prefrontal cortex. The trend suggested by the current findings is in line with such a model. In this case, greater amplitude was noted in response to reconsolidated stimuli left frontally than both old and new consolidated stimuli (a significant difference was only found between reconsolidated and old consolidated stimuli with the combined data set), followed by a greater amplitude for

reconsolidated stimuli right frontally compared to old stimuli for both Experiment 2a and the combined data. This trend was also found between reconsolidated and newly consolidated stimuli for Experiment 2a, albeit non-significantly. Thus, according to the model, it would appear that participants initially retrieved previous knowledge concerning prior exposure to all trial types from *semantic* memory, but to a greater extent for reconsolidated stimuli. The right prefrontal region may have subsequently been recruited to isolate episodic related information concerning previous exposure to both reconsolidated and old consolidated traces, but to a greater extent for reconsolidated stimuli. This model also serves to explain the behavioural pattern, that reconsolidated stimuli elicited greater response accuracy than old consolidated stimuli in Experiment 2a and newly consolidated stimuli in Experiment 2b.

A quintessential finding of many ERP studies of recognition memory is that presentation of old/repeated items elicits more positive-going ERPs than does presentation of new/unrepeated items (reviewed in Johnson, 1995; Rugg, 1995; Rugg & Allan, 2000). Such ERP 'old/new effects' typically onset approximately 300–400 ms post-stimulus, last 300–600 ms and, when words are used as stimuli, are generally of greatest magnitude at left parietal and adjacent centro-parietal electrodes. This was effect was found at channel P6 for reconsolidated and old consolidated comparisons for Experiments 2a and the combined data, as well as for reconsolidated and newly consolidated comparisons for Experiment 2a. However, only the comparison between reconsolidated and newly consolidated stimuli reached statistical significance. In this case, exposure to reconsolidated stimuli yielded significantly greater amplitude at this juncture than did exposure to new consolidated stimuli. Such a finding correlates with the behavioural finding of faster RTs to reconsolidated stimuli than newly consolidated stimuli. Thus, it may be the case that participants recognized the reconsolidated stimuli as old when tested immediately after memory trace reactivation.

The parietal old/new effect also comprises two posterior components. The first is a parietal distributed negative wave (N400) that has been attributed to implicit memory processes (Rugg *et al*., 1998) such as integration of the stimulus with the already-present information in memory (i.e., semantic knowledge). A reduction in its amplitude for repeated (i.e., old) items is interpreted as easier access to the trace (Anderson & Pirolli, 1984; Morton, 1969). This effect was found across both old and new comparisons with reconsolidated stimuli for both Experiment 2a and combined data. In all cases, the reconsolidated stimulus presentation led to greater amplitudes than both old and new consolidated stimuli, with old stimuli eliciting the lowest amplitude. However, these differences did not reach statistical significance. The second component involves a late positivity, termed the LPC or P300 (Van Petten *et al.*, 1991). The LPC has been attributed to elaboration or mnemonic binding that leads to formation or retrieval of an episodic trace consisting of the item and its context. The modulation of this component is thought to reflect the reactivation of memory representation and to constitute the substrate of episodic information retrieval (McClelland *et al*., 1995). Indeed, the LPC amplitude has also been found to be larger for those items rated as being consciously remembered (Smith, 1993; Smith & Guster, 1993) and is larger for words whose study context is correctly retrieved (Trott, 1999; Wilding & Rugg, 1996). The LPC modulation is larger for old stimuli than for new stimuli (Rugg, 1995; Johnson, 1995). This effect was found comparing reconsolidated and both new and old consolidated stimulus presentations in Experiment 2a, as well as comparing reconsolidated and old consolidated stimuli using the combined data set. However, the difference was only significant between reconsolidated and newly consolidated stimuli when participants were tested *immediately following* reactivation and updating of the original trace (i.e., 1-2 hours).

Furthermore, the work of several groups (reviewed in Friedman & Johnson, 2000) has promoted the idea that an early (300–500 ms), mid-frontal, negative ERP effect is related

to familiarity (termed the ‘‘FN400 old/new effect’’, for frontal N400), and a later (400–800 ms), parietal, positive ERP effect is related to recollection (here called the ‘‘parietal old/new effect’’). The FN400 effect was observed at channels F9 and FP2 between reconsolidated and newly consolidated stimuli for Experiment 2a, with greater negative-going amplitude evident for reconsolidated stimuli, albeit non-significantly. This effect was also observed between reconsolidated and old consolidated stimulus presentations at channel FP2 for both Experiment 2a and the combined data, albeit non-significantly. This suggests a *trend* whereby the reconsolidated stimuli are eliciting familiarity-based processing at this time point. The later parietal positive-going ERP effect is evident at channel P6 between reconsolidated and old consolidated stimuli for Experiments 2a and the combined data, as well as between reconsolidated and newly consolidated stimuli for Experiment 2a only. The only significant difference found in this regard is between reconsolidated and newly consolidated traces in Experiment 2a. Thus, it would appear that participants are employing episodic-mediated, strategic, conscious recollection based processing at this time point to distinguish previously presented reconsolidated stimuli from newly consolidated traces. The lower amplitudes found predominantly in response to old consolidated stimuli may be interpreted as easier access to the trace than in response to reconsolidated stimuli which have been both reactivated and updated.

Dipole modeling for these differences identified possible generators for these modulations at distinct and similar yet hemispherically divergent regions. Comparing reconsolidated and old consolidated stimulus presentations in Experiment 2a, similar dipoles were located in the region of the precuneus, bilaterally in and around the medial frontal gyrus, the bilateral temporal poles, bilaterally near the tempero-parietal junction and left frontally. Combining data, similar dipoles were generated bilaterally near the frontal region and near the right anterior cingulate gyrus. Regarding, MTL activation patterns, dipoles were

generated bilaterally near the temporal gyrus, in and around the middle temporal gyrus for old consolidated stimuli, and near the superior temporal gyrus for reconsolidated stimuli in Experiment 2a. The right inferior and middle temporal gyrus was further located for reconsolidated stimuli *only* in for combined data. Thus, for reconsolidated stimuli, dipoles suggest the activation of a distributed network involving the precuneus (often associated with procedural/habit learning), the medial frontal gyrus (responsible for executive processing such as the ability to recognize future consequences resulting from current actions and semantic memory storage), the temporal gyrus (associated with the visual processing involved in object perception and recognition as well as episodic/declarative memory and possible transference from episodic to semantic memory), the tempero-parietal junction (the parietal lobe of which is associated with a role in the integration of sensory information and visuospatial processing) and the anterior cingulate gyrus (which functions as an integral component of the limbic system, which is involved with emotion formation and processing, learning, and memory. Also, executive control needed to suppress inappropriate unconscious priming is known to involve the anterior cingulate gyrus).

Such a pattern of dipoles does not conform to Classic Consolidation Theory (Squire, 1992) stipulating that remote memories are stored in the neocortex as opposed to MTL regions. The pattern of dipoles found herein conforms to a greater extent to the Multiple Trace Theory proposed by Nadel and Moscovitch (1997) which posits that the establishment of long-term memories involves a lengthy interaction between the hippocampal region of the medial temporal lobes (MTLs) and neocortical regions both adjacent to the MTL (e.g., perirhinal and parahippocampal cortices) and at a distance (e.g., prefrontal cortex). Unlike standard theory, Multiple Trace Theory posits that the hippocampus remains an integral part of the memory trace and is thus always involved in retrieval of long-term episodic memories regardless of the age of the memory. Evidence supporting this view comes from

neuroimaging studies showing that retrieval of detailed episodic memories activates the hippocampus irrespective of how old these memories are (e.g., Maguire *et al*., 2001; Rekkas & Constable, 2005) and from studies showing that remote episodic memories retrieved by amnesic patients lack the detail present in remote episodic memories of an individual with an intact hippocampus (Moscovitch *et al*., 2005). However, a confound of this study could reside in the fact the dipole models were only generated for old consolidated stimuli tested only a few hours following initial exposure to the memory trace. In line with previous research documenting that sleep exerts an impact on the stabilization of both remote and reconsolidated memory traces (Stickgold & Walker, 2005), future neuroimaging studies could ascertain the impact of a night's sleep on both old consolidated and reconsolidated memory traces, not just behaviourally but also anatomically.

Regarding neocortical activation patterns, such similarities suggest large-scale network-level reorganization with stabilization, as proposed by Frankland and Bontempi (2005). The superior frontal gyrus was localised for old consolidated stimuli, whereas the middle frontal gyrus was localised for reconsolidated stimuli in Experiment 2a; by contrast, the opposite pattern was observed for when data were combined. The superior frontal gyrus is thought to contribute to higher cognitive functions and particularly to working memory (Rowe *et al*., 2000) with the left hemisphere particularly involved in spatially oriented processing (Boisgueheneuc *et al*., 2006). The middle frontal gyrus however has been shown to mediate access to phonology and semantics (e.g., Liu *et al*., 2006). Further, it has been suggested that executive mechanisms operative within the medial frontal gyrus preserve fundamental aspects of input processing streams (Talati & Hirsch, 2005). Thus, it may be the case that working memory processes are mediating access to remote traces, whereas participants are attempting to access what they remember concerning semantic features of the reconsolidated traces they were exposed to in Study Block 1 prior to reactivation. In any

case, increased cortical activation is predicted by both the Standard Theory of Consolidation and Multiple Trace Theory, which both suggest that cortical-cortical connections will be strengthened as a memory is consolidated. However, Multiple Trace Theory emphasizes the importance of repeated retrieval for reconsolidation rather than the mere passage of time, while Standard Theory does not directly address this issue. We assume that these cortical patterns of activity are related to the behavioral changes described earlier, but further research is needed to clarify how the specific behavioral changes are related to neuroimaging changes.

Interestingly, the anterior cingulate activation observed in response to reconsolidated stimuli suggest the involvement of the limbic system in memory reconsolidation in humans, which has thus far been predominantly demonstrated in context memory in animals (e.g., Hall *et al*., 2002). Such a finding therefore has important implications regarding potential treatment directions for drug addicted populations wherein relapse to drug taking is often precipitated by exposure to emotionally significant drug-related contextual cues (see General Introduction for more comprehensive discussion). Indeed, the learning of an addictive behaviour involves phylogenetically old brain structures such as the amygdala of the limbic system in which the process of contextual learning is influenced by basic emotional states. Furthermore, the executive control required to suppress inappropriate unconscious priming is known to involve the anterior cingulate gyrus. Priming refers to the facilitated remembrance of similar experienced situations or previous perceived patterns of stimuli. A repeated stimulus or sensation is remembered or recognized preconscious and in dependence of its context, even if the new stimulus is not completely identical with the previous one (see Markowitsch, 1999). Activity in this region in response to reconsolidated stimuli would therefore provide further support for a role for reconsolidation in the updating of previously encountered memory traces on an unconscious level. Given that the memory of addiction reflects coherence of the history of one's

own life together with the environmental context, which is not consciously reflected or verbalized, the present demonstration of the involvement of brain regions associated with both episodic memory and priming in response to reconsolidation-based processing could have important therapeutic ramifications.

In conclusion, frontal and fronto-parietal modulations were identified for reconsolidated compared to both old and new memories. It is suggested that the similarity of component morphologies accompanied by ERP amplitude differences may imply a quantitative rather than qualitative difference in the nature of reconsolidation compared to consolidation processes. Dipoles were located bilaterally in and around the medial frontal gyrus, the bilateral temporal poles, bilaterally near the tempero-parietal junction and left frontally. Ultimately the pattern of activation elicited by exposure to reconsolidated stimuli in the current study suggests a network comprising frontal, parietal, temporal and limbic regions which all work in tandem to 'update' already consolidated memory traces. The present study therefore represents an important step in terms of mapping reconsolidation-based processing within the human sphere, both with respect to timing and memory updating effects, and has important ramifications regarding the successful treatment of addiction memories in particular which are associated with similar networks to those isolated in response to reconsolidated stimuli herein (e.g., reward and executive functioning within frontal regions and cue-based memories within the limbic system). We further added to the debate concerned with the involvement of the hippocampus in long-term memory, ultimately contending, in line with Multiple Trace Theory, that the hippocampus remains an integral component of the memory trace and is thus always involved in retrieval of long-term episodic memories regardless of the age of the memory.

6

Chapter VI

The effect of stress and context on reconsolidation of episodic hippocampally-based memory in humans

We wish to thank Niamh Merriman and Jennifer Murphy for assistance with data collection.

Abstract

The present experiment attempted to elucidate the impact of stress during reconsolidation, in order to unravel the phenomenon whereby "re-activated" memories can be weakened, altered or erased by inhibited protein synthesis in the hippocampal formation. In particular, we were concerned with the special role of context cues. It was predicted that acute stress induction would impair hippocampal functioning, and hence context coding, in an associative memory task involving both consolidation and reconsolidation. Three groups were used for this task; a 'Consolidation' group (n=14), a 'Reconsolidation' group (n=14) and a Control group (n=10). Visual paired-associates (VPAs) were either presented with unique local contextual backgrounds for the Reconsolidation group, or with no backgrounds for the Consolidation group. Memory traces were subsequently given time to consolidate. 24 hours later, participants were first exposed to a psychosocial stressor task (based on the Trier Social Stress Task). Immediately afterwards, participants were exposed to reactivation of the original memory trace. In the Reconsolidation group, participants were exposed to a filler task wherein contextual backgrounds were reinstated, thereby reactivating the consolidated memory trace. Alternately participants in the Consolidation group were shown the same filler task superimposed upon a white background. Recall of original VPA pairs was then tested *without* context presentation. It was predicted that stress would impair memory retrieval to a greater extent for the Reconsolidation group than the Consolidation group. In terms of accuracy performance, although a non-significant main effect was found for context, the stressor impaired both Consolidation and Reconsolidation groups relative to the Control group. However, the stressor did not impact on Consolidation and Reconsolidation groups differently. Given that retrieval was affected, albeit non-significantly, it was concluded that stress impaired reconsolidation. Results are discussed in light of context findings.

6.1 Introduction

There is extensive evidence indicating that elevated glucocorticoid (GC) levels inhibit memory *retrieval* in animals and healthy human participants (Buss *et al*., 2004; De Quervain *et al*., 2003; Het *et al*., 2005; Kuhlmann *et al*., 2005a; Roozendaal *et al*., 2003; Roozendaal *et al*., 2004b; Sajadi *et al*., 2007; Wolf *et al*., 2001). Furthermore, this impairment seems to be dependent upon the activity of the adrenergic system (Kuhlmann & Wolf, 2006; Roozendaal *et al.*, 2004; Tollenaar *et al.*, 2008a). The hippocampus is highly susceptible to stress given that it is equipped with a dense concentration of receptors for glucocorticoids (McEwen *et al.* 1986) and is critically involved in episodic memory (Strange *et al*., 1999). There is considerable evidence that stress, or the high levels of glucocorticoids accompanying stress, can disrupt hippocampal functioning, thereby weakening or completely disrupting those aspects of contextual and episodic memory subserved by this structure (Kim & Diamond, 2002; De Quervain *et al.*, 2000, Newcomer *et al.,* 1999; Lupien *et al.,* 1998; Nadel & Jacobs, 1998; Diamond & Rose, 1994) and consequently impairing performance on contextual and episodic memory tasks. Context is a critical component in memory reconsolidation, particularly for hippocampally-based learning, since the hippocampus is critical for learning about context (Nadel, Payne & Jacobs, 2002). Although the modulating effect of stress has thus far been elucidated in terms of encoding, consolidation and retrieval, its role in the *reconsolidation* of hippocampal context-based memory is relatively unknown in normal human samples.

Memories for hippocampus-dependent tasks undergo reconsolidation (Mactutus *et al.*, 1979; Przybyslawski, Roullet & Sara, 1999; Schneider & Sherman, 1968). For example, using a radial arm maze with rats, systemic postreactivation injections of propranol were

effective at producing amnesia if the memory was first reactivated (Przybyslawski *et al*., 1999). Similarly, disruption of CREB-mediated transcription in the forebrain interferes with the reconsolidation of contextual fear memories (Kida *et al*., 2002). In support of the possibility that memories stored within the hippocampus itself might undergo reconsolidation are the findings showing that reactivation of contextual memories induces the expression of *zif268,* a gene implicated in the consolidation of new hippocampal-dependent memories (Hall *et al*., 2001). In the majority of studies conducted thus far, memory reconsolidation has been demonstrated by the amnesic effects induced by the administration of blockers, such as protein synthesis inhibitors or β-blockers such as propranolol (Przybyslawski *et al*., 1999; Nader *et al*., 2000a), or by the learning of a new memory (Walker *et al*., 2003; Boccia *et al*., 2005), following the presentation of a reminder.

Only a few groups have thus far addressed the effects of stress or glucocorticoids on the reconsolidation of memory, or post-retrieval memory. In animal studies, post-retrieval administration of propranolol has been found to disrupt spatial memory and inhibitory avoidance learning in rodents (Przybyslawski *et al*., 1999), as well as auditory fear conditioning (Debiec & Ledoux, 2004), with *both* findings explained in terms of impaired reconsolidation processes. Tronel and Alberini (2007) demonstrated that reconsolidation might also be dependent upon the glucocorticoid system, as they found that a glucocorticoid receptor antagonist disrupted conditioned fear in rats after reactivation of an inhibitory avoidance memory. In a similar vein, Maroun and Akirav (2007) found an impairing effect of stress on reconsolidation in rats, which was reversed by a glucocorticoid receptor antagonist. Cai and colleagues (2006) reported that when glucocorticoids were administered immediately after reactivation of a contextual fear memory, subsequent recall was significantly diminished. However, the effect of postreactivation glucocorticoid on contextual fear memory was reversed by a reminder shock, thereby suggesting that augmentation of single-

trial contextual fear memory extinction is the more likely mechanism for these effects of postreactivation corticosterone on subsequent memory (Cai *et al*., 2006). Maroun and Akirav (2008), however, provided evidence that stress might have an inhibitory effect on the reconsolidation of recognition memory. They found that in habituated (i.e., high arousal level) and nonhabituated (i.e., low arousal level) rats, exposure to an out-of-context stressor impaired long-term reconsolidation of object recognition memory. Further, Zhao and colleagues (2007) were the first to demonstrate that cocaine-conditioned place preference (i.e., context cue memory) was blocked in rats experiencing stress following re-exposure to the previously drug-paired chamber, thereby demonstrating a potential inhibitory effect of stress on the reconsolidation of contextually mediated drug memory.

Extensive evidence suggests that the basolateral amygdala (BLA) is a key region that regulates the effects of stress and glucocorticoids on memory formation, consolidation *and* reconsolidation (Roozendaal & McGaugh, 1997; Roozendaal *et al*., 2002; Roozendaal, 2003). Lesions of the BLA block the dexamethasone-induced memory enhancement in an inhibitory avoidance task, suggesting that the BLA is a critical site for the modulatory effect of glucocorticoids on memory formation (Roozendaal & McGaugh, 1996). It has been reported that glucocorticoids in BLA contribute to memory consolidation. Post-training infusions of a GR agonist into the BLA enhance memory performance (Roozendaal & McGaugh, 1997). Immediate postretrieval intra-BLA infusion of RU486 selectively impairs long-term auditory fear memory, suggesting that glucocorticoid receptors in the BLA are required for reconsolidation of auditory fear memory (Jin *et al*., 2007). Wang and colleagues (2008) also demonstrated that a GR antagonist infused into the BLA reversed the inhibitory effect of post-reactivation stress on a morphine reward memory. This finding suggests that activation of GRs in the BLA plays a critical role in the effects of postreactivation stress on context-cue dependent drug-related memory.

Presently there is a paucity of *human* studies concerned with the effects of cortisol on the reconsolidation process. Tollenaar and colleagues (2008a) recently examined the effects of elevated stress hormones on postretrieval processes in humans. In line with animal studies, a postretrieval decline in memory performance was observed when memories were reactivated *during* stress (i.e., 5 weeks after encoding). More recently Tollenaar and colleagues (2009) examined *both* the immediate and prolonged effects of a single administered dose of cortisol or propranolol on memory retrieval in healthy young men, with a one week interval between acquisition and retrieval. Memory retrieval for *both* neutral and emotional information was impaired by a single dose of cortisol compared to placebo. The cortisol-induced memory impairment remained, even following the one week interval. Conversely, *no* immediate or prolonged effects of propranolol on memory retrieval were found, despite significant reductions in sympathetic arousal. Such a finding lends support to the hypothesis that cortisol is capable of attenuating emotional memory recall over longer time spans and may therefore be more beneficial in terms of augmenting the treatment of disorders such as PTSD and phobias using beta-blockers such a propranolol.

The effect of *blocking* adrenergic activity during memory reactivation has recently been studied in humans (e.g., Brunet *et al*., 2008; Miller *et al*., 2004). Miller and colleagues reported that fear conditioning was reduced when a conditioned cue was reactivated and followed by noradrenaline beta-blockade. Furthermore, Brunet and colleagues found that postretrieval propranolol reduced psycho-physiological responding to mental imagery of a past traumatic event in PTSD. Given that the hippocampus is highly susceptible to stress, the current study intends to isolate the locus of effect and determine the mechanisms through which stress interacts with reconsolidation, and in particular how it influences the special role of context cues. It is hereby hypothesized that acute stress induction will impair hippocampal

functioning, and hence context coding, in an associative memory task involving consolidation and reconsolidation.

6.2 Method

6.2.1 Participants

Thirty-four undergraduate and postgraduates students recruited from the NUIM campus took part in the study. Participants were recruited on the basis that the study involved ascertaining physiological reactions to a psychosocial stressor. Participants were randomly assigned to one of three experimental groups in a between-subjects design; Control (n=10), Consolidation (n=10) and Reconsolidation (n=14). Of the total sample, participants comprised 21 females and 13 males, with a mean age of 26.79 yrs (±6.66; age range 19-28 yrs); of which the Consolidation group (n=10) included 7 females and 3 males, with a mean age of 26.70 yrs (±8.97; age range= 20-47 yrs), the Reconsolidation group (n=14) contained 9 females and 5 males, with a mean age of 27.21 yrs (±6.34; age range= 19-45 yrs), and the Control group (n=10) was composed of 5 females and 5 males, with a mean age of 25.3 yrs (±4.85, age range= 20-35 yrs). Given that saliva samples were not obtained from the Control group (we were primarily interested in within-group differences between Consolidation and Reconsolidation groups which acted as their own controls; further, such analysis was not possible due to lab restrictions) and four participants' salivary cortisol samples were withdrawn due to deemed contamination, 21 saliva samples were analyzed for salivary cortisol concentration. Of these 21 participants, 13 were female and 8 were male, with a mean age of 27.62 yrs (±7.63; age range= 19-47 yrs); the Consolidation group (n=9) comprised 6 females and 3 males, with a mean age of 27.44 yrs (±9.18; age range= 20-47 yrs) and the Reconsolidation group (n=12) comprised 7 females and 5 males, with a mean age of 27.62 yrs (± 7.63; age range= 19-47 yrs).

To account for possible confounds to cortisol samples, participants were screened *prior* to inclusion (see Appendices 10 and 11). Participants were excluded from the study if they reported current or recent use of prescribed medication including corticosteroid-containing ointments, beta-blockers, or any medication which may affect central nervous system functioning or endocrine systems; any chronic diseases which may affect cortisol levels such as Cushing's syndrome, Syndrome X or any metabolic disorders; recent use of psychotropic drugs or intake of alcohol which may have affected cognitive functioning; previous diagnosis of learning and/or memory impairments (e.g., dyslexia); recent diagnosis of depression and/or anxiety related disorders, and non-fluency in the English language.

Details were further noted (see Appendices 10 and 11) concerning extraneous possible confounds as reported in the cortisol sampling literature. Details were taken concerning participants' use of oral contraceptives, current menstrual cycle stage [i.e., Day 1 (menstruation), Day 2-12, Day 14 (ovulation), Day 15-22, or Day 22-Day 1 of next cycle] and pregnancy status and trimester (Kirschbaum *et al*., 1996a; Kirschbaum *et al*., 1999); medication use within the preceding 24 hrs prior to saliva collection in case participants were unaware of possible cortisol-related or cognitive confounds; participants' recent sleeping patterns such as quality and quantity of sleep on the night prior to saliva collection, any unusual waking patterns, whether the participant was recently involved in shift work, was currently jet-lagged, or experienced recent insomnia, given that cortisol follows a strong circadian rhythm (Born & Fehm, 1998; Pollard, 1995); whether the participant partook in any vigorous exercise in the preceding 24 hrs prior to saliva sampling (Kirschbaum & Hellhammer, 1994), the intensity and timing of which were noted, whether the participant had recently taken part in 'fasting' type behaviour (Haussman *et al*., 2007) or recent bouts of the cold or flu; a *detailed* account of all foods and drink consumed within the preceding 24 hours paying particular attention to caffeine, carbohydrate, dairy and alcohol intake (e.g., Ice

et al., 2004; Smyth *et al*., 1998); and finally, given that nicotine causes increased levels of cortisol (Kirschbaum & Hellhammer, 1989), and that smoking yields an elevation in salivary cortisol levels, peaking 25-35 minutes after smoking (Wüst *et al*., 1992), details were noted concerning amount of cigarettes smoked within the preceding 24 hours. The experimenter reviewed the completed version of this screening sheet *prior* to conducting cortisol analysis. If deemed necessary by the experimenter, participants were either excluded from further participation or allocated to the Control group.

Before participation, written informed consent was obtained from each participant (Appendix 19). The study protocol was approved by both the NUIM Psychology Department and University Ethics Boards. Prior to experimentation, participants were provided with printed details concerning the experiment and were informed that they were free to withdraw from the study at any stage. Participants were further informed of the expected 2.5 hour duration. As recommended by Kirschbaum and colleagues (1995), all experiments were conducted between 3 pm and 6 pm to minimize the effects of time of day on the expected cortisol responses. To minimize confounding influences on baseline cortisol levels, participants were instructed to refrain from drinking any sweet, acidic, dairy-based or caffeinated drinks and eating dairy products or carbohydrate-heavy meals at least one hour prior to saliva sampling (see Appendix 12). They were also instructed to refrain from using aspirin, paracetamol, and other non-steroidal inflammatories on the morning of sampling. Furthermore, they were explicitly instructed not to eat or drink anything but water, and *not* to smoke an hour before saliva sampling (see Appendix 12, for participant guidelines). To further ensure adherence to aforementioned stipulations, participants were also required to complete a *post*-experiment screening form (see Appendix 13).

Control measures included measures of general memory functioning (CFQ), screening for *psychological* characteristics such as anxiety (STAI), self-esteem (Rosenberg

Scale), resilience (RS-10), and general health with particular regard to depression and anxiety (GHQ28). Refer to Chapter 2 for detailed description of tests and scoring procedures employed. No differences between groups were found for *psychological* characteristics such as depression, self-esteem, resilience, or general health. Trait anxiety was significantly higher in the Control group (48.30±5.10) than in the Reconsolidation group (43.93±4.73; $t(22)= 2.161$, $p= .042$) and cognitive failure scores were significantly higher for the Reconsolidation group (48.57±14.56) compared to the Consolidation group (35±14.99; $t(22)= 2.223$, $p= .037$), at the $p<0.05$ level, thereby suggesting that participants in the Reconsolidation group may be prone to memory lapses to a greater extent than are participants in the Consolidation group. In terms of cortisol data, no differences between groups were found for depression, trait anxiety, self-esteem, resilience, or general health.

6.2.2 Procedures and tasks

The study consisted of two experimental sessions, with a visual paired-associate (VPA) *memory* task study block presented to participants on Day 1, followed on Day 2 by a psychosocial stress task which was immediately followed by a *distractor* task which served to either *reactivate* the consolidated local context memory trace (i.e., Reconsolidation group) or did not reactivate any contextual background trace (i.e., Consolidation group). This distractor task was followed by a VPA test-block wherein participants were tested on retrieval of previously presented VPA stimulus pairs which were *all* presented *without* corresponding local context backgrounds.

6.2.2.1 Memory Task

6.2.2.1.1 Stimuli

The task used for this experiment was a standard VPA task which was created using the E-Prime experimental presentation program. The task comprised 12 non-verbalisable achromatic stimulus pairs, half of which were presented in front of an emotionally arousing (pleasant or unpleasant) contextual background, the other half of which were presented without a local context background (see Figure 6.1). The experiment took place in the Department of Psychology at the National University of Ireland, Maynooth on a Dell Personal Computer with Pentium 4 processors (3.00GHz CPU) and standard LCD monitor and computer.

6.2.2.1.2 Procedure

Study Block

The task consisted of a study block containing 72 trials, followed by a test block containing 96 trials. The study block (see Figure 6.2) involved presenting the study 12 stimulus pairs three times each in a randomized order, with 6 of the stimulus pairs incorporating an emotionally arousing contextual background, and the other 6 comprising no local context background. Each stimulus pair was presented for 3500ms with a 750ms inter-trial interval consisting of a fixation-cross. Participants were required to learn which stimuli formed a stimulus pair and to remember these pairs for the test phase. No explicit instructions were given regarding the learning of the contextual backgrounds (see Chapters 3 & 4).

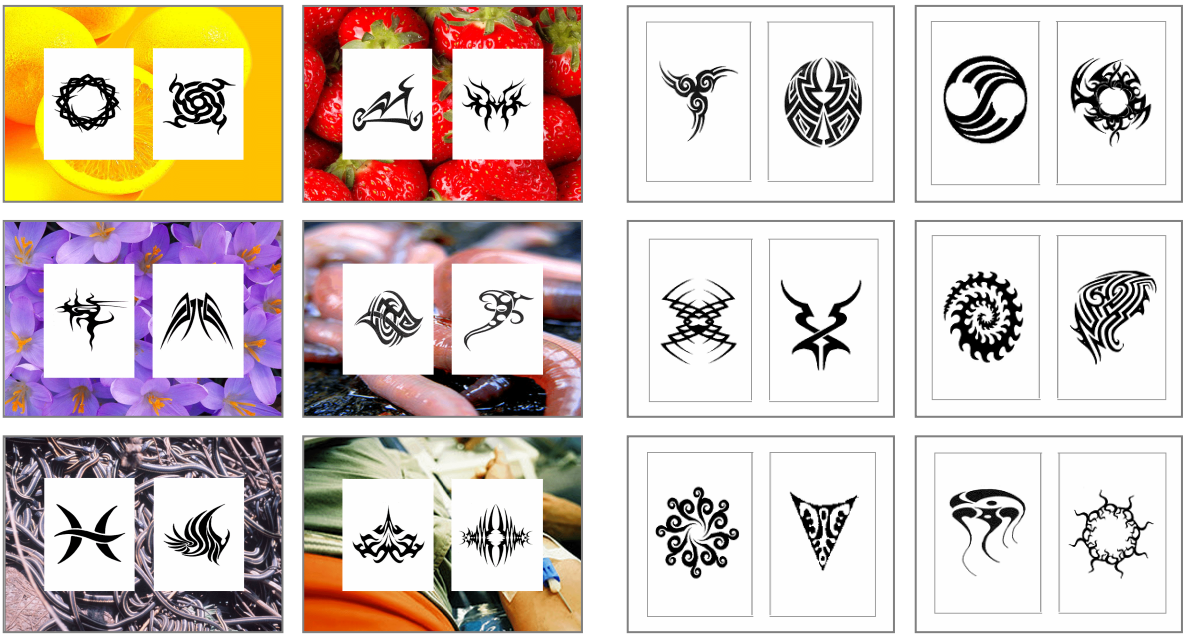


Figure 6.1: Complete set of visual paired-associate stimulus pairs. *Left*-hand side shows stimulus pairs incorporating a contextual background whereas *right*-hand side shows stimulus pairs that did not incorporate a contextual background.

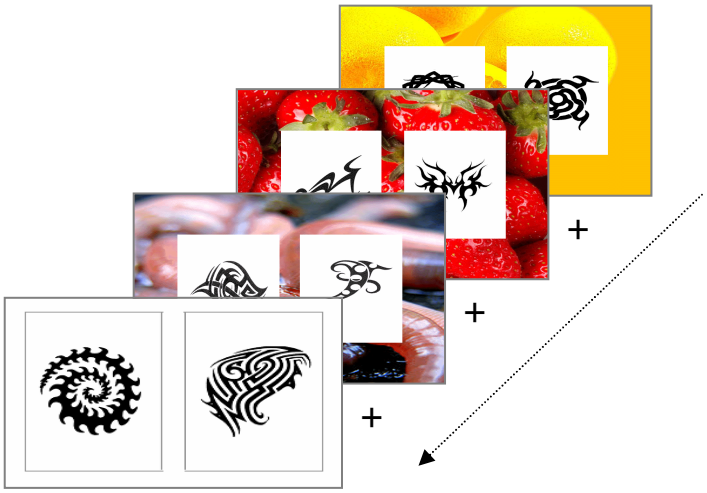


Figure 6.2: Graphical representation of study block which involved presenting 12 stimulus pairs three times each in randomized order, with 6 pairs incorporating a contextual background, and the other 6 pairs comprising no contextual background. There were 72 trials in total. Each stimulus pair was presented for 3500ms with a 750ms inter-trial interval consisting of a fixation-cross.

Test Block

The test-block was presented to participants approximately 20 minutes *after* the stress task in order to allow for stress-induced cortisol levels to peak. During the test-block, a probe stimulus was first presented for 1000ms. A probe stimulus consisted of one half of a stimulus pair and a contextual background. The probe stimulus was positioned in either the right or left – hand side of the screen, consistent with where it had been positioned during the study phase. This was followed by a full pair (i.e., the same probe and background along with the second stimulus), which remained on screen until the participant responded. The full pairs can be referred to as the *test pairs* given that participants were required to judge whether the pair had been previously viewed during the study phase (i.e., a *true-pair*) or whether it was *not* presented during the study phase (i.e., a *false-pair*). The false-pairs consisted of the same stimuli shown in the study phase however the pairs were recombined (see Figure 6.3). 24 trials were presented for stimulus pairs that were previously associated with a background context[6] (i.e., Reconsolidation group) and for stimulus pairs presented with no background context (i.e., Consolidation group), during the study block, together with 48 presentations of recombined stimulus pairs that were previously unencountered. No feedback was provided for any of the trials throughout the experiment. Each trial comprised a probe stimulus, immediately followed by the test pair. Prior to the onset of the next trial, a fixation cross appeared for 750 ms.

[6] The probe stimulus was not employed as the memory reactivator presently in response to previous literature stipulating that the updating effect, with respect to reconsolidation-based processing, only occurs when the context is part of the reminder manipulation (Hupbach *et al*., 2008). Thus, when in the same context – updating and transformation of an existing memory trace ensues, but when in a new context, an entirely new memory representation is formed.

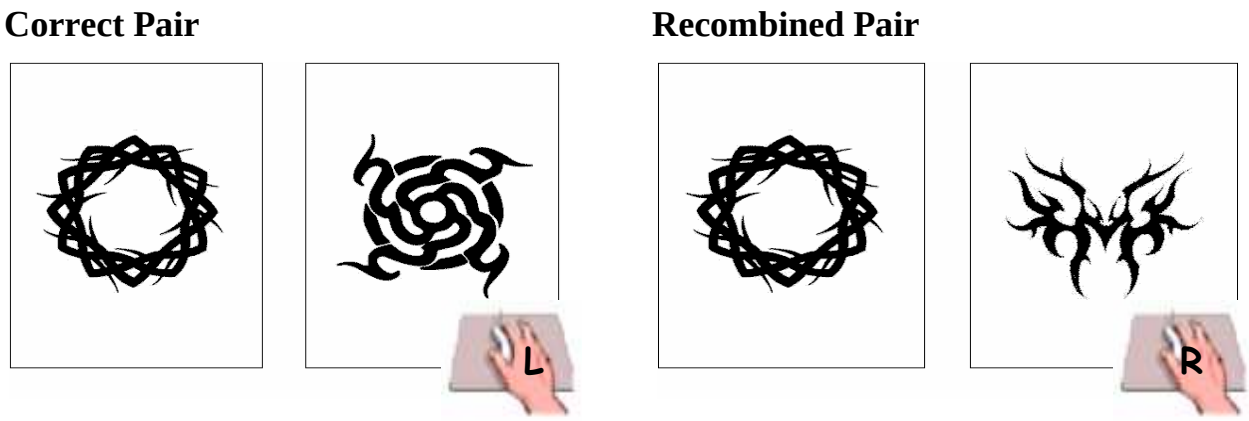


Figure 6.3: Graphical representation of Test-block. *All* participants were shown a single probe stimulus, followed by either its correct match (*left*) or by a stimulus from a different pair (*right*). There were 96 trials in total.

6.2.2.2 Stress task

The Trier Social Stress Task (TSST) is a well established laboratory stress task that has been shown to consistently induce significant endocrine and cardiovascular responses in a large sample of participants (Kirschbaum *et al*., 1993, see also Dickerson & Kemeny, 2004). In the present study, the TSST consisted of a short preparation period of 10 minutes (i.e., anticipation period), in which the participant was instructed to prepare for a 5-minute speech to be presented in front of an audience located in another room. Participants were told that this audience consisted of undergraduate and postgraduate students, who would assume the role of potential employers and were encouraged to ask a series of questions throughout the 'interview'. Participants were told that the speech would mimic a job interview for a fictitious job of their choice in which they had to present themselves and convince the audience of their suitability, adequacy and knowledge pertaining to the specified job. In addition, they were told that the 'interview' would be voice-recorded for later voice frequency analysis and that the experimenter was trained to monitor non-verbal behavior. They were also told the speech would be critiqued on content and presentation style and were equipped with various presentation techniques. Following preparation time, the participant

was led by the experimenter to another room which comprised a two-way mirror and an 'interview panel' composed of three confederates. Participants were instructed to stand in front of a table with the 'interview panel' located at the other side, and the 'interview' commenced. After the interview, the designated chief interviewer asked the participant to do a mental arithmetic task in which they were required to serially subtract 13 from 2063. The audience responded to *any* mistake by instructing participants to start over. This lasted for another three minutes before the experimenter came into the room to perform physiological measures and the questionnaire battery (see below). The control condition consisted of a reading period of 15 minutes, comparable to the timing of the TSST.

6.2.2.3 Distractor Task

The purpose of the Distractor task was to either *reactivate* the background context memory trace for the Reconsolidation group or act as a non-reactivating filler task for both Consolidation and Control groups (see Figure 6.4). In the Reconsolidation group participants were presented with a previously presented background context superimposed with two rectangular placeholders instead of paired-associates (i.e., the probe stimulus), whereas in the Consolidation group participants were presented with *no* background context, just a blank white screen superimposed with the same two rectangular placeholders as mentioned above. Participants were instructed to click on the left mouse button if an "X" appeared in ONE of the windows, regardless of whether it appeared in either the left or right window. If an "X" appeared in both windows, participants were instructed to withhold a response. The probe stimulus remained onscreen for 1000ms. The Distractor task remained onscreen until either the participant made a response or 1000ms had elapsed. No feedback was provided for any of the trials throughout the experiment. Each trial comprised a probe stimulus, immediately

followed by the Distractor task. Prior to the onset of the next trial, a fixation cross appeared for 500ms. The Distractor task comprised 128 trials presented in a sequential manner. Neither the accuracy nor RT was analyzed.

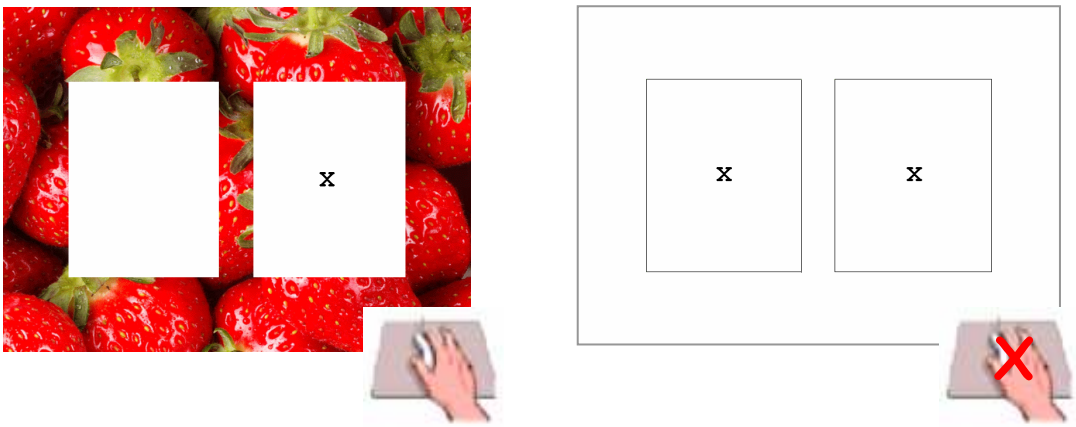


Figure 6.4: Graphical representation of Distractor task. Participants were instructed to click on the LEFT mouse button if a single 'X' appeared in either window and to withhold a response if an 'X' appeared in both windows (128 trials).

6.2.2.4 Saliva sampling and biochemical analyses

Refer to Chapter 2 for reasoning behind salivary cortisol sampling. To collect the saliva samples required for cortisol analysis, participants were asked to provide a saliva sample via Salivette plain cotton devices (Sarstedt, Wexford, Ireland). Participants were required to chew the small cotton swab in their mouth for 1 minute which absorbed saliva. After the absorption phase, the cotton swab was transferred into a small plastic tube, which was then inserted into an l0-ml polystyrol tube. Samples were taken at seven consecutive time points throughout the course of the experiment (see Figure 6.5). The first sample (T1) was taken immediately upon participant arrival at the lab, a second sample was taken after a 30-minute 'rest' period (T2), a third sample was taken after a 10-minute stress 'anticipation' period (T3), a fourth sample was taken immediately after the modified TSST (T4), a fifth sample

was taken immediately after the Distractor task (T5), a sixth sample was taken immediately after the VPA test-block and pre-recuperation (T6), and a final sample was taken following a 30-minute post-recuperation period (T7). Saliva samples were collected into the salivettes in strict accordance with the manufacturer's instructions (Refer to Chapter 2). Samples were stored at −20°C within 30 minutes of sampling. The time samples were obtained and frozen were noted by the experimenter on a specifically prepared time record sheet (Appendix 15).

The quantitative measurement of cortisol in saliva was performed using a salivary cortisol ELISA according to the manufacturer's instructions (Salimetrics™). Essentially, the ELISA microplate was pre-coated with monoclonal antibodies to cortisol. Cortisol in saliva samples and in a set of standards (termed "cold" cortisol) was added to the 96-wells of the microplate. After this, cortisol linked to horseradish peroxidase (termed "hot" cortisol) was added to each well. "Cold" and "hot" cortisol competed for a limited number of antibody-binding sites, and, after an incubation period, unbound components were washed away. Bound "hot" cortisol was measured by the reaction of its peroxidase enzyme on a substrate (i.e., tetramethylbenzadine). This reaction produced a color that was measured at 450 nm on a plate reader. The intensity of the color reflected the amount of peroxidase detected, which was inversely proportional to the amount of cortisol present. Duplicate assays were conducted on each sample, and the resultant pairs of readings compared. A detailed account of the biochemical protocol employed can be found in Chapter 2.

6.2.3 Design and procedure

Participants were randomly assigned to one of three experimental groups in a between-subjects design; Control (n=10), Consolidation (n=10) and Reconsolidation (n=14). Four participants' data were withdrawn from the Consolidation group due to non-compliance with these instructions. After arrival in the laboratory, which preferentially occurred at 3pm,

participants were told about the general nature of the experimental procedure and subsequently gave written consent. Afterwards, participants were asked to wash their hands and rinse their mouths with water to ensure non-contaminated saliva sampling. At this stage the first saliva sample was obtained and details concerning time taken were noted by the experimenter on a specifically prepared time record sheet (Appendix 15). Participants were then given a 30 minute 'rest' period in a relaxing room equipped with a comfortable chair, soft lighting, a relaxing lavender odour, and neutral reading materials (e.g., the National Geographic magazine). During this 'rest' period, participants were also furnished with a battery of questionnaires to complete which ascertained stable psychological variables such as anxiety (STAI; Appendix 5), self-esteem (Rosenberg Scale; Appendix 7), resilience (RS_{10}; Appendix 8) and general health (GHQ28; Appendix 9). State measures of mood (PANAS; Appendix 6), anxiety (STAI; Appendix 4), and current subjective 'stress' levels (Appendix 3) were also ascertained, together with documentation of aforementioned screening measures such as intake of foods and behaviours which may have potentially adversely affected cortisol readings (e.g., consumption of carbohydrates, caffeine, milky products, alcohol or drugs and smoking at least one hour prior to sampling; Appendices 10 and 11). Please refer to Appendices for full battery given to participants during the 'rest' phase of the experiment. The second saliva sample was obtained at the end of the 'rest' period.

Both Consolidation and Reconsolidation groups were subsequently exposed to the stress 'anticipation' period of the modified TSST. Control groups were exposed to a neutral reading task for the duration of the TSST task, with saliva samples taken at the same time periods as 'stressed' participants. The 'anticipation period' lasted 10 minutes at which point the third saliva sample was taken. At the end of the 'anticipation period' participants were required to detail state mood (PANAS) and anxiety (STAI), as well as indicate how 'stressed' they currently felt, and give details of any bodily stress reactions (i.e., state battery).

Participants were then exposed to the stress task as detailed above. The 'psychosocial' phase lasted 5 minutes and the cognitive challenge lasted 3 minutes. Upon completion of the stress phase, the fourth saliva sample was immediately taken. The state battery (see above) was administered also.

Participants were then immediately led to another room where they were first exposed to the requisite Distractor task, after which the fifth saliva sample was taken and state battery was given. After the Distractor task, participants were all given the same test-block as detailed previously, followed by the state battery. The participants were then returned to the relaxing room and given a 30 minute 'recuperation' period. The sixth and seventh saliva samples were taken pre- and post-recuperation, together with a final state battery. The 1st (baseline), 2nd (post-rest), 6th (pre-recuperation) and 7th (post-recuperation) saliva samples were used to ascertain baseline cortisol levels, while the 3rd (post-anticipation), 4th (post-stressor), and 5th (pre-VPA test) samples were used to determine cortisol concentrations throughout the 'stress' period. Figure 6.5 details the time line of the experimental procedure. During the rest phases, participants engaged in unrelated and undemanding filler tasks (e.g., reading a neutral text).

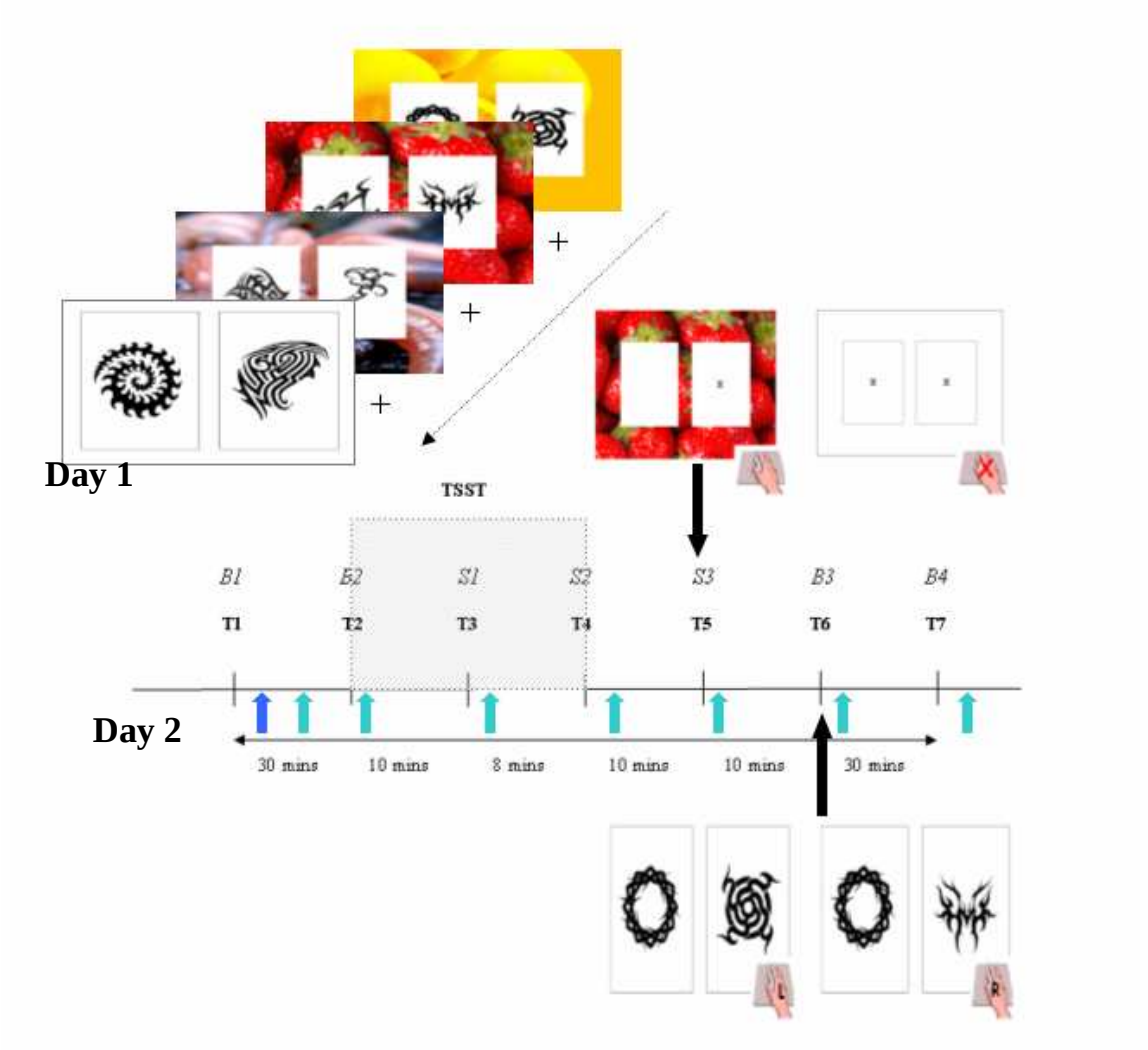


Figure 6.5: Flow chart representing experimental design. Study block presented to participants on Day 1. T: Time saliva sample taken, B: Baseline phase, S: Stress phase. ⬆Time complete questionnaire battery administered. ⬆Time state battery administered. ⬆ Time either distractor task or test-block administered. + symbol represents fixation-cross presented during inter-trial interval.

6.2.4 Data Analysis and Statistics

Demographic data in each condition were analyzed by chi squared analysis (for categorical data) or Independent samples t-tests (for continuous data). Baseline values, measured at T1, T2, T6, and T7 time points for *both* physiological and subjective measures.

Results of various studies (Walker *et al*., 1984; Allolio *et al*., 1985) indicate that cortisol concentration continuously falls during the course of the day in a nearly linear manner due to its circadian rhythm, and even more so if participants were active or aroused prior to the experiment. For this reason, it does not seem adequate to relate change in cortisol level after TSST presentation exclusively to baseline values measured before the TSST. Regarding salivary cortisol measures herein, an artificial baseline[7] was primarily calculated by averaging cortisol concentration across the two pre- and post-rest periods (i.e., T1 and T2) and the two pre- and post-recuperation periods (i.e., T6 and T7), as a measure of pre-and post-stress basal cortisol stress levels. As such, the baseline for the session was created by linking the four pre and post measures. Using this artifical baseline, we simultaneously determined whether participants were actually stressed in terms of cortisol measurements in response to the TSST and accounted for the circadian related fall in cortisol concentration by calculating changes in cortisol from the mean artificial baseline across the three stressor phases (i.e., T3, T4 and T5; see Figures 6.6 and 6.7). In accordance with Gregg and colleagues (1999), mean change scores (i.e., stressor phase score minus baseline score) were determined across both Consolidation and Reconsolidation groups (see Figures 6.8 and 6.10). A positive difference at a specific point in time above zero suggested that the empirically measured cortisol concentration was higher than the concentration expected by the artificial baseline.

In order to account for possible remnant stress levels following the stressor task as well as to ascertain whether participants remained ‘stressed’, in terms of cortisol levels, both pre- and post-VPA task, we subsequently conducted a more stringent baseline measurement of

[7] In field studies, an individual’s cortisol baseline would normally be obtained over a period of a few days, even as long as a week, to get a succinct conceptualization of resting or 'normal' cortisol concentration. This is not feasible in a laboratory session. As such, an artificial baseline allows for the measurement of pre- and post-stress resting and recovery cortisol levels, respectively. In terms of recovery measures following stress, gauging how long it takes a person to recover from a stressor provides detail concerning an individual's response to the stressor employed and their ability to cope with the demand.

unstimulated cortisol levels which averaged only the first and last (i.e., T1: immediately upon arrival at the lab and T7: post-recuperation) cortisol concentrations (see Figures). These two reference points were chosen on the supposition that the first baseline value (first reference point) was not yet influenced by the effects of the stressor and represented basal cortisol levels and that 50 minutes after the TSST (second reference point) the stressor-related effect had already faded away (Thornsteinsson, James & Gregg, 1998). Therefore, the effects of the stressor task were ascertained on the basis of the difference between observed and expected (practical baseline) values which were represented as change scores for stressor phases T3-T6 (see above for change score calculation). In doing so, we employed the method suggested by Hellhammer and colleagues (1987) for establishing a "practical" time-related baseline, which once again takes into account the continuous fall of cortisol over time and represents the TSST-related phasic cortisol responses as deviation scores from this decreasing trend. This practical baseline involved connecting T1 and T7 concentrations by a straight line which represented unstimulated (i.e., unaffected by stress-induction) cortisol levels (see Figure 6.8). As above for the artifical baseline, the stressor related phasic cortisol changes were obtained by representing the empirically measured cortisol values for the sampling intervals T3-T6 (i.e., post-anticipation, post-TSST, post-distractor, and post VPA test-block) as deviation concentrations from the theoretically computed level of the practical baseline (i.e., mean cortisol concentration across T1 and T7). Again a positive difference at a specific point in time above zero meant that the empirically measured cortisol concentration was higher than the concentration expected by the practical baseline.

In order to determine the impact of assessment time on salivary cortisol concentration in general, a 2x7 mixed factorial ANOVA with group (Reconsolidation/Consolidation) as the between-subject factor and assessment time (*pre*-rest, *post*-rest, *post*-anticipation, *post*-TSST, *post*-distractor, *post*-VPA test-block, *post*-

recuperation) was primarily conducted, with further paired- and independent samples t-tests conducted where necessary. Comparing salivary cortisol change scores representing stress-induced deviations from the respective Consolidation and Reconsolidation unstimulated artificial baseline (i.e., measuring T3, T4, and T5 stressor phases only), a 2x3 mixed between-within factorial ANOVA, with change score across stressor phase as the within-subjects variable and group (i.e., Consolidation or Reconsolidation) as the between-subjects variable was employed, with subsequently conducted paired-samples t-tests, measuring within-subjects variables; and independent-samples t-tests, measuring between groups variables, conducted where necessary. Subsequently, comparing salivary cortisol change scores representing stress-induced deviations from the respective Consolidation and Reconsolidation unstimulated artificial baseline (i.e., measuring T3, T4, T5 *and* T6 phases), a 2x4 mixed between-within factorial ANOVA, with change score across phase as the within-subjects variable and group (i.e., Consolidation or Reconsolidation) as the between-subjects variable was conducted, again with subsequently conducted paired-samples t-tests, measuring within-subjects variables; and independent-samples t-tests, measuring between groups variables, conducted where necessary.

For assessment of memory performance, percentage accuracy was calculated across 24 trials for both Background context and No background context, and 48 trials for Recombined Stimulus Pairs. Mean RT was calculated for both Correct and Incorrect responses. A series of 3x3 mixed factorial repeated measures ANOVAs with context type (3 levels: Background, No Background and Recombined) as the withi-subjects factor and group (3 levels: Control, Consolidation and Reconsolidation) as the between-subjects factor were conducted with paired- and independent samples t-tests subsequently conducted where necessary. A series of 3x6 mixed factorial ANOVAs, with group (3 levels: Control, Consolidation and Reconsolidation) as the between-subjects factor and assessment time (6

levels: post-rest, post-anticipation, post-TSST, post-distractor, post VPA test-block, and post-recuperation) as the within-subjects factor were conducted across the various subjective stress measurements (i.e., PANAS, stress-appraisal rating and STAI). Subsequent paired- and independent-samples t-tests were conducted where necessary.

All analyses were performed using SPSS Version 13 statistical package for Windows (SPSS, Inc., Chicago, IL, USA). A star-based system for significance representing p-values of $p<0.05$ *, $p<0.01$ **, $p<0.001$ ***, respectively, was used throughout. The symbol ± is employed throughout to denote standard deviation from the mean. Error bars, where present, show standard error of the mean, which is in turn denoted by 'SEM'.

6.3 Results

6.3.1 Cortisol levels

Unexpectedly, upon cursory inspection (see Figure 6.6), the Trier Social Stress Test (TSST) showed elevated cortisol levels from baseline concentrations (Figure 6.6) for the Consolidation group but *not* the Reconsolidation group. A 2x7 mixed factorial ANOVA with group (Reconsolidation/Consolidation) as the between-subject factor and assessment time (*pre*-rest, *post*-rest, *post*-anticipation, *post*-TSST, *post*-distractor, *post*-VPA test-block, *post*-recuperation) as the within-subject factor, revealed a significant main effect of assessment time (Wilks' Lambda= .379, $F(6,11)= 3.007$, $p<0.05$, $\eta_p^2= .621$), together with a non-significant interaction effect between group and assessment time (Wilks' Lambda= .742, $F(6,11)= .742$, $p>0.05$, $\eta_p^2=.288$). *No* significant main effect was found for group at the $p<0.05$ level. Using sex as a between groups variable, neither a significant main effect nor interaction effect was found at the $p>0.05$ level. Paired samples t-tests revealed no significant cortisol concentration differences in terms of assessment time between the baseline and stress phases for either the Consolidation group [$t(8)= -1.918$, $p=.091$] nor the Reconsolidation group [$t(11)= .020$, $p=.984$]. However, when comparing across each time point individually, the Consolidation group's cortisol concentration was significantly higher post-anticipation (.334μg/DL ±.28 μg/ DL) than post-rest [.170μg/ DL ±.13 μg/ DL; $t(7)= -2.577$, $p=.037$], as well as post-distractor task (.295 μg/ DL ±.25 μg/ DL) compared to post VPA study-block [.189 μg/ DL ±.13; $t(8)= 2.281$, $p=.052$]; in the Reconsolidation group cortisol concentration was significantly higher post-rest (.187μg/ DL ±.11 μg/ DL) than post-anticipation [.132 μg/ DL ±.05 μg/ DL; $t(10)= 2.205$, $p=0.52$]. Independent samples t-tests revealed no significant differences across groups for individual time point concentrations, nor practical baseline or stress phase cortisol levels. No significant sex differences were observed either.

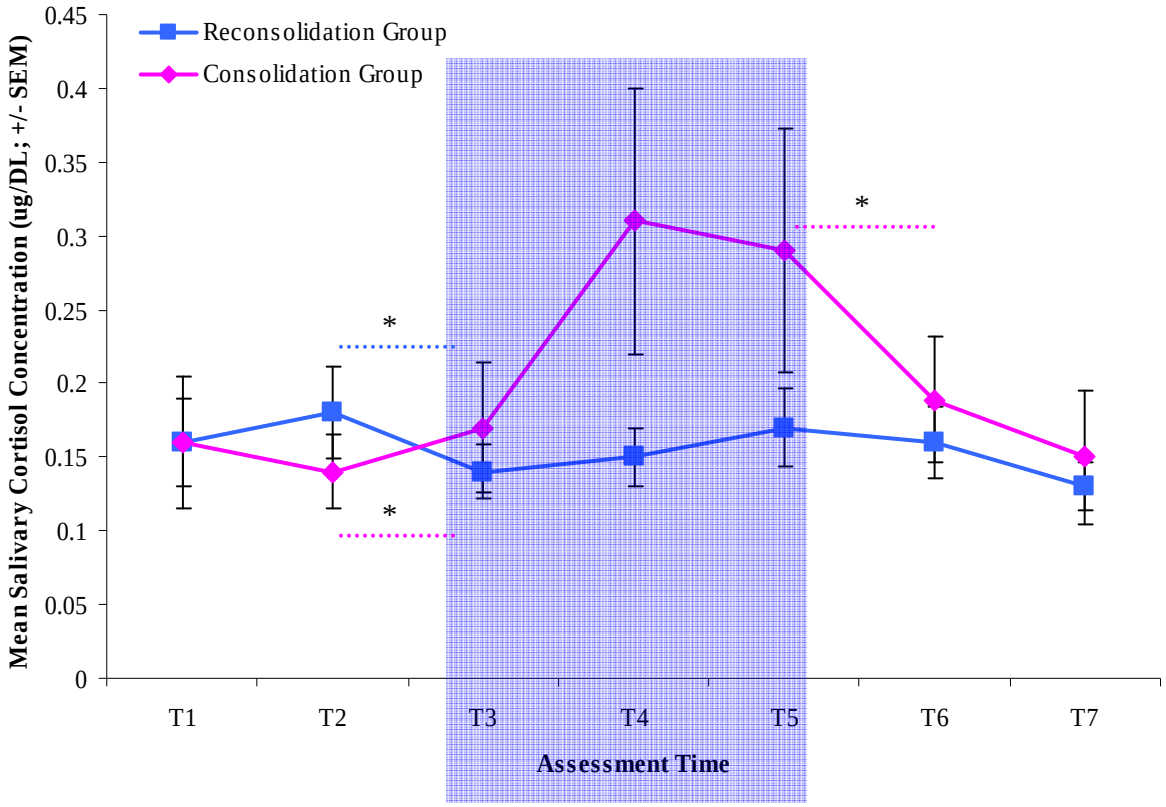


Figure 6.6: Mean salivary cortisol concentration (µg/dL) across assessment time (+/- SEM). Note: Purple shaded area represents phases during which cortisol was predicted to show a stress effect.

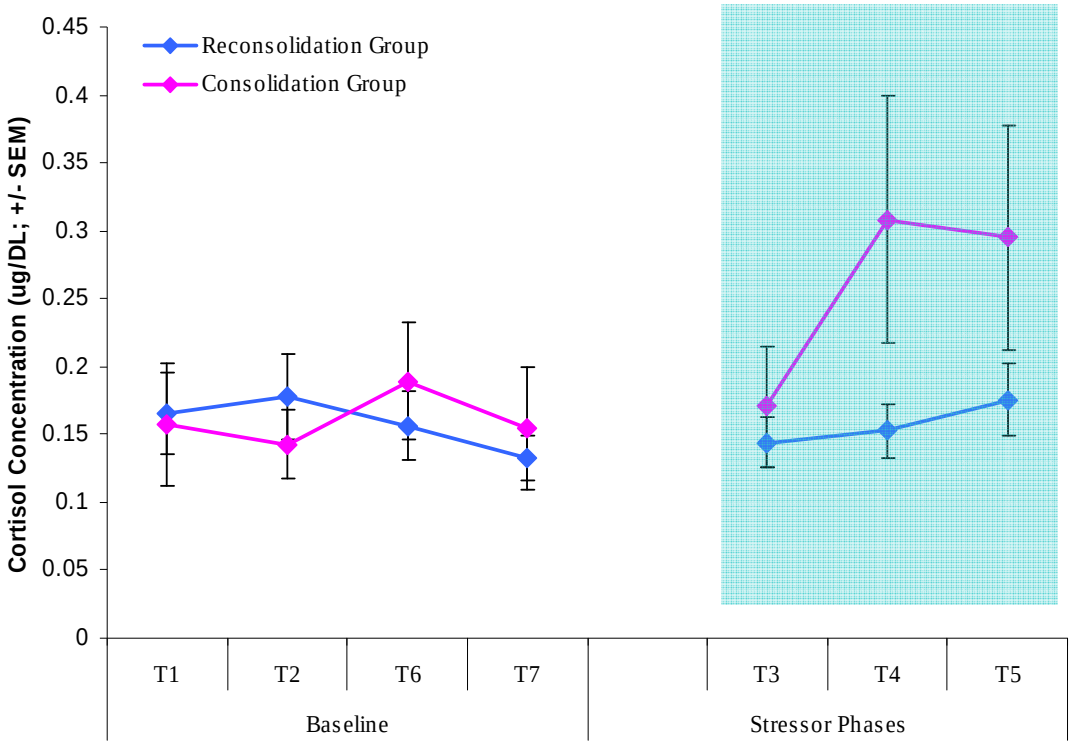


Figure 6.7: Graphical comparison of baseline versus stressor-related mean salivary cortisol concentration (green shaded area). *Left:* Mean salivary cortisol concentration across pre- and post- stressor baseline (+/- SEM). *Right:* Mean salivary cortisol concentration (µg/dL) across stressor phases (+/- SEM).

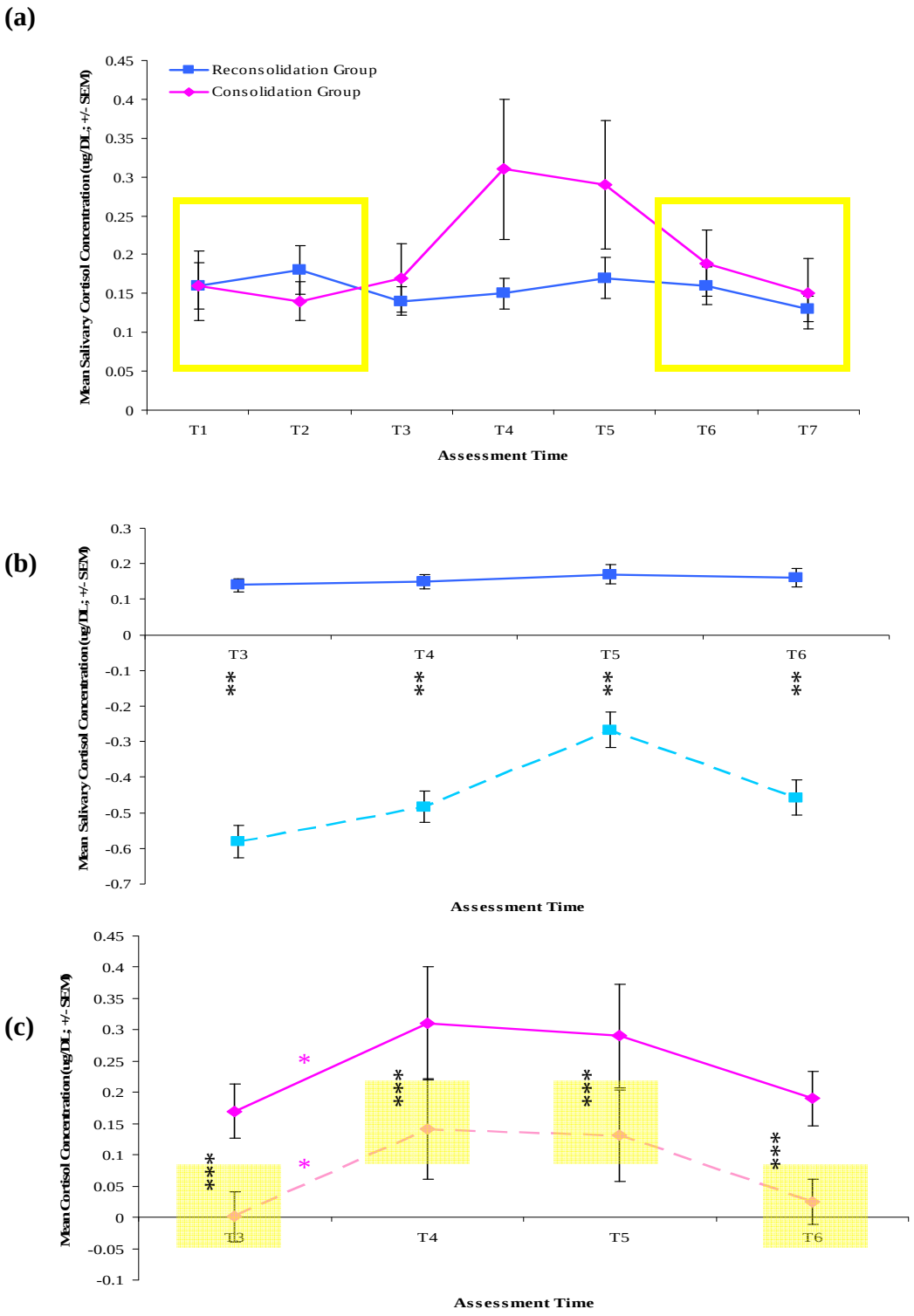


Figure 6.8: (a) 'Artificial' Baseline method with yellow boxes representing averaging of cortisol concentration across the two pre- and post-rest periods (i.e., T1 and T2) and the two pre- and post-recuperation periods (i.e., T6 and T7), with the baseline for the session created by linking the four pre and post measures (b) **Reconsolidation Group**: Graphical representation of actual cortisol concentration across stressor phases T3, T4, and T5 (top line) together with deviation scores from the theoretical artificial baseline across stressor phases (bottom broken line). (c) **Consolidation Group**: Graphical representation of actual cortisol concentration across stressor phases T3, T4, and T5 (top line) together with deviation scores from the theoretical artificial baseline across stressor phases (bottom broken line). Yellow shaded boxes represent change score deviations from baseline above zero thereby indicating that participants in the Consolidation group showed raised cortisol levels in response to the stressor task.

In terms of 'artifical' baseline measurement (see Figure 6.8), comparing salivary cortisol change scores representing stress-induced deviations from the respective Consolidation and Reconsolidation unstimulated artificial baselines (i.e., T3-artificial baseline, T4-artificial baseline, T5-artificial baseline), a 2x3 mixed factorial ANOVA, with change score across stressor phases (i.e., deviations from the practical baseline) as the within-subjects variable and group as the between-subjects variable, revealed a significant main effect for change score, Wilks' Lambda= .645, F(2,17)= 4.682, p=.024, η_p^2=.355), together with a significant interaction effect, Wilks' Lambda= .705, F(2,17)= .705, p=.051, η_p^2=.580. However, no significant main effect for group was found at the p>0.05 level. For the Consolidation group (Figure 6.8), subsequently conducted paired t-tests revealed significant differences in obtained cortisol concentration between T3 (.17 μg/DL±.126 μg/DL) and T4 (.33 μg/DL±.278 μg/DL; t(7)= -2.577, p=.037) and deviation from baseline score between T3 (.001 μg/DL±.112 μg/DL) and T4 (.164 μg/DL±.246; t(7)= -2.522, p=.040). In terms of the Reconsolidation group (Figure 6.8), paired samples t-tests revealed no such significant differences in obtained versus change score across stressor phase, at the p>0.05 level. Compared to baseline levels, cortisol increased significantly during *all* stress phases in the Consolidation group; T3; t(7)= 7.724, p<0.001, T4; t(8)= 8.701, p<0.001, T5; t(8)= 8.533, p<0.001. Similarly, cortisol increased significantly during *all* stress phases in the Reconsolidation group; T3; t(11)= 4.129, p=.002, T4; t(11)= 4.136, p=.002, T5; t(11)= 4.184, p=.002. Given that all mean change scores obtained in the Consolidation group across stressor phase were above zero, according to both obtained and diurnal variation in cortisol responding, participants in the Consolidation group were 'stressed' in terms of cortisol response across *all* stress phases. However, given the negative deviation from baseline mean

scores obtained across all stress phases in the Reconsolidation group, it would appear that the Reconsolidation group was *not* ‘stressed’ in terms of cortisol response across all stress phases.

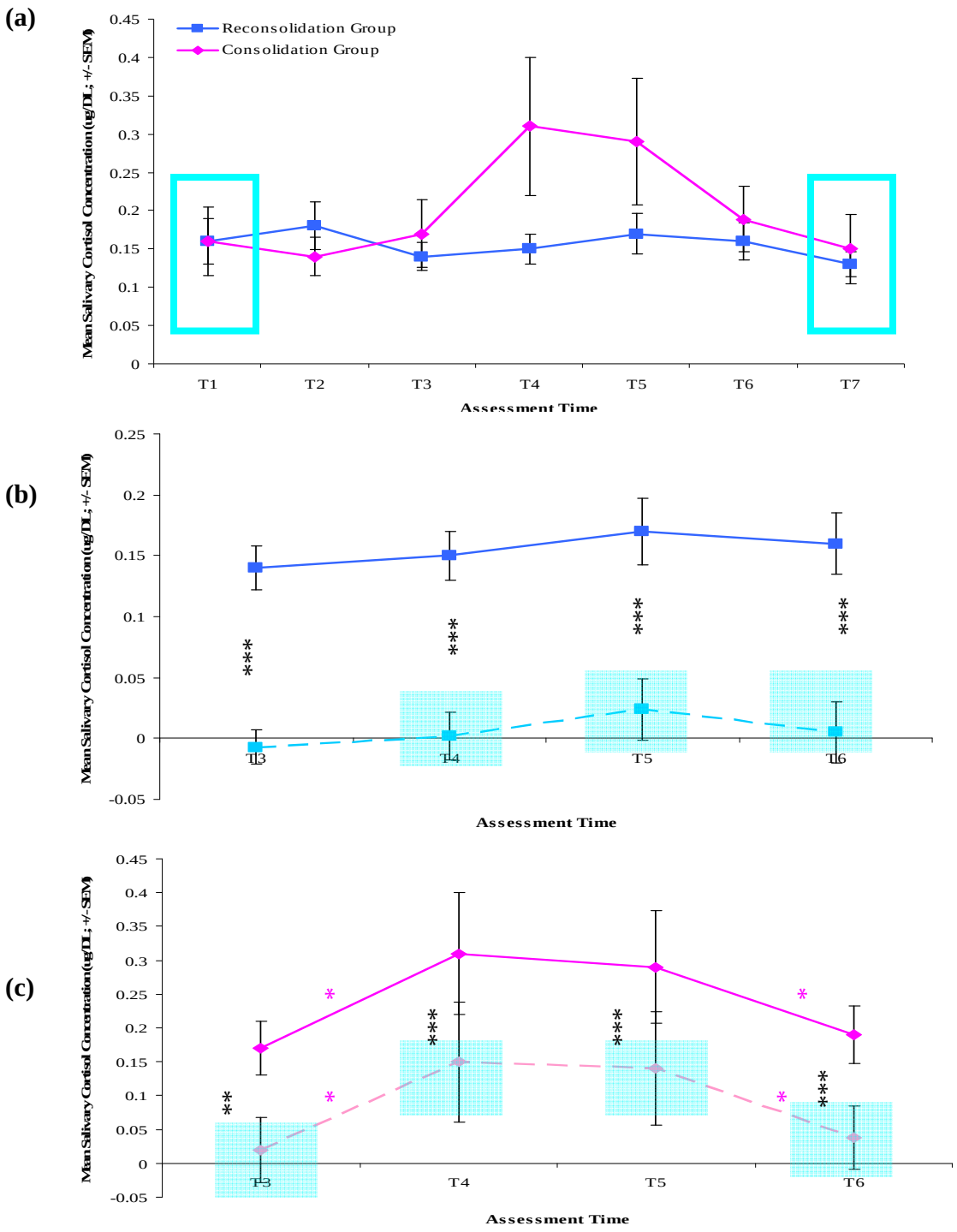


Figure 6.9: (a) 'Practical' Baseline method with blue boxes representing averaging of cortisol concentration across the first and last pre- and post-TSST periods, respectively (i.e., T1 and T7), with the baseline for the session created by linking the two pre and post measures (b) **Reconsolidation Group**: Graphical representation of actual cortisol concentration across phases T3, T4, and T5 and T6 (top line) together with deviation scores from the theoretical artificial baseline across stressor phases (bottom broken line). (c) **Consolidation Group**: Graphical representation of actual cortisol concentration across stressor phases T3, T4, T5 and T6 (top line) together with deviation scores from the theoretical artificial baseline across stressor phases (bottom broken line). Blue shaded boxes represent change score deviations from baseline above zero thereby indicating that participants in the both the Reconsolidation and Consolidation groups showed raised cortisol levels in response to the stressor task.

In terms of 'practical' baseline measurement (see Figure 6.9), comparing salivary cortisol change scores representing stress-induced deviations from the respective Consolidation and Reconsolidation unstimulated practical baselines (i.e., T3-practical baseline, T4-practical baseline, T5-practical baseline, T6-practical baseline), a 2x4 mixed factorial ANOVA, with change score across stressor phases (i.e., deviations from the practical baseline) as the within-subjects variable and group as the between-subjects variable, revealed a significant main effect for change score, Wilks' Lambda= .628, F(3,16)= 3.154, p=.05, η_p^2=.372), together with a non significant interaction effect or main effect for group at the p>0.05 level. For the Consolidation group (Figure 6.9), subsequently conducted paired t-tests revealed significant differences in obtained cortisol concentration between T3 (.17 μg/DL±.126 μg/DL) and T4 (.33 μg/DL±.278 μg/DL; t(7)= -2.577, p=.037) and deviation from baseline score between T3 (.020 μg/DL±.136 μg/DL) and T4 (.18 μg/DL±.270; t(7)= -2.522, p=.040), as well as between T5 (.29 μg/DL±.250 μg/DL and T6 (.19 μg/DL±.130 μg/DL; t(8)= 2.281, p=.052) and deviation from baseline score between T5 (.14 μg/DL±.251 μg/DL) and T6 (.04 μg/DL±.142 μg/DL; t(8)=2.308, p=0.05). In terms of the Reconsolidation group (Figure 6.9), paired samples t-tests revealed no such significant differences in obtained versus change score across stressor phase, at the p>0.05 level. Compared to baseline levels, cortisol increased significantly during *all* stress phases in the Consolidation group; T3; t(7)= 4.874, p=.002, T4; t(8)= 5.672, p<0.001, T5; t(8)= 5.535, p=.001, T6; t(8)= 5.515, p=.001. Similarly, cortisol increased significantly during *all* stress phases in the Reconsolidation group; T3; t(11)= 7.163, p<0.001, T4; t(11)= 7.176, p<0.001, T5; t(11)= 7.270, p<0.001, T6; t(11)=7.278, p<0.001. Given that all mean change scores obtained in the Consolidation group across stressor phase were above zero, according to both obtained and diurnal variation in

cortisol responding, participants in the Consolidation group were 'stressed' in terms of cortisol response across *all* measured phases (i.e., T3-T6). With respect to this practical baseline measurement, different to the aforementioned artificial method, given the positive deviation from baseline mean scores obtained across T4, T5 and T6 in the Reconsolidation group, it would appear that the Reconsolidation group was indeed 'stressed' in terms of cortisol response across these phases.

6.3.2 Subjective stress

Refer to Figure 6.10 for Bonferroni-adjusted subjective stress data. A 3x6 mixed factorial ANOVA, again with group (3 levels; Control, Consolidation and Reconsolidation) as the between-subject factor and assessment time (6 levels; post-rest, post-anticipation, post-TSST, post-distractor, post VPA test-block, and post-recuperation) as the within subject factor, revealed a significant main effect of group for negative affect as measured by the PANAS [$F(5,27)= 9.106$, $p<0.001$] and a significant group by assessment time interaction [$F(10,54)= 2.460$, $p<0.05$]; a significant main effect for stress appraisal ratings [$F(5,19)= 48.614$, $p<0.001$] and a significant group by assessment time interaction [$F(10,38)= 6.067$, $p<0.001$]; a significant main effect for STAI state anxiety ratings [$F(5,27)= 3.356$, $p<0.05$] but no significant interaction effect between assessment time STAI score and group [$F(10,54)= 1.315$, $p>0.05$]. No significant main effect or interaction effect was found for *sex* across stress appraisal, state anxiety or negative affect at the $p>0.05$ level.

In terms of the Reconsolidation group, paired t-tests indicated that exposure to the TSST significantly elevated stress-appraisal ratings when compared to post-rest ratings immediately after the anticipation period [$t(11)= -8.158$, $p<0.001$: Bonferroni-adjusted $p=0.015$], after the TSST [$t(13)= -5.628$, $p<0.001$], and post-distractor task [$t(13)= -2.474$, $p<0.05$: Bonferroni-adjusted $p=0.75$]. Furthermore, stress appraisal ratings were significantly

lower when compared to post-anticipation ratings post-distractor task [$t(11)= 5.933$, $p<0.001$], post VPA test-block [$t(11)= 9.025$, $p<0.001$, and post-recuperation [$t(11)= 11.413$, $p<0.001$]. In terms of STAI state anxiety ratings, anxiety was significantly lower post-recuperation when compared to post-distractor ratings [$t(13)= -3.108$, $p<0.05$] and post VPA test-block ratings [$t(13)= -2.407$, $p<0.05$]. In terms of PANAS negative affect, scores were significantly higher post-anticipation when compared to post-distractor [$t(13)= 3.234$, $p=.007$: Bonferroni-adjusted $p=.105$], post VPA test-block [$t(13)= 4.185$, $p=.001$] and post-recuperation [$t(13)= 4.898$, $p<0.001$], ratings. Further, negative affect scores were significantly higher post-TSST when compared to post-distractor [$t(13)= 3.975$, $p=.002$: Bonferroni-adjusted $p=0.03$], post VPA test-block [$t(13)= 4.729$, $p<0.001$], and post-recuperation [$t(13)= 4.734$, $p<0.001$] scores.

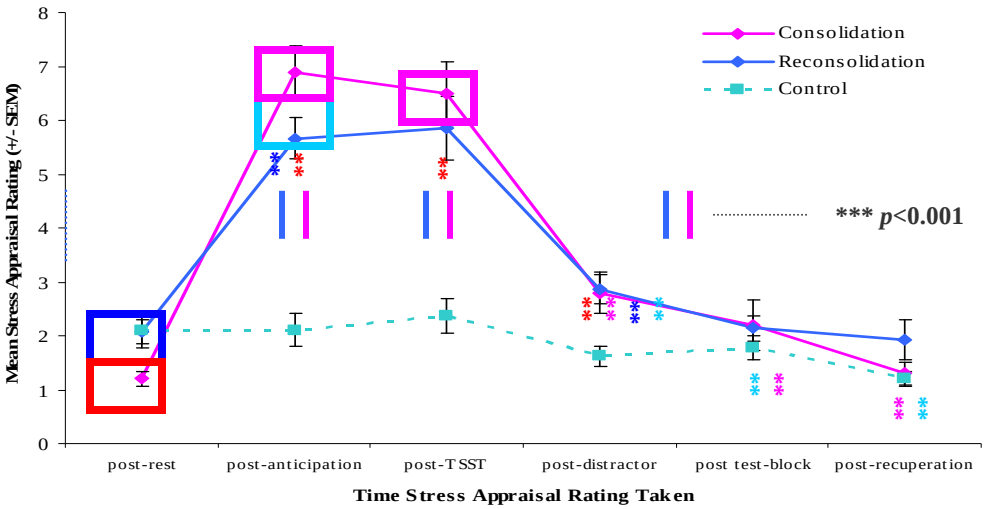
For the Consolidation group, in terms of stress appraisal ratings, similar to the Reconsolidation group, stress appraisals were significantly higher post-anticipation [$t(8)= -10.560$, $p<0.001$], post-TSST [$t(7)= -8.232$, $p<0.001$], and post-distractor [$t(9)= -3.207$, $p=.011$: Bonferroni-adjusted $p=.165$], than post-rest appraisals. Also similar to the Reconsolidation group, post-anticipation ratings were significantly higher than post-distractor [$t(8)= 12.572$, $p<0.001$], post VPA test-block [$t(8)= 7.854$, $p<0.001$] and post-recuperation [$t(8)= 11.704$, $p<0.001$]. Unlike the Reconsolidation group however, stress appraisal ratings were also significantly higher post-TSST when compared to post-distractor [$t(7)= 7.329$, $p<0.001$], post VPA test-block [$t(7)= 4.856$, $p=.002$], and post-recuperation [$t(7)= 8.394$, $p<0.001$]. Also, appraisals were significantly higher post-distractor when compared to post-recuperation [$t(9)= 3.737$, $p=.005$]. In terms of STAI state anxiety, scores were significantly higher post-rest [$t(9)= 2.280$, $p=.049$: Bonferroni-adjusted $p=.735$] and post-TSST [$t(9)= 2.782$, $p=.021$: Bonferroni-adjusted $p=.315$] than post VPA test-block. Unlike the Reconsolidation group, negative affect was significantly lower post-rest than post-

anticipation [$t(9)= -4.228$, $p=.002$] and post-TSST [$t(9)= -2.652$, $p=.026$: Bonferroni-adjusted $p=0.39$], and conversely significantly higher than post-recuperation [$t(9)= 2.236$, $p=.052$: Bonferroni-adjusted $p=0.78$]. Also negative affect was significantly higher post-anticipation than post-distractor [$t(9)= 5.281$, $p=.001$], post VPA test-block [$t(9)= 5.286$, $p=.001$], and post-recuperation [$t(9)= 4.732$, $p=.001$]. Similar to the Reconsolidation group, negative affect was significantly higher post-TSST than post-distractor [$t(9)= 2.861$, $p=.019$: Bonferroni-adjusted $p=.285$], post VPA test-block [$t(9)= 2.973$, $p=.016$], and post-recuperation [$t(9)= 2.982$, $p=.015$: Bonferroni-adjusted $p=.225$]. Finally, negative affect was significantly lower post-recuperation than post VPA test-block [$t(9)= 2.279$, $p=.049$: Bonferroni-adjusted $p=.735$].

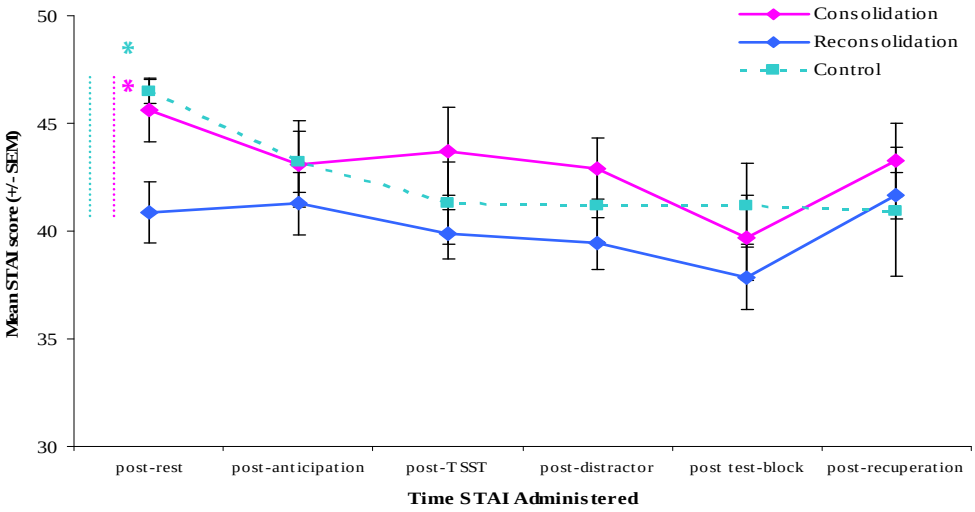
An Independent samples t-test revealed predicted differences across groups for subjective stress. Comparing the Control and Reconsolidation data, the Reconsolidation group indicated higher 'stress' levels in terms of negative affect post-rest [$t(15)= -3.099$, $p=.007$], post-anticipation [$t(17)= -3.549$, $p=.003$], and post-TSST [$t(14)= -3.708$, $p=.002$], as well as in terms of stress appraisal post-anticipation [$t(19)= -6.953$, $p<0.001$], post-TSST [$t(20)= -4.212$, $p<0.001$], and post-distractor [$t(20)= -3.149$, $p=.005$]. Interestingly, state anxiety STAI scores were significantly higher for the Control group post-rest than the Reconsolidation group [$t(17)= 3.623$, $p=.002$]. Comparing the Control and Consolidation data, the Consolidation group generally indicated higher stress levels in terms of negative affect post-anticipation [$t(11)= -3.595$, $p=.004$] and post-TSST [$t(9)= -2.635$, $p=.027$], as well as in terms of stress appraisal post-anticipation [$t(16)= -8.314$, $p<0.001$], post-TSST [$t(14)= -6.068$, $p<0.001$], and post-distractor [$t(16)= -2.519$, $p=.023$]. In a similar manner to the Reconsolidation group, the Control group showed significantly higher stress appraisal ratings post-rest than did the Consolidation group [$t(18)= 2.635$, $p=.077$]. Comparing Consolidation and Reconsolidation data (see Figure 6.10), the Reconsolidation group showed higher

baseline stress levels (i.e., post-rest) in terms of negative affect [$t(14)= 2.931$, $p=.011$] and stress appraisal [$t(22)= 3.042$, $p=.006$], with the Consolidation group showing higher state anxiety [$t(22)= -2.254$, $p=.034$].

(a)



(b)



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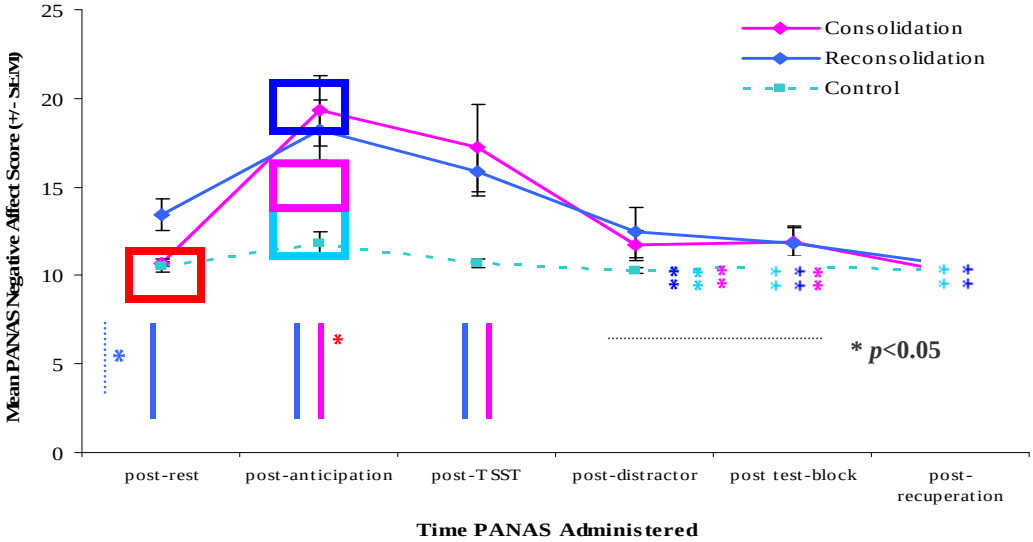

Figure 6.10: (a) Mean stress appraisal rating (1=not at all stressed, 5=moderately stressed, 10=extremely stressed) per group across assessment time (+/- SEM); (b) Mean STAI state-anxiety score per group across assessment time (+/- SEM); (c) Mean PANAS negative affect score per group across assessment time (+/- SEM). Vertical lines represent significant differences between the control and reconsolidation (blue) and consolidation (pink) group scores, respectively.

6.3.3 Memory Performance: Visual Paired Associate Task

6.3.3.1 Accuracy

Descriptively (see Figure 6.11), the 'non-stressed' Control group performed with a higher percentage accuracy than *both* the 'stressed' (i.e., Consolidation and Reconsolidation) groups, across *all* contexts (i.e., Background, No Background, Recombined). As expected, the *lowest* accuracy was obtained for the background context in the Reconsolidation group. Both Consolidation and Reconsolidation groups showed divergent context-based patterns, with the Reconsolidation group performing worse on the background context and best on the recombined context, with the Consolidation group showing an opposite pattern. A 3x3 repeated measures mixed factorial ANOVA with context type (3 levels; Background, No Background, Recombined) as the within-subjects factor and group (i.e., Control, Consolidation, Reconsolidation) as the between-subjects factor revealed *no* significant main effect for Context, nor was there an interaction effect between Accuracy and Group, or a main effect for Group at the $p<0.05$ level. *No* significant differences were found between Consolidation and Reconsolidation groups at the $p>0.05$ level.

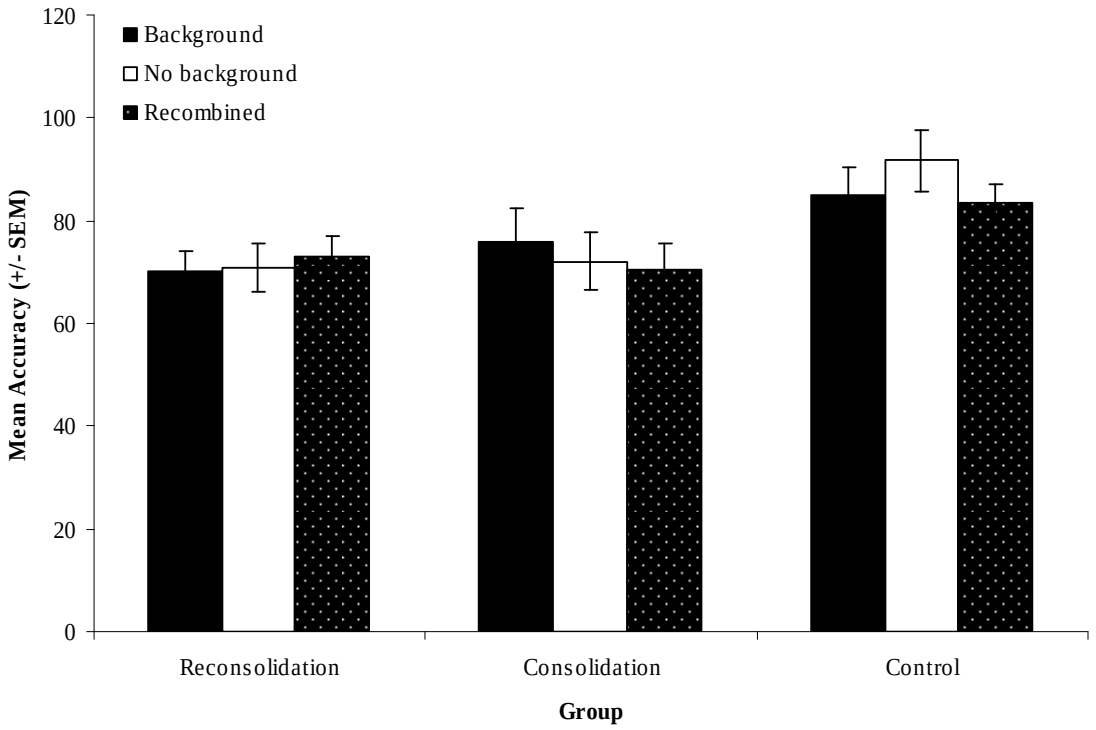

Figure 6.11: Mean percentage accuracy across Group (Consoldiation, Reconsolidation and Control) and previously presented Context type (background, no background, recombined) +/- SEM.

6.3.3.2 Reaction Time

Descriptively, in terms of Correct Responses (see Figure 6.12), the quickest RT was achieved for the previously presented background context in the 'non-stressed' Control group, with the slowest RTs obtained for Recombined stimulus pairs in the 'stressed' (Consolidation and Reconsolidation) groups. A 3x3 repeated measures mixed factorial ANOVA with context type (i.e., Background, No Background, Recombined) as the within-subjects factor and group (i.e., Control, Consolidation, Reconsolidation) as the between-subjects factor was conducted for RTs for both Correct and Incorrect responses. For Correct response, there was a significant main effect for Context type (Wilks' Lambda= .644, F(2,28)=7.738, p= .002, η_p^2=.356). There was no significant interaction effect between Context type and Group and

the main effect for Group was non-significant at the $p>0.05$ level. Paired samples t-tests per Group revealed a significant increase in RT from the Background context (904.06±211.55) to Recombined context (1033.97±298.34) in the Consolidation group [$t(10)= -2.923$, $p=.015$], as well as in the Control group (Background context- 813.45±222.79; Recombined- 967.63±203.38) [$t(6)= -2.663$, $p=.037$]; together with a significant increase in RT from the No Background (854.20±196.33) to the Recombined context (966.63±203.38) in the Control group [$t(6)= -3.796$, $p=.009$].

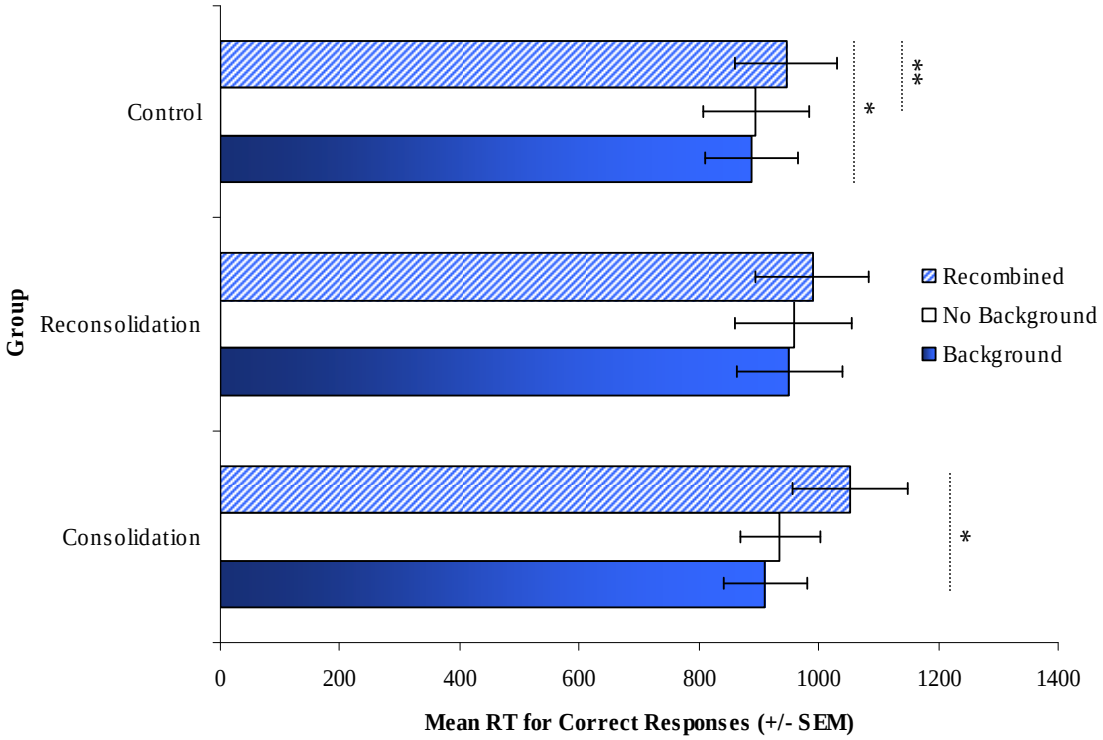

Figure 6.12: Mean reaction time across Group and Context type for correct responses (+/- SEM).

In terms of Incorrect Responses (see Figure 6.13), the fastest RT was obtained for the Background context in the 'non-stressed' Control group, while the slowest RT was found for the No background context in the Control group. A 3x3 repeated measures ANOVA (see

above) yielded *no* significant main effect for Context type, Group or Interaction effect at the $p>0.05$ level.

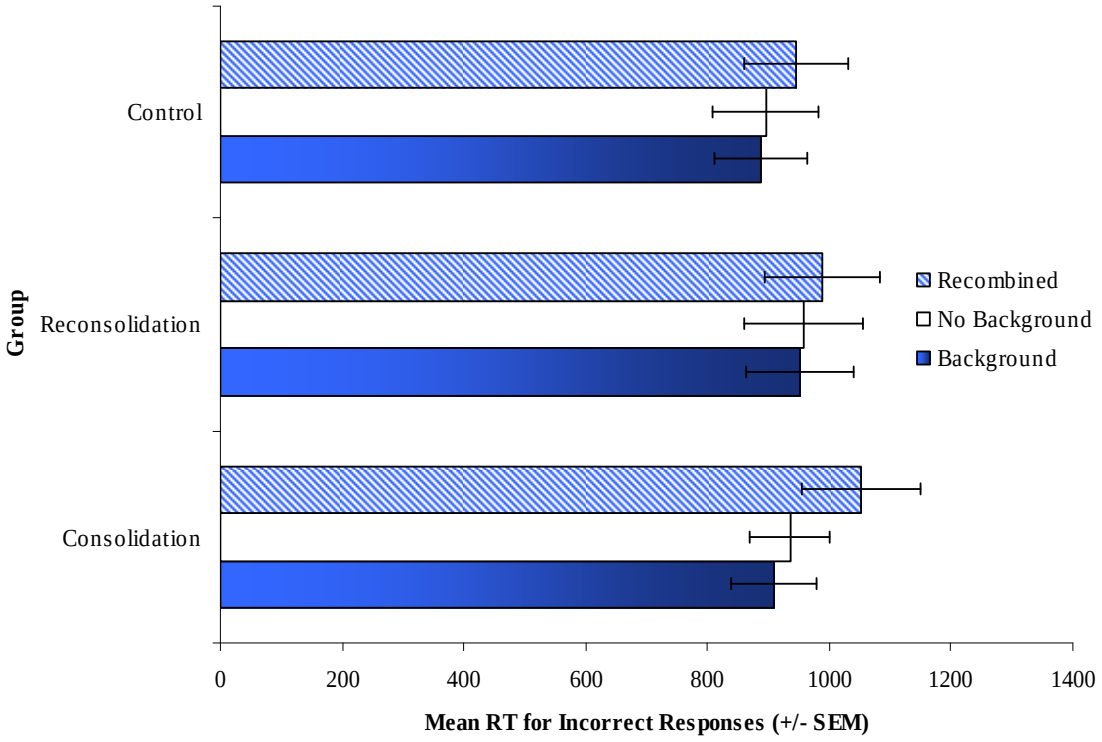

Figure 6.13: Mean reaction time across Group and Context type for incorrect responses (+/- SEM).

Sex was included in the above analyses because it is an important factor determining the impact of stress on memory (Wolf *et al*., 2001). However, significant sex differences did *not* emerge in any of the memory analyses.

Overall therefore, in terms of whether the TSST succeeded in stressing participants, it would appear that the Consolidation group responded as predicted to the stressor with respect to HPA axis *cortisol* response, whereas the Reconsolidation group did not react in the predicted manner. The Consolidation group showed higher cortisol across *all* stress phases when compared to both artificial and practical baseline levels. In terms of artificial baseline, the Reconsolidation group did not show higher cortisol across any stress phases when

compared to baseline levels. However, it must be stipulated that more stringent practical baseline results revealed a positive difference post-TSST (T4), post-distractor (T5) and post-VPA test-block (T6) for the Reconsolidation group, thereby indicating that the empirically measured cortisol concentration was *higher* than the concentration expected by the practical baseline, and as such participants *were* indeed 'stressed' during the VPA test-block.

In terms of stress appraisal measures, a significant main effect of group for *negative affect* as measured by the PANAS and a significant group by assessment time interaction was found; a significant main effect for stress appraisal ratings and a significant group by assessment time interaction was also found; and a significant main effect for STAI state anxiety ratings but *no* significant interaction effect between assessment time STAI score and group was found. Thus, it would appear that assessment time exerted an effect on subjective negative affect and appraisal scores, but not in terms of STAI state anxiety ratings. Regarding the Reconsolidation group, exposure to the TSST significantly elevated subjective stress ratings. The Consolidation group also responded in the predicted manner to the TSST in terms of subjective response. *Both* Consolidation and Reconsolidation groups also showed higher subjective stress response ratings for negative affect and stress appraisal ratings than the Control group for stressor phases.

In terms of memory performance in the VPA test-block, while the TSST stressor appears to have impaired both Consolidation and Reconsolidation groups relative to the Control group, the stress effect did not impact on Consolidation and Reconsolidation groups differently. However, such a finding must be tempered with the fact that the background context in the reconsolidation group yielded the lowest accuracy (albeit non-significantly). In terms of Correct Response, the quickest RT was achieved for the previously presented background context in the 'non-stressed' Control group, with the slowest RTs obtained for Recombined stimulus pairs in the 'stressed' (Consolidation and Reconsolidation) groups. The

TSST stressor appears to have exerted an effect on both Consolidation and Reconsolidation groups, with quicker response obtained in the Control group, albeit non-significantly. In terms of context, within groups, there was a significant increase in RT from the Background context to Recombined context in the Consolidation group, as well as in the Control group; together with a significant increase in RT from the No Background to the Recombined context in the Control group.

6.4 Discussion

The aim of the current study was to isolate the locus of effect of, and determine the mechanisms through which stress interacts with reconsolidation, and in particular how it influences the special role of context cues, through testing correlates of hippocampal function. It was conjectured that acute stress induction would impair hippocampal functioning, and hence context coding, in an associative memory task involving consolidation and reconsolidation. More specifically, it was hypothesized that contextual reactivation of the original VPA stimulus pair trace following stress induction, would destabilize the strength of the trace and lead to memory impairment in the Reconsolidation group. Conversely, it was predicted that non-contextual reactivation of the original trace, would prove to further strengthen the original trace in the Consolidation group, thereby leading to memory facilitation. A control group was employed to ascertain whether the stressor task, as suggested by the literature, would exert a deteriorative effect upon hippocampal functioning.

Regarding whether the TSST stressor task employed succeeded in stressing participants, it would appear that the Consolidation group responded as predicted to the stressor with respect to HPA axis cortisol response, whereas the Reconsolidation group did not react in the predicted manner. The Consolidation group showed higher cortisol across all stress phases when compared to practical baseline levels. However, it must be stipulated that, accounting for diurnal variation, stringent practical baseline results revealed a positive difference post-TSST, post-distractor and post-VPA test-block for the Reconsolidation group, thereby indicating that the empirically measured cortisol concentration was *higher* than the

concentration expected by the practical baseline, and as such participants *were* indeed 'stressed' during the VPA test-block.

In terms of stress appraisal measures, it would appear that assessment time exerted an effect on subjective negative affect and appraisal scores, but not in terms of STAI state anxiety ratings. Regarding the Reconsolidation group, exposure to the TSST significantly elevated subjective stress ratings. The Consolidation group also responded in the predicted manner to the TSST in terms of subjective response. Therefore, *both* Consolidation and Reconsolidation groups also showed higher subjective stress response ratings for negative affect and stress appraisal ratings than the Control group for stressor phases.

In terms of memory performance during the VPA test-block, while the TSST stressor appears to have *impaired* both Consolidation and Reconsolidation groups relative to the Control group, the stress effect did *not* impact on Consolidation and Reconsolidation groups differently, contrary to expectations. However, such a finding must be tempered with the fact that the background context in the Reconsolidation group yielded the lowest accuracy, albeit non-significantly. Subjective stress responses could shed some light on this finding. In terms of PANAS negative affect, scores were significantly higher post-TSST when compared to post-distractor, post VPA test-block, and post-recuperation scores, in *both* Consolidation and Reconsolidation groups. Thus, it could be the case that the higher negative affect scores immediately post-stressor when compared to post-distractor and post VPA test-block (the point at which memory retention is being assessed) could account for such a non-significant finding. However, the lack of significant accuracy and RT performance differences, between Consolidation and Reconsolidation groups reported could also be related to the dose-dependent effects of glucocorticoids. Indeed, evidence supporting this interpretation derives from a study conducted by Domes and colleagues (2005) who subdivided participants that were administered a moderate dose of hydrocortisone into

subjects with high cortisol concentrations (high cortisol group) and subjects with low cortisol concentrations (low cortisol group). They found impaired retrieval of verbal memory in the high cortisol group but a retrieval enhancement in the low cortisol group. The Trier-Social Stress Task, as detailed in Chapter 2, is known to induce only moderate levels of stress (Dickerson & Kemeny, 2004). Perhaps future studies within this realm could control for the dose-dependent effects of glucocorticoids, and as such possibly show increased memory impairment for reconsolidation than presently allowed for.

Explaining the current findings however, it could also be the case that low levels of corticosteroids (in which mineralocorticoid receptors are fully occupied) may influence attention to and encoding of relevant stimuli, while increasing levels of corticosteroids acts on consolidation processes, with moderate doses facilitating memory and very high doses impairing it (Beckner *et al*., 2006). Thus, we hereby report moderate stress results, wherein cortisol levels were not raised beyond the peak of the inverted U-shaped function between GCs and memory (see Chapter 1). As such, the current study may actually have served to raise stress levels to the optimal peak for humans, thereby being the first study of its kind to demonstrate relative effects on consolidation and reconsolidation-based processes at this peak.

The accuracy results obtained herein serve to extend previous findings suggesting that the effect of stress on memory function is not solely detrimental but that stress may also *enhance* memory performance (Cahill *et al*., 2003; Schwabe *et al*., 2008a). Several authors, however, found declarative memory retrieval to be impaired when subjects were stressed or administered GCs *prior* to retention testing (Kuhlmann *et al*., 2005a; Kuhlmann *et al*., 2005b; de Quervain *et al.*, 2007). Given that the study reported presently compared both consolidation and reconsolidation groups, we may be the first to hint at the disparity between memory retrieval in terms of consolidated and reconsolidated traces when participants are

stressed prior to retention testing. In this case, consolidated traces were enhanced whereas reconsolidated traces were impaired, with both impaired relative to controls.

An advantage bestowed by the present study concerns the timing of cortisol manipulation. In the majority of human studies demonstrating an impairing effect of elevated cortisol on memory, the stressor or GC is applied before stimulus presentation and encoding, and recall is tested within 1-2 hours. In such a paradigm, cortisol levels are elevated during *all* memory phases (i.e., encoding, consolidation and retrieval). Disruption of any one of these memory processes could account for detrimental effects on memory and might obscure any facilitated process. By conducting the encoding phase 24 hours prior to stress induction, and retrieval following stress induction in the current study, such confounds were accounted for.

An ancillary finding of the current study is that emotionally arousing backgrounds appear to have been more affected by stress than neutral blank backgrounds in the Reconsolidation group, albeit non-significantly. In support of such a finding, previous studies have observed enhanced consolidation of emotionally arousing material when compared with neutral material following cortisol or stress treatment (Buchanan & Lovallo, 2001; Cahill *et al*., 2003). Thus, the beneficial and detrimental effects of glucocorticoids might be particularly pronounced for emotionally arousing material, with facilitative effects observed for consolidated stimuli and impairing effects observed for reconsolidated stimuli. Previous studies (e.g., Buchanan & Lovallo, 2001; Kuhlmann *et al*., 2005) have further suggested that the effects of cortisol are similar for positive as well as negative material, which suggests that emotional arousal rather than valence is the critical aspect of the observed interactions. These observations are in accord with neuroimaging studies showing that the activity of the amygdala is associated with memory formation of arousing stimuli (Cahill *et al*., 1996; Canli *et al*., 2000), apparently independent of stimuli valence (Hamann *et al*., 1999; Kensinger &

Corkin, 2004). Pharmacological functional magnetic resonance imaging studies have recently shown that this effect is dependent on β-adrenergic activation in the amygdala (Strange & Dolan, 2004; van Stegeren *et al*., 2005), thereby replicating the effects demonstrated in rats (McGaugh & Roozendaal, 2002; Roozendaal, 2002). However, the role of the amygdala in emotional memory retrieval is not as well understood (Taylor *et al*., 1998; Dolan *et al*., 2000; Smith *et al*., 2004; Strange & Dolan, 2004). More imaging studies are warranted that investigate the effects of stress or stress hormones on memory retrieval. The only study on this topic to date in humans observed a reduced blood flow in the right posterior medial temporal lobe following cortisol treatment (de Quervain *et al*., 2003).

In animal studies however, evidence suggests that while the amygdala is involved in conditioning, the hippocampus plays an important role in forming memories of contextual cues associated with the conditioning event (Phillips & LeDoux, 1994). Pugh and colleagues (1997) conditioned rats to an auditory cue while placed in a white cooler (i.e., context). A glucocorticoid antagonist administered prior to conditioning or immediately after did not affect auditory cue conditioning 24 later (i.e., freezing behaviour in response to tone in a novel environment). The treatment did, however, impair contextual fear conditioning (i.e., failing to freeze when put inside the cooler without a tone) in treated animals compared to vehicle-treated controls. Similar findings have been observed in relation to the effects of corticosteroids on spatial memory (e.g., Conrad *et al*., 1997). Importantly in this regard, spatial memory paradigms in animal research typically involve some form of associative learning. Generally, a behaviour is learned over several trials through operant conditioning (i.e., the location of food in a radial arm maze or escape routes). Successful recall of the learned behaviour then required memory for spatial information in these tasks, which some consider explicit (i.e., episodic memory).

Related to previous studies (see Chapters 3, 4, and 5), the Consolidation group, in the current study, displayed superior true recognition for the emotional background context than the neutral no background context. Further, true recognition for the background context was higher than that obtained for the (false) recombined context. The Reconsolidation group, on the other hand, demonstrated reduced true memory performance, particularly for the emotional background context. Such results differ from those obtained in previous experiments (see Chapters 3 & 4 in particular), wherein recognition memory for false stimulus pairs in congruent contexts was superior to that obtained for true-pairs. However, corroborating results obtained herein, Smeets and colleagues (2008) recently found that memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Participants were first exposed to a cold pressor stressor prior to encoding, during consolidation, and before retrieval, or were not stressed and were subsequently subjected to neutral and emotional versions of the Deese-Roediger-McDermott (DRM; see Chapter 1) word list learning paradigm. Twenty-four hours later, recall of presented words (i.e., true recall) and non-presented critical lure words (i.e., false recall) was assessed. Results showed that stress exposure yielded superior true memory performance in the *consolidation* stress group and reduced true memory in the *retrieval* stress group compared to other groups, particularly for emotional words. Neutral and emotional false recall, on the other hand, was neither affected by stress exposure, nor related to cortisol activity following stress. The current results extend these findings on a behavioural level, showing that true recognition was higher for emotional contexts than neutral contexts in the Consolidation group, and false recognition was higher than both emotional and neutral contexts in the Reconsolidation group. In a related vein, Nadel and Payne (2002) showed that, compared to controls, participants exposed to the TSST showed elevated rates of false recognition for false lures using the DRM paradigm. Thus, as shown in the current study,

stressed participants appeared to lose the ability to distinguish “true” and “false” memories when stressed, which the authors discussed as reflective of the role of both the hippocampal and prefrontal systems in contextual remembering, and the modulation of these systems by stress.

A potential confound regarding the present study, however, could reside in the nature of context-dependent memory tested. Nadel and Payne (2002) conjectured that if binding involves spatial context, it follows that stress would disrupt it. However, if spatial context is not involved, stress should be without effect. Such a possibility would explain the behavioural data obtained presently. Perhaps inclusion of a more complex spatial arrangement during the VPA study and test-blocks may serve to further explain the non-significant accuracy differences between Consolidation and Reconsolidation groups obtained in the present study. Furthermore, in terms of false recognition, and importantly in terms of false memory research such as eye-witness testimony, future research needs to address the issue concerning why exactly participants in the Reconsolidation group showed higher accuracy to false, recombined pairs than to true, previously presented pairs, as well as longer RTs for recombined pairs when compared to contextual backgrounds in the Consolidation and Control groups, and when compared to neutral backgrounds in the Control group. In the current study, a further condition should have been incorporated including completely new, previously unencountered stimulus pairs. Doing so would allow for separation of the relative merits and demerits of false recognition in response to stress induction.

To conclude, at the outset we predicted that acute stress induction would impair hippocampal functioning, and hence context coding, in an associative memory task involving both consolidation and reconsolidation. More specifically, it was hypothesized that contextual reactivation of the original VPA stimulus pair trace following stress induction, would destabilize the strength of the trace and lead to memory impairment in the

Reconsolidation group. Conversely, it was predicted that acontextual reactivation of the original trace, would prove to further strengthen the original trace in the Consolidation group, thereby leading to memory facilitation. In terms of accuracy performance, although a non-significant main effect was found for context, the stressor impaired both Consolidation and Reconsolidation groups relative to the Control group. However, the stressor did not impact on Consolidation and Reconsolidation groups in a significantly different manner. However, consolidated traces did appear to be enhanced whereas reconsolidated traces did appear to be impaired, with both impaired relative to controls. Given that retrieval was affected, albeit non-significantly, it was concluded that stress impaired memory retrieval in the reconsolidation group. We also found, in an ancillary manner, that emotionally arousing backgrounds appeared to have been more affected by stress than neutral blank backgrounds in the Reconsolidation group, albeit non-significantly. Thus, the beneficial and detrimental effects of glucocorticoids might be particularly pronounced for emotionally arousing material, with facilitative effects observed for consolidated stimuli and impairing effects observed for reconsolidated stimuli. Related to previous findings (see Chapters 3, 4, and 5); the Consolidation group, in the current study, displayed superior true recognition for the emotional background context than the neutral no background context. Further, true recognition for the background context was higher than that obtained for the (false) recombined context. The Reconsolidation group, on the other hand, demonstrated reduced true memory performance, particularly for the emotional background context. Such results differ from those obtained in previous experiments, wherein recognition memory for false stimulus pairs in congruent contexts was superior to that obtained for true-pairs. Such findings were explained by the assertion that stressed participants appeared to lose the ability to distinguish “true” and “false” memories when stressed, which has been previously

discussed as reflective of the role of both the hippocampal and prefrontal systems in contextual remembering, and the modulation of these systems by stress.

7

Chapter VI

General Discussion

General Discussion

7.1. Summary of Research

Previous human-based studies within the field of memory reconsolidation have, for the mostpart, tackled only implicit forms of memory that do not require *conscious* recollection. We reasoned however, that if reconsolidation is to have any therapeutic value within both anxiety and addiction treatment realms, for which current treatment options have shown limited effectiveness, it is pertinent to both demonstrate and address contentious issues in *humans*, through adopting declarative-based methods. In so doing, we reasoned that episodic memory, which has been previously shown to be susceptible to post-event information, would allow for us to achieve these aforementioned goals.

As a consequence, the core objectives underpinning this thesis involved exploring the effects of both context and stress on episodic memory consolidation and reconsolidation using behavioural and electrophysiological approaches. Specifically, the behavioural effects on visual paired-associate memory of global and local context manipulations were first investigated in order to identify the relative contributions of each form of context to episodic encoding and retrieval (Chapters 3 & 4). Subesquently, the electrophysiological correlates of local contextual memory facilitation or decrement were examined to further elucidate the cortical nature of these context-dependent effects with respect to implicitly encoded episodic memory (Chapter 4). Next, behavioural and event-related and dipolar indices of memory consolidation and reconsolidation were studied in the context of a memory updating task (the first of its kind to be executed with human participants: Chapter 5). Finally, interactions between psychosocially induced stress and context on episodic, paired-associate indices were investigated in an experiment combining salivary cortisol measures and behavioural indices

to explore the putative effects of protein synthesis inhibition on memory encoding and retrieval (Chapter 6). Given that contextual information is a pivotal component of episodic memory, it was deemed necessary to first turn our attention to context-based processing.

7.2 Context

The contribution of contextual factors upon learning and memory has been well-established, and it has been repeatedly shown that reinstating a learning context facilitates, while changing context impairs, retrieval. Further, contexts can differ in terms of their position on a local-global continuum. However, the literature is replete with research addressing *global* context, with a paucity of research considering *local* context. The research that *has* addressed local context has only examined verbal recall, with little evidence available in terms of episodic processing, a fundamental component underlying the formation and perpetuation of both traumatic and addiction memories. Further, research concerning the contextual binding between target items and surrounding context has been thus far limited to pre-existing *semantic* relationships. We deemed it necessary to clarify the cue congruency related elements that function in local and global context-dependent memory processes both within the episodic and implicit memory domains, given that everyday memory as well as pathological memory (e.g., drug addiction, PTSD) are of this type. This research stream is particularly important given that the vast majority of research conducted to date in terms of environmental context-dependent memory reinstatement effects has been conducted, for the mostpart, in relation to verbal memory and semantic cues.

The first set of experiments was motivated by three main research questions. First, we attempted to ascertain whether context reliably facilitates episodic paired-associate stimulus recognition in the same way that it influences episodic word recognition and

semantic object identification. Second, we investigated the relative effects of local and global background context, encoded implicitly, on episodic item retrieval. In so doing, we attempted to determine whether the binding of item and context occurs implicitly, or whether item and context are separate entities in this regard. We achieved this aim through employing context-dependent measures such as the context-shift decrement, as well as employing a visual paired-associate task, known to elicit episodic processing. Third, we decided to investigate the impact of both local and global context on true and false recognition measures, given the importance of true and false recognition within the premise of implicit-explicit, unconscious-conscious, familiarity-recollection and item-inter-item (i.e., binding of item and context) dichotomies, respectively. To achieve this, we used the 'old/new' paradigm, wherein participants were required to judge whether items presented during the test phase were previously encountered during the initial study phase. The first experiment was concerned with ascertaining the implicit contextual congruency effect of *local* context on the recognition of true versus false paired-associate stimulus pairs. Conversely, the second experiment was concerned with determining the implicit contextual congruency effect of *global* context on the recognition of true versus false paired-associate stimulus pairs.

We found predicted congruency effects, in line with previous context-dependent verbal recognition and semantic object identification experiments, for episodic paired-associate recognition across both local and global experiments, with participants responding more accurately to 'false', as opposed to 'true' previously presented stimulus pairs. We conjectured that the increased false over true recognition findings, indicate that perhaps such episodic processing took place on a conscious, item-familiarity based level. Further, the context-dependent congruency results would appear to suggest that context facilitates episodic stimulus recognition in the same way that it influences episodic word recognition and semantic object identification.

Our next line of investigation investigated the neural correlates of implicit local context processing, together with an episodic paired-associates task. Much controversy has prevailed as to the significance of a congruent context for memory formation, and therefore the effect of context on cortical brain activation is of critical importance. Moreover, the act of learning associations between stimuli and their contextual backgrounds is a fundamental requirement of everyday memory; however, relatively little is known about the electrophysiological correlates and functional neuroanatomy subserving this process. The contribution of the present research within this field is thus prolific. Previous neuroimaging studies of scene processing, object identification, and intentional retrieval of visual context information suggest that the medial temporal lobes, most likely the parahippocampal cortex (PHC), may be involved in visual context effects mediating episodic object recognition. Hayes, Nadel and Ryan (2007) recently found that the PHC is important not only for processing of scene information, but also plays a role in successful episodic memory encoding and retrieval. Furthermore, it is widely acknowledged that the hippocampal and PHC regions are responsible for the association of objects with their spatial location in the stimulus environment. Other neuroimaging evidence indicates that these regions are also involved in relational processing, that is, in integrating or binding disparate elements in a complex scene to form a meaningful representation. For example, greater activation of the HF and PHC region occurs when stimulus elements are encoded relationally or bound together rather than encoded individually (Henke *et al.*, 1997, 1999). Thus far, in vivo demonstrations of HF and PHC activations during binding operations have used paradigms that required effortful encoding (Henke *et al.*, 1997, 1999; Montaldi *et al.*, 1998). However, behavioral data suggest that these processes operate without explicit intention.

Using a local context paired-associate task paradigm, we attempted to isolate the electrophysiological and source correlates underpinning the retrieval of episodic local

contextual memory. In so doing, it was hoped that electrophysiological indices could shed some light on contentious issues within the field such as implicit item-context binding, together with the functional role of MTL regions in episodic retrieval. To achieve this, eight pairs of stimuli were learned during the study phase, with each pair presented superimposed upon a unique contextual background. The test phase involved the presentation of a single visual stimulus on a contextual background (i.e., probe stimulus), which was followed by a full stimulus pair. Participants were required to judge whether a presented stimulus pair was *true* (previously presented during the study phase) or *false* (rearranged pairs), irrespective of background, allowing for the manipulation of implicit local contexts.

Behavioural findings revealed higher accuracy for the false (i.e., recombined) pairs together with a non-significant main effect for context. Electrophysiological data, however, revealed statistically significant context effects on the P1-N2 latency for the four test conditions occurring maximally over parietal electrodes, with the true-congruent condition peaking approximately 30ms earlier than the incongruent conditions. Such findings suggest, in our opinion, that implicit local context interacted to affect learning of visual pairs at a relatively early stage in the information-processing stream, and that such scenes were processed as a unitary percept rather than as a set of linked elements. When compared to behavioural findings showing the superior retrieval of false-pairs, the electrophysiological data suggested that the association between context and stimulus pair occurs unconsciously and somewhat separate from later processing. Dipolar sources were located for false-pairs in the superior temporal gyrus, thereby indicative, we conjectured, of conscious item-based processing, whereas sources located for true-pairs within the medial temporal lobe suggested unconscious context-based processing. We ultimately contended that, in line with Multiple Trace Theory, these findings may imply that implicit contextual processing of episodic

memory remains within the remit of MTL regions, whereas explicit item-based processing no longer relies upon MTL regions at this juncture.

Implications of context findings within the broader research sphere

The special role of false recognition in episodic memory

The most important results emanating from these context experiments point to a particular role for false recognition in episodic memory, with recognition generally higher for false pairs when compared to true pairs. The implications of these findings are widespread, elucidating the role of episodic binding of abstract arbitrary stimulus pairs within the realm of false memory. Indeed, retrieving an episodic memory is largely a reconstructive act (Schacter & Tulving, 1994), and under some conditions this reconstruction can go awry. Our results suggest that correctly reconstructing an episode requires binding together the different elements of that episode, and as such depends integrally upon congruency between available contexts at encoding and retrieval. Conversely, the facilitative effect of false recognition emerges when local contexts in particular differ between encoding and retrieval. Employing global context cues appears to weaken the impact of this facilitative effect in incongruent contexts, with both true and false recognition showing significantly higher accuracy in congruent as opposed to incongruent contexts. Providing a local context together with a global context[8] appears to exert a facilitative effect for false recognition over true recognition also. However, again, this effect was found for both congruent and incongruent contexts. Thus, overall, in terms of false recognition effects, it would appear that employing local contextual cues confers a distinct advantage over global contextual cues. Thus, local context plays an important role in episodic paired associate binding. Failure to bind properly leads to the possibility of incorrect retrieval and consequently, false memory. Our research has thus

[8] These findings emanate from research not incorporated in the present thesis.

targeted local context, via its role in episodic binding, and identified it as an important element in the understanding of memory distortions.

The associative nature of memory representations has been widely investigated. For example, in a standard semantic priming paradigm (e.g., Neely, 1977, 1991), the speed of deciding that a letter string (‘doctor’) is a word is increased if it has been preceded by an associatively related word (‘nurse’) relative to an unrelated word (‘house’). The basic explanation for such an effect is that the activation of the word ‘nurse’ spreads through an associative-semantic network, thereby partially activating the related word ‘doctor’ such that it can be identified quicker. Similarly, in the false-recognition paradigm employed by Underwood (1965), the presence of a word such as ‘table’ in a list had the effect of increasing false recognition of a related word such as ‘chair’, relative to unrelated concepts such as ‘flower’. An interpretation of such an effect is that presentation of the word ‘table’ may have aroused an implicit associative response.

Spreading activation theories of false recognition assert that exposure to a word causes the activation of semantically-related words (e.g., Collins & Loftus, 1975; Underwood, 1965). According to semantic priming, the speed of deciding that a letter string is a word is increased if it has been preceded by an associatively related word relative to an unrelated word. Thus, activation of the related word spreads through an associative-semantic network, thereby partially activating the test word such that it can be identified quicker. Similarly, in terms of false recognition, presentation of an entire list of related words virtually guarantees that the critical lure will undergo considerable activation. An interpretation of such an effect pertains to an implicit associative response. Thus, activation of a non-presented word may result in a sense of familiarity, or even the recollection that one actually encountered the word on the list when indeed they did not. Further, gist-processing accounts of false recognition (Brainerd & Reyna, 1998; Schacter *et al.*, 1998) assert that subjects

remember the gist of what they have experienced (i.e. the 'theme' of the word-list), rather than the specific details (i.e. the individual words). This reliance on gist leads naturally to false recognition of similar, but non-presented, words due to the high degree of semantic-relatedness between lures and presented words.

The results obtained herein provide unique insight into implicitly mediated false recognition effects for abstract arbitrarily related paired-associates. As such, unless the participants utilized personally constructed semantic cues to remember the paired associates during the encoding task (a possibility which was not accounted for presently), semantic relatedness was *not* the critical issue in this respect. Instead, it would appear that participants employed the local context cues, particularly in response to incongruent contexts, to retrieve information concerning the paired-associates during retrieval. Further, given the increased false over true recognition findings, it would appear that participants employed familiarity-based processing resources to ascertain whether they had previously viewed the target pair previously or not. Thus, the experiments conducted herein showed that recognition for implicit episodic memory traces occurs in a similar manner to that observed extensively in relation to verbal recognition and semantic object identification, with a particular context-dependent congruency effects isolated for local as opposed to global contextual cueing. Furthermore, we showed, through parsing the impact of contextual incongruity on both abstract paired-associates and everyday objects[9], that episodic memory is more adversely affected by local context incongruity than is semantically mediated object memory. Such a finding informed our reasoning for using local context manipulations to reactivate previously consolidated memory traces in Chapter 6. Given that reactivation of an already consolidated memory trace has been shown to destabilize this trace, we postulated that local context

[9] These findings emanate from research not incorporated in the present thesis.

manipulations would allow for optimal destabilization of the trace, thereby enabling us to 'block' the reconsolidation process through using a stress-induction protocol.

Further adding to such aforementioned context findings, building upon previous findings stipulating that unique medial temporal, parietal and prefrontal regions are associated with context-dependent and context-independent episodic memory representations, we were able to isolate the neural correlates of implicit episodic local item-context processing (see Chapter 4). The findings indicated that although implicit local context effects were not observed in terms of true recognition in the above mentioned behavioural studies, electrophysiologically, implicit local context interacted to affect learning of visual pairs at a relatively early stage in the information-processing stream. This finding is important if we redirect our attention to the findings of Slotnick and Scahcter (2004; see Chapter 3), who reported evidence of a functional-anatomic dichotomy between forms of access to late and early visual processing regions wherein late visual processing regions supported conscious recognition (and were associated with both true and false recognition), whereas early visual processing regions supported implicit memory (and were preferentially associated with true, as opposed to false recognition). In a related vein, the behavioural and electrophysiological findings emanating from the present thesis provide evidence that the form of recognition employed by participants, in terms of episodic paired-associate recognition, occurred at later in the processing stream and was consciously mediated. This assertion is attributable to the finding of greater false over true recognition in the behavioural studies, together with electrophysiological findings that the latency in response to the true-congruent test condition peaked approximately 30ms earlier than all other test conditions. Further, and importantly in terms of current concerns, this congruent condition peaked earlier than the incongruent conditions. Thus, in line with the findings of Slotnick and Schacter (2004), we have shown that, in terms of episodic memory, true recognition is associated with

contextual processing that is largely inaccessible to conscious recognition. Conversely, false recognition is associated with item oriented familiarity-based processing that is accessible to conscious recognition. As such, with respect to the current research, implicit local context interacted to affect learning of visual pairs at a relatively early stage in the information-processing stream, and the pairings between item and context were processed as a unitary percept rather than as a set of linked elements. Thus, when compared to the behavioural findings showing superior retrieval of false-pairs, the electrophysiological data implies that the association between context and stimulus pair occurred unconsciously and somewhat separate from later processing. Thus true paired-associate recognition is implicit, whereas false paired-associate recognition is explicit.

As previously stipulated (see Chapter 1), although there is a general consensus that episodic memory is supported by the hippocampus, the specific nature of the neuronal processing that occurs there is a contentious issue. Contributing significantly to this debate, we located sources for false paired-associate recognition within the superior temporal gyrus, suggesting conscious item-based processing in this region, whereas sources were located for true-paired-associate recognition within the medial temporal lobe, suggesting unconscious context-based processing in this region. Thus, our findings indicate that implicit contextual processing of episodic memory remains within the remit of MTL regions, whereas explicit item-based processing no longer relies upon MTL regions at this juncture. These findings provide support for the Multiple Trace account of hippocampal involvement in new and consolidated memory traces, which proposes that the hippocampus is involved in episodic memories for as long as they exist with only a time-limited contribution to other forms of memory (i.e., semantic) which are stored elsewhere in the brain. Our findings however further add to the literature that implicit episodic context processing involves MTL structures, whereas explicit episodic item processing does not. Such a finding is important in

terms of deriving appropriate treatment strategies for patient groups such as those with trauma-induced memories which are mediated and maintained by implicit processing of the memory trace (Ecker & Toomey, 2008).

7.3 Reconsolidation in Episodic Memory in Humans

The *next* phase of our research was interested in isolating the impact of updating an episodic trace, together with interfering with a retrieved trace through stress-induction. To recap briefly, in terms of reconsolidation, there are a number of findings demonstrating that reactivation of consolidated memories returns them to a *labile state* which can be modified again (Land *et al*., 2000; Lewis, 1979; Sara, 2000). For example, several studies in rodents have shown that protein synthesis inhibition immediately upon retrieval of memory impairs the subsequent expression of this type of memory (e.g., Tronson & Taylor, 2007). This phenomenon termed 'reconsolidation' has thus far been *mainly* demonstrated within the remit of animal models using UCS-CS preparations. In humans, reconsolidation has been observed in procedural memory (Walker et al., 2003), implicit memory in infants (Galluccio, 2005; Galluccio & Rovee-Collier, 2005), and most recently, in episodic (Hupbach *et al*., 2007) and declarative (Forcato *et al*., 2007) memory.

Research has indicated that consolidation and reconsolidation employ similar mechanisms; both the consolidation and reconsolidation of memory require protein synthesis and glutaminergic input, and both seem to be associated with the hippocampal formation. Despite this, other data has argued that the two concepts are entirely separate and individual processes (see Chapter 5 for more comprehensive discussion). We conducted two experiments aimed at addressing these issues, both behaviourally and electrophysiologically. We specifically designed a task to compare reconsolidation of an existing memory trace and

the new consolidation of additional updated information. The first experiment compared the behavioural correlates (i.e., measures of recall and recognition memory) of consolidation- and reconsolidation-based processing of paired-associates, finding clear differentiation between both processes at both group and stimulus levels. Further, in accordance with the retrieval view of reconsolidation, this study differentiated consolidation and reconsolidation by showing that the distinction between the two processes was more evident in the case of free recall as opposed to recognition. The second experiment compared the electrophysiological correlates and neural generators of remote and newly-consolidated memory traces with reconsolidated traces, investigated indices of memory updating, and addressed the contentious issue concerning variations in the age of memory traces by manipulating time between study and memory updating. Behaviourally, we found that probing episodic memory within hours of reactivation of the original trace rendered previously consolidated memories labile once again, as suggested by the reconsolidation hypothesis. Conversely, updating the memory or probing memory 24 hours following reactivation affected these newly-consolidated traces, as opposed to old/remote traces.

We therefore demonstrated, in line with recent findings of Hupbach and colleagues (2007), that reactivation of a pre-consolidated episodic memory trace allows for the integration of new information into the trace. We further demonstrated that this effect is time-dependent, by showing that administering the memory test immediately following reactivation lead to destabilization of the original memory, whereas administering the memory test 24 hours after reactivation lead to destabilization of the newly formed trace only. Thus, it would appear, based on these findings, that reactivation of an episodic memory trace exerts an immediate effect on memory for that trace. As such, the modification of episodic memories depends critically upon their preceding reactivation as suggested by the reconsolidation account. Similar to what has been found for Pavlovian conditioning (e.g.,

Nader *et al.,* 2000), instrumental conditioning (e.g., Wang *et al*., 2005), and human procedural memory (Walker *et al.,* 2003), reactivated episodic memories, in our study, underwent similar time-dependent reconsolidation processing. We consider that the demonstration of reconsolidation in human episodic memory as evidence for the universality of this phenomenon and has potential clinical relevance.

Furthermore, we were the first to differentiate between consolidation and reconsolidation in humans, both behaviourally and electrophysiologically. Behaviourally, we found clear differentiation between both processes at both group and stimulus levels. Further, in accordance with the retrieval view of reconsolidation (Riccio *et al*., 2006), we showed that the distinction between the two processes was more evident in the case of free recall as opposed to recognition. Electrophysiologically, frontal and fronto-parietal modulations were identified for reconsolidated compared to both old and new memories. Dipoles were located bilaterally in and around the medial frontal gyrus, the bilateral temporal poles, bilaterally near the tempero-parietal junction and left frontally. Overall, we concluded that the similarity of component morphologies, accompanied by ERP amplitude differences, may imply a quantitative rather than qualitative difference in the nature of reconsolidation compared to consolidation processesing.

After showing reconsolidation-based processing in human episodic memory, we subsequently attempted to induce reconsolidation-based amnesic effects on episodic memory by disrupting protein synthesis while traces were labile (Chapter 6). The literature indicates that hippocampus has a dense concentration of receptors for glucocorticoids (GCs), hormones released during stress (eg., McEwen *et al.,* 1986). Further, human and animal studies firmly establish that the high levels of glucocorticoids released during stress impair the function of the hippocampus, thereby weakening or completely disrupting those aspects of contextual and episodic memory subserved by this structure (De Quervain *et al.,* 2000; Nadel & Jacobs,

1998; Newcomer *et al.* 1999). We therefore reasoned that if stress interferes with the normal functions of the hippocampus, and the hippocampus is central to context effects in memory, then stress might interfere with those forms of memory depending on context and the binding it supports. Further, results emanating from the preceding experiment demonstrated, both behaviourally and electrophysiologically, that memories for hippocampus-dependent tasks undergo reconsolidation (see also Hupbach *et al*., 2007). The aim of this experiment was to isolate the locus of effect and determine the mechanisms through which stress interacts with reconsolidation, and in particular how it influences the special role of context cues, through testing correlates of hippocampal function. It was conjectured that acute stress induction would impair hippocampal functioning, and hence context coding, in an associative memory task involving consolidation and reconsolidation. More specifically, it was hypothesized that contextual reactivation of the original paired-associate stimulus pair trace following stress induction, would destabilize the strength of the trace and lead to memory impairment in the Reconsolidation group. Conversely, it was predicted that acontextual reactivation of the original trace, would prove to further strengthen the original trace in the Consolidation group, thereby leading to memory facilitation. A control group was employed to ascertain whether the stressor task, as suggested by the literature, would exert a deteriorative effect upon hippocampal functioning. The results obtained broadly supported these hypotheses.

In terms of accuracy performance, although a non-significant main effect was found for context, the stressor impaired both Consolidation and Reconsolidation groups relative to the Control group. However, the stressor did not impact on Consolidation and Reconsolidation groups differently. Given that retrieval was affected, albeit non-significantly, it was concluded that stress impaired reconsolidation. However, such a finding must be tempered with the fact that the background context in the Reconsolidation group yielded the lowest accuracy, albeit non-significantly.

The accuracy results obtained served to extend previous findings suggesting that the effect of stress on memory function is not solely detrimental but that stress may also enhance memory performance (Cahill *et al*., 2003; Schwabe *et al*., 2008). Several authors, however, found declarative memory retrieval to be impaired when subjects were stressed or administered GCs prior to retention testing (Kuhlmann *et al*., 2005a; Kuhlmann *et al*., 2005b; de Quervain *et al.*, 2007). Given that the study reported compared both consolidation and reconsolidation groups, we may be the first to demonstrate the disparity between memory retrieval in terms of consolidated and reconsolidated traces when participants are stressed prior to retention testing. In this case, consolidated traces are enhanced whereas reconsolidated traces are impaired

An important finding, regarding the broader experimental context, was that emotionally arousing backgrounds appeared to be more affected by stress than neutral blank backgrounds in the Reconsolidation group, albeit non-significantly. In support of such a finding, previous studies have observed enhanced consolidation of emotionally arousing material when compared with neutral material following cortisol or stress treatment. Thus, the beneficial and detrimental effects of GCs might be particularly pronounced for emotionally arousing material, with facilitative effects observed for consolidated stimuli and impairing effects observed for reconsolidated stimuli.

Related to previous studies (see Chapters 3 & 4), in the current study, the Consolidation group displayed superior true recognition for the emotional background context than the neutral no background context. Further, true recognition for the background context was higher than that obtained for the false recombined context. The Reconsolidation group, on the other hand, demonstrated reduced true memory performance, particularly for the emotional background context. Such results differ from those obtained in previous experiments, wherein recognition memory for false stimulus pairs in congruent contexts were

superior to that obtained for true pairs. However, corroborating these findings, Smeets and colleagues (2008) recently found that memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval, finding that stress exposure yields superior true memory performance in the consolidation stress group and reduced true memory in the retrieval stress group compared to other groups, particularly for emotional words. Neutral and emotional false recall, on the other hand, was neither affected by stress exposure, nor related to cortisol activity following stress.

The current results extend these findings on a behavioural level, showing that true recognition was higher for emotional contexts than for neutral contexts in the Consolidation group, and false recognition was higher than both emotional and neutral contexts in the Reconsolidation group. Also, Nadel and Payne (2002) showed that, compared to controls, participants exposed to the TSST showed elevated rates of false recognition for false lures using the DRM paradigm. Thus, as shown presently, stressed participants appeared to lose the ability to distinguish "true" and "false" memories when stressed, which the authors discussed as reflective of the role of both the hippocampal and prefrontal systems in contextual remembering, and the modulation of these systems by stress. More specifically, while not interfering with memory for the individual items, which are represented in cortex, stress impaired the ability of the hippocampus to code the context, and to bind the items and context into a contextually-specific episode. Without the hippocampus acting as a contextual anchor, 'true' details are more easily confused with 'false' details of a similar appearance and nature (Nadel *et al*., 2002). This pattern of results can also be understood if one assumes that emotional and neutral aspects of memory depend upon the amygdala and hippocampus respectively, and that a sufficiently high concentration of stress hormones potentiates the former in terms of consolidation based processing but inhibits the latter, with opposite effects occurring for reconsolidation based processing. Such a possibility may have important

ramifications for both Standard and Multiple Trace theories of memory consolidation, favouring the latter which proposes that the hippocampus is always involved in storage and retrieval of episodic memory, but semantic memory can be established in neocortex. Future neuroimaging studies should address this issue.

7.4 Broader Implications and Future Directions

In the broader context of the present thesis, the concept of reconsolidation has wider implications for patient groups. For example, the persistent retrieval and reconsolidation of traumatic memories in post-traumatic stress disorder patients enables such memories to persist. Thus, these patients suffer from intrusive memories of the original traumatic event, which are often precipitated by implicitly mediated contextual cues that have become associated with the event. Furthermore, contexts and discrete cues associated with drug-taking are often responsible for relapse among addicts (Childress *et al.*, 1999), as well as relapse to drug seeking in experimental animals (de Wit & Stewart, 1981; Fuchs *et al*., 1998; Meil & See, 1996; Weiss *et al.*, 2000). Attempts to extinguish the powerful acquired properties of such contextual cues have not generally been successful as a treatment strategy for drug addiction (Di Ciano & Everitt, 2004; Conklin & Tiffany, 2002). As a result, relapse is a constant risk, despite extended periods of abstinence (Hernandez & Kelley, 2005). The concept of Reconsolidation allows for the possible inhibiting or erasing of such implicit memories by interrupting the reconsolidation process which sustains them; see Chapter 1 for greater detail). Indeed, animal models have shown that interference with the reconsolidation of drug-cue memories can reduce seeking of drugs or drug-paired stimuli (see Chapter 1).

The problem however, which has thus far plagued literature concerning the therapeutic merit of reconsolidation within the human realm, concerns the fact that the majority of human-based studies demonstrating reconsolidation have tackled only implicit

forms of memory that do not require conscious recollection. However, therapeutic interventions that may be able to target implicit unconscious traumatic or drug related schemas need to do so by rendering such schemas both conscious and explicit. In both PTSD and drug addiction, there is no conscious thought as to why the feeling and/or the behavior are occurring, no conscious recall of the experiences and episodes located in the past that created this response, and no sense that one is experiencing a memory at all. However, full conscious retrieval of the coherent material generating this response usually elicits well-defined, specific knowledge structures as well as explicit, episodic memory of the original, concrete scenes and experiences in which these implicit 'knowings' were formed (see Toomey & Ecker, 2008). Indeed, Coherence therapy (Ecker, 2008; Ecker & Hulley, 1996, 2000a, 2004, in Toomey & Ecker, 2008), a therapy of implicit memory depotentiation consists, by definition, of locating, accessing, and depotentiating the specific, unconscious personal constructs that require production of the presenting symptom.

It is not yet apparent to neuroscientists how the disruption of synapses allowed by the process of reconsolidation can be used therapeutically in humans. Symptoms, as a rule, are beyond conscious control not because subcortical brain systems are malfunctioning, but only because a lack of neural and psychological integration keeps the cortex disconnected from the 'knowings' and the agency actually governing the person's responses. Current therapies of cognitive regulation can be regarded as variations on extinction learning—that is, they all use approximately the same region of the prefrontal cortex to counteract and suppress the responses of subcortical implicit memory. In terms of such extinction learning, Bouton (2002) suggested that relapse (i.e., recurrence of symptoms after counteracting/extinguishing seems effective) is fairly easily produced by (a) an established trigger (conditioned stimulus) occurring in a new context (termed *reinstatement*); (b) an established trigger occurring in an old context covered by counteractive training (termed *spontaneous recovery*); (c) relatively

high levels of stress; or (d) passage of time since the counteractive/extinction learning. The viability of the option of implicit memory depotentiation, through reconsolidation, would render relapse impossible and the implicit memory that was initially responsible for symptom production would no longer exist.

Importantly, in this regard, the current research has shown important findings which could allow for numerous strides to be made within this therapeutic realm. First, we demonstrated that episodic processing takes place, behaviourally, on a conscious, item-familiarity based level. Further, we found that context facilitates episodic stimulus recognition in the same way that it influences episodic word recognition and semantic object identification. Learned paired-associate target pairings were further found to be more adversely affected when local information is altered but not when global information is changed, and episodic memory was more adversely affected by local context incongruity than was semantically mediated object memory. These findings have important implications concerning the methodology that could be applied to induce depotentiation of implicit memory traces in an explicit manner. Importantly in this regard, Taylor and colleagues (2009) recently asserted that the context specificity of extinction might allow for extinction to be enhanced in one context while reconsolidation is disrupted in another context to produce a greater reduction in the motivational properties of cue to produce relapse.

Further, we isolated the neural correlates of implicit local context processing, showing that implicit local context interacted to affect learning of paired-associates at a relatively early stage in the information-processing stream and that item-context pairings were processed as a unitary percept rather than as a set of linked elements. The electrophysiological findings suggested that the association between context and stimulus pair occurs unconsciously and somewhat separate from later processing. Sources were located for false-pair recognition in the superior temporal gyrus, thereby indicative, we

conjectured, of conscious item-based processing, whereas sources were located for true-pair recognition within the medial temporal lobe suggested unconscious context-based processing. We ultimately contended that, in line with Multiple Trace Theory that these findings suggest that implicit contextual processing of episodic memory remains within the remit of MTL regions, whereas explicit item-based processing no longer relies upon MTL regions at this juncture. Our findings therefore add to the literature that implicit episodic context processing involves MTL structures, whereas explicit episodic item processing does not. Such a finding is important in terms of deriving appropriate treatment strategies for patient groups such as those with trauma-induced memories which are mediated and maintained by implicit processing of the memory trace (Ecker & Toomey, 2008). Thus there are implications for therapy, suggesting that both MTL and neocortical regions need to be targeted: the MTL regions in terms of blocking reconsolidation of implicit traces, and neocortical regions for extinction training of conscious memory. Further, when compared to the behavioural findings showing superior retrieval of false-pairs, the electrophysiological data implies that the association between context and stimulus pair occurred unconsciously and somewhat separate from later processing. Thus true paired-associate recognition is implicit, whereas false paired-associate recognition is explicit.

Finally, we found that reactivation of a pre-consolidated episodic memory trace allows for the integration of new information into the trace, and that reactivation of an episodic memory trace exerts an immediate effect on memory for that trace. As such, the modification of episodic memories depends critically upon their preceding reactivation as suggested by the reconsolidation account. We consider that the demonstration of reconsolidation in human episodic memory, together with behavioural and electrophysiological differentiation between consolidation and reconsolidation, as evidence for the universality of this phenomenon and has potential clinical relevance. After showing

reconsolidation-based processing in human episodic memory, we subsequently attempted to induce reconsolidation-based amnesic effects on episodic memory by disrupting protein synthesis while traces were labile, finding ultimately that stressed participants appear to lose the ability to distinguish "true" and "false" memories when stressed, which we discussed as possibly reflective of the role of both the hippocampal and prefrontal systems in contextual remembering, and the modulation of these systems by stress. More specifically, while not interfering with memory for the individual items, which are represented in cortex, stress impairs the ability of the hippocampus to code the context, and to bind the items and context into a contextually-specific episode. Without the hippocampus acting as a contextual anchor, 'true' details are more easily confused with 'false' details of a similar appearance and nature. These findings have enormous implications for treatment of patient group wherein stress is often a precipitating factor in terms of relapse. To conclude, the results emanating from the present thesis have numerous widespread implications for the attenuation of implicit pathological memory traces through reconsolidation of consciously mediated episodic memory.

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Appendices

Appendix 1: National Adult Reading Test (NART)

Appendix 2: Cognitive Failures Questionnaire (CFQ)

Appendix 3: Stress Appraisal Measure

Appendix 4: State-Trait Anxiety Inventory (STAI): State Form

Appendix 5: STAI Trait Form

Appendix 6: Positive and Negative Affects Scale (PANAS)

Appendix 7: Rosenberg Self-Esteem Scale

Appendix 8: RS_{10} Resilience Scale

Appendix 9: General Health Questionnaire (GHQ)

Appendix 10: Pre-experiment participant details Form for cortisol studies

Appendix 11: Pre-experiment screening questionnaire

Appendix 12: Pre-experiment instructions

Appendix 13: Post-experiment screening form

Appendix 14: Procedural timing protocol

Appendix 15: Time record sheet for salivary cortisol sampling

Appendix 16: *Informed Consent Form:* Behavioural Memory Tasks (Chapters 3 and 4)

Appendix 17: *Informed Consent Form:* ERP study 1 (Chapter 4)

Appendix 18: *Informed Consent Form:* ERP study 2 (Chapter 5)

Appendix 19: *Informed Consent Form:* Stress Induction (Chapter 7)

Appendix 1: National Adult Reading Test

The WAIS-R Full Scale, Verbal and Performance IQ's predicted from the number of errors made on the NART

Nart Errors	Predicted Full Scale IQ	Predicted Verbal IQ	Predicted Performance IQ
0	131	127	128
1	129	126	127
2	128	125	126
3	127	124	125
4	126	123	123
5	124	122	122
6	123	121	121
7	122	119	120
8	121	118	119
9	120	117	118
10	118	116	117
11	117	115	116
12	116	114	115
13	115	113	114
14	113	111	112
15	112	110	111
16	111	109	110
17	110	108	109
18	108	107	108
19	107	106	107
20	106	105	106
21	105	103	105
22	103	102	104
23	102	101	102
24	101	100	101
25	100	99	100
26	98	98	99
27	97	97	98
28	96	95	97
29	95	94	96
30	94	93	95
31	92	92	94
32	91	91	93
33	90	90	91
34	89	89	90
35	87	87	89
36	86	86	88
37	85	85	87
38	84	84	86
39	82	83	85
40	81	82	84
41	80	81	83
42	79	80	82
43	77	78	80
44	76	77	79
45	75	76	78
46	74	75	77
47	73	74	76
48	71	73	75
49	70	72	74
50	69	70	73

National Adult Reading Test

Ache	**Simile**
Debt	**Aeon**
Psalm	**Cellist**
Depot	**Zealot**
Chord	**Abstemious**
Bouquet	**Gouge**
Deny	**Placebo**
Capon	**Façade**
Heir	**Aver**
Aisle	**Leviathan**
Subtle	**Chagrin**
Nausea	**Détente**
Equivocal	**Gauche**
Naïve	**Drachm**
Thyme	**Idyll**
Courteous	**Beatify**
Gaoled	**Banal**
Procreate	**Sidereal**
Quadruped	**Puerperal**
Catacomb	**Topiary**
Superfluous	**Desmesne**
Radix	**Labile**
Assignate	**Phlegm**
Gist	**Syncope**
Hiatus	**Prelate**

FOR EXPERIMENTER'S USE

NART pronunciation and definitions

Word	Say	Definition
Ache	*Rhymes with* take	Any dull, continuous pain
Debt	Det	Anything which one owes to another
Psalm	Sahm	A sacred song or hymn
Depot	Deppo (or deepo)	A place where things are kept or stored
Chord	Kord	1. *Maths*: a straight line segment joining two points on a curve. 2. a string on a musical instrument 3. *Music*: a group of three or more notes played together in harmony
Bouquet	Bo-**kay** or boo-**kay**	1. a bunch of flowers 2. the characteristic smell of wines or liqueurs
Deny	De-**nigh**	1. to declare as untrue 2. to refuse to believe or acknowledge 3. to refuse to grant
Capon	**Kay**-pon	A domestic cock which has been castrated to improve its flesh for eating
Heir	Air	1. a person who inherits, or will inherit, money, property, title, etc. 2. a person, group or society to which something such as tradition, ideas, etc. is passed on
Aisle	Ile	Any passage between blocks of seats, as in a theatre
Subtle	**Sutt**'l	Fine, slight or delicate, so as to be difficult to detect, etc.
Nausea	**Naw**sia	1. a feeling of sickness in the stomach, often followed by vomiting 2. a feeling of extreme disgust or loathing
Equivocal	Ik**kwi**vvi-k'l	Ambiguous or unclear
Naïve	Nie-**eev**	Unaffected or unsophisticatedly simple and artless (free from deceit or cunning)
Thyme	Time	A low shrub with fragrant leaves used in cooking
Courteous	**Ker**tius	Polite and well-mannered
Gaoled	Jaled	Also spelt **jail**: a building where convicted criminals are kept
Procreate	**Pro**-kree-ate	To produce offspring
Quadruped	**Kwod**roo-rep	Any animal with four feet
Catacomb	**Katta**-koom *or* **Katta**-kome	(*usually plural*) an underground cemetery consisting of tunnels with recesses for graves
Superfluous	Soo-**per**floo-us	More than is needed
Radix	**Ray**-diks	Maths: a number used as the base of a system of numbers, logarithms, etc.
Assignate		

FOR EXPERIMENTER'S USE ONLY

Gist	Jist	The essential part of something
Hiatus	High-**ay**tus	A gap or interruption
Simile	**Simm**i-lee	A figure of speech in which two unlike things are compared
Aeon	**ee**-on	An immensely long period of time
Cellist		
Zealot	**zell**ot	1. an eager of enthusiastic person 2. a fanatic
Abstemious	Ab-**stee**mius	Tending to eat and drink sparingly
Gouge	Gowj	1. *noun* a chisel with a curved blade for cutting blades 2. *verb* to scoop out with or as if with a gouge
Placebo	Pla-**see**bo	A medicine given to a patient for psychological reasons and having no physiological effect
Façade	Fa-**sahd**	1. the outside of a building 2. a false or deceptive exterior
Aver	a-**ver**	To declare in a positive way
Leviathan	Lev-**eye**-a-th'n	Anything which is very large, especially in the sea
Chagrin	**Shag**rin *or* sha-**green**	A feeling of vexation or disappointment
Détente	Day-**tont**	An easing or relaxing of strained relationships between countries
Gauche	**goash**	Awkward or tactless
Drachm	Dram	A unit of mass equal to about 3.89g
Idyll	**Eye**-dill *or* **idd**il	A short poem or piece of descriptive music concerned with romanticized rural life
Beatify	Bee-**att**i-fie	
Banal	Ba-**nahl**	Hackneyed, ordinary or trivial
Sidereal	Sigh-**deer**iul	Of or relative to the stars
Puerperal	Pew-**er**-peral	Of, relating to, or occurring during childbirth or the period immediately following
Topiary	To-**pie**-ary	Of, relating to, or being the practice or art of training, cutting, and trimming trees or shrubs into odd or ornamental shapes
Demesne	Da-**mane** *or* da-**meen**	1. the possession of land as one's own 2. the land and buildings possessed
Labile	**Lay**-bile	Changeable or unstable
Phlegm	Flem	Also called **sputum**: the thick mucus of the throat, brought up by coughing during a cold, etc.
Syncope	**Sin**-co-pay	1. the loss of consciousness resulting from insufficient blood flow to the brain 2. the loss of one or more sounds or letters in the interior of a word (as in fo'c'sle for forecastle)
Prelate	**prell**it	A high-ranking clergyman, such as a bishop or archbishop

Appendix 2: Cognitive Failures Questionnaire (Broadbent *et al*., 1972)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to your in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasion-ally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

Appendix 3: Stress Appraisal

Please rate on this scale how stressed you *CURRENTLY* feel (0= not at all stressed; 5=modertately stressed; 10= extremely stressed).

Appendix 6: Positive and Negative Affects Scale (PANAS)

Negative and Positive Affect Scales

Instructions: Below are some words that may describe how you felt during the last month. Read each one and circle a number (from 1 to 5) to show if you felt this way.

1 = Not at all true
2 = A little true
3 = Somewhat true
4 = Pretty true
5 = Very true

During the last month I felt:

1. tense	1	2	3	4	5
2. afraid	1	2	3	4	5
3. dissatisfied with things	1	2	3	4	5
4. cheerful	1	2	3	4	5
5. weak	1	2	3	4	5
6. sad	1	2	3	4	5
7. healthy	1	2	3	4	5
8. satisfied with things	1	2	3	4	5
9. enjoyed things	1	2	3	4	5
10. worried	1	2	3	4	5
11. hostile	1	2	3	4	5
12. nervous	1	2	3	4	5
13. interested in things	1	2	3	4	5
14. happy	1	2	3	4	5
15. alert	1	2	3	4	5
16. confident about things	1	2	3	4	5
17. irritated	1	2	3	4	5
18. angry	1	2	3	4	5

Appendix 7: **Rosenberg Self-Esteem Scale** (Rosenberg, 1965)

Instructions: Below is a list of statements dealing with your general feelings about yourself. If you strongly agree, circle **SA**. If you agree with the statement, circle **A**. If you disagree, circle **D**. If you strongly disagree, circle **SD**.

1.	On the whole, I am satisfied with myself.	SA	A	D	SD
2.*	At times, I think I am no good at all.	SA	A	D	SD
3.	I feel that I have a number of good qualities.	SA	A	D	SD
4.	I am able to do things as well as most other people.	SA	A	D	SD
5.*	I feel I do not have much to be proud of.	SA	A	D	SD
6.*	I certainly feel useless at times.	SA	A	D	SD
7.	I feel that I'm a person of worth, at least on an equal plane with others.	SA	A	D	SD
8.*	I wish I could have more respect for myself.	SA	A	D	SD
9.*	All in all, I am inclined to feel that I am a failure.	SA	A	D	SD
10.	I take a positive attitude toward myself.	SA	A	D	SD

Scoring: SA=3, A=2, D=1, SD=0. Items with an asterisk are reverse scored, that is, SA=0, A=1, D=2, SD=3. Sum the scores for the 10 items.

Appendix 8: Resilience Scale (RS_{10})

Please circle a number indicating how much you Disagree or Agree with each statement.

	Disagree						Agree
1.	I usually manage one way or another.						
	1	2	3	4	5	6	7
2.	I feel proud that I have accomplished things in my life.						
	1	2	3	4	5	6	7
3.	I usually take things in my stride.						
	1	2	3	4	5	6	7
4.	I am friends with myself.						
	1	2	3	4	5	6	7
5.	I am determined.						
	1	2	3	4	5	6	7
6.	I keep interested in things.						
	1	2	3	4	5	6	7
7.	My belief in myself gets me through hard times.						
	1	2	3	4	5	6	7
8.	My life has meaning.						
	1	2	3	4	5	6	7
9.	When I am in a difficult situation, I can usually find my way out of it.						
	1	2	3	4	5	6	7
10.	I have enough energy to do what I have to do.						
	1	2	3	4	5	6	7

Appendix 9: The General Health Questionnaire

Please read this carefully.

We should like to know if you have had any medical complaints and how your health has been in general, *over the past few weeks.* Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

Have you recently

A1	**been feeling perfectly well and in good health?**	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2	**been feeling in need of a good tonic?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A3	**been feeling run down and out of sorts?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A4	**felt that you are ill?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A5	**been getting any pains in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A6	**been getting a feeling of tightness or pressure in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A7	**been having hot or cold spells?**	Not at all	No more than usual	Rather more than usual	Much more than usual

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B1	**lost much sleep over worry?**	Not atall	No more than usual	Rather more than usual	Much more than usual
B2	**had dIfficulty in staying asleep once you are off?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B3	**felt constantly under strain?**	Not at all	No more than usual	Rather more than usual	Much more than usual
*					
B4	**been getting edgy and bad-tempered?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B5	**been getting scared or panicky for no good reason?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B6	**found everything getting on top of you?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B7	**been feeling nervous and edgy**	Not	No more	Rather more	Much more

Please turn over

Have you recently

C1	**been managing to keep yourself busy and occupied?**	More so than usual	Same asusual	Rather less than usual	Much less than usual
C2	**been taking longer over the things you do?**	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3	**felt on the whole you were doing things well?**	Better than usual	About the same	Less well than usual	Much less well
C4	**been satisfied with the way you've carried out your task?**	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
C5	**felt that you are playing a useful part in things?**	More so than usual	Same as usual	Less useful than usual	Much less useful
C6	**felt capable of making decisions about things?**	More so than usual	Same as usual	Less so thanusual	Much less capable
C7	**been able to enjoy your normal day-to-day activities?**	More so than usual	Same as usual	Less so than usual	Much less than usual

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D1	**been thinking of yourself as a worthless person?**	Not at all	No more than usual	Rather more than usual	Much more than usual
D2	**felt that life is entirely hopeless?**	Not atall	No more than usual	Rather more than usual	Much more than usual
D3	**felt that life isn't worth living?**	Not at all	No more than usual	Rather more than usual	Much more than usual
D4	**thought of the possibility that you might make away with yourself?**	Definitely not	I don't thinkso	Has crossed my mind	Definitely have
D5	**found at times you couldn't do anything because your nerves were too bad?**	Not atall	No more than usual	Rather more than usual	Much more than usual
D6	**found yourself wishing you were dead and away from it all?**	Not at all	Nomore than usual	Rather more than usual	Much more than usual
D7	**found that the idea of taking your own life kept coming into your mind?**	Definitely not	I don't think so	Has crossed my mind	Definitely has

A	B	C	D	Total

Appendix 10: Participant Details Sheet for Cortisol Analysis

- Participant # :
- Date:
- Age:
- Date of Birth:
- Sex: M F
- BMI:
- Estimated weight:
- If F; current menstrual cycle stage:
  Day 1 (menstruation)
  Day 2-12
  Day 14 (Ovulation)
  Days 15-22
  Day 22 - Day 1 of next cycle
- Education Level:
- If F; currently using contraceptive pill?
- If Y; pill name:
- Are you currently using ANY medications?
- If Y; please list:
- If currently taken medication, please list times within the preceding 24 hrs prior to saliva collection:
- Do you suffer from ANY chronic diseases?
- If Y; please list:
- Do you do shift work?
- If Y; please list times:
- Have you participated in a 'fast' recently?
- If Y; please give length of time and when fast was completed:
- Are you currently jet-lagged?
- If Y; please give details of flight duration/date and time:
- Please list your food & drink intake in the past 24 hours:
- Have you consumed any carb-heavy foods within the preceding 24 hours?
- If Y; please list details:
- Sleep quality and quantity on night prior to saliva collection:
- Have you participated in ANY exercise in the past 24 hrs?
- If Y; please note level of intensity and time taken:
- What time did you wake up at this morning?
- What time do you usually wake up at?
- Are you a smoker? Y N
- If Y; please list amount of cigarettes smoked in past 24 hrs:
- Are you a regular alcohol drinker?
- If Y; please list amount usually consumed during a typical week as well as amount consumed in preceding 24 hrs:
- Please give details of the most stressful event encountered today prior to this experiment:
- the most stressful event of the day (time, duration, degree of stress—not at all stressed, somewhat, moderately, very stress, the most stressed I've ever felt)
- How **typical** has this day been prior to participating in this experiment in terms of how busy, pressured or stressed you felt during the day:

Appendix 11: Pre-Experiment Screening Questionnaire

Please answer the following questions as **accurately** as possible. If it is decided that you do not meet required criteria it is only because this experiment involves salivary cortisol analysis and we would not be able to use your data for such purposes. Please note that ANY information provided is in **complete confidence** and will not be revealed publicly in any way (you will be provided with a participant code number and this code number will be used throughout the experimentation process: not even the Experimenter will be aware of Participant Details)

Please circle **Yes** or **No** where appropriate

Have you been previously diagnosed with any **learning and/or memory impairments** (e.g., dyslexia)?	If Y; please give details:
Are you a **fluent** English speaker? Yes No	Please give details if English is NOT your first language:
Are you currently taking **prescription medication** that **may affect cognitive processes*?** Yes No	If Y; please give details:
Are you currently taking **oral contraceptives**? Yes No	If Y; please give details of brand used:
Are you currently taking **beta-blockers, steroids**, or any medication which may affect **central nervous system functioning** or **endocrine systems**? Yes No	If Y; please give details:
Do you suffer from Cushing's syndrome, Syndrome X or any other **metabolic syndromes?** Yes No	If Y; please give details:
Have you been **recently** diagnosed with depression or anxiety related disorders? Yes No	If Y; please give details of dates diagnosed and diagnoses given:
Do you have a history of **head injury**? Yes No	If Y; please give details:
Are you a **smoker**? Yes No	If Y; please give details concerning amount of cigarettes typically smoked per day:
Please indicate your average weekly **alcohol** intake:	
Have you been **ill** recently (i.e., flu/cold)? Yes No	If Y; please give details (i.e., how long ago, for how long, type of illness, and so on:
Are you **pregnant**? Yes No	If Y; please give trimester:
Have you been suffering from **insomnia** in the past few weeks? Yes No	If Y; please give details (including length of time you have been experiencing insomnia and usual times of sleeping/waking):
Do you currently do **shift-work**? (i.e., work during the night and sleep during the day) Yes No	If Y; please give details (i.e., typical working hours etc):
Age:	Date of Birth:

*The level of salivary cortisol is influenced by drugs such as prednisone, dexamethasone and other **steroids** administered orally or i.v. While prednisone usually crossreacts with the antiserum used for assaying cortisol (leading to false high values), dexamethasone will significantly suppress the HPA axis (resulting in low cortisol levels).
*If currently taking prescription medication and you are unaware of its cognitive effects please report the medication being used (in complete confidence) to the experimenter

Appendix 12: Pre-Experiment Instructions

First of all, thank you for participating in this research. Broadly, the current experiment is being carried out in an effort to help conceptualize new therapeutic interventions for those suffering from PTSD and other anxiety-related disorders. As such your participation in such a study has widespread ameliorative implications.

Please read the instructions below at least 24 hours prior to participating in the study. We will be collecting saliva samples at various points throughout the experiment and it is IMPERATIVE that you read, understand and adhere to the instructions below, otherwise the samples you provide will be contaminated and we will not be able to use your data.

Instructions pertaining to saliva sampling

Please read the following guidelines relating to saliva sampling. It is imperative that you follow the instructions given otherwise your data will need to be withdrawn from analysis.

- Please make sure to eat a light breakfast on the morning of the experiment
- If you are to eat a breakfast, make sure it is no later than 7am on the day of the experiment
- Smoking, eating, and drinking beverages containing alcohol, caffeine, fruit juices or milk is strictly **NOT** allowed for at least **1 hour** prior to saliva sampling or during the saliva collection
- Please do not brush your teeth immediately prior to saliva sampling in order to avoid contamination of saliva with blood caused by micro-injuries to the oral cavity
- Please **refrain** from strenuous physical exercise, coffee, cigarette smoking, heavy meals, alcoholic beverages and low PH soft drinks **at least 1hr prior to testing** given the known effects of these variables on HPA functioning
- Please refrain from acidic or high sugar foods within the **20 minutes** preceding the experiment
- Please refrain from using any possible salivary stimulants such as chewing gum, lemon drops, granulated sugar, drink crystals, and so on within **1 hour** prior to the experiment
- Please give the experimenter details of any **prescription medications you are currently taking** which **may affect cognitive processes**.
- If currently taking prescription medication and you are unaware as to its cognitive effects please report the medication being used (in complete confidence) to the experimenter.
- Please do **not** consume **alcohol** or other **recreational drugs** within the **preceding 24 hours of testing**.
- It is important that the cotton plug is chewed for 1-2 minutes to ensure it is fully saturated with saliva
- Rinse your mouth at least twice with cool water prior to saliva sampling. Then chew the sugarless gum provided for 1-2 minutes, swallowing saliva as usual, only if saliva stimulation required.
- Do not eat OR drink anything (***even water***) during the 10 minutes before giving each sample
- If you do accidentally eat or drink during the 10 minutes before your scheduled sampling time, please rinse your mouth with water as soon as you remember. Then, delay your sample until 10 minutes after you rinsed your mouth.
- Hormones left on hands from creams can potentially contaminate the saliva during collection. Therefore, if using a cream, wash your hands thoroughly with soap and water before beginning.
- Throughout the entire sampling period, we ask that you particularly refrain from cranberry juice, chocolate, bananas, caffeinated *and* decaffeinated coffee, tea and soda (naturally caffeine free items such as Sprite are ok), and avoid the use of toothpaste. We also ask that you avoid the use of Aspirin, Ibuprofen, and other non-steroidal anti-inflammatories. Consult the experimenter if you have a question about whether a certain medication falls into this category

- I understand all of the above: _____ Date: _____

Appendix 13: Post-Experiment Screening Form

We very much appreciate your time and participation in the experiment. It is very important to have **complete** information concerning the samples collected even if the "rules" were not followed. Please answer the following questions about the day that the samples were collected to the best of your knowledge.
(1) Was today a typical day?
❑ Yes
❑ No (explain) _____
(2) Were you feeling healthy and feeling well today?
❑ Yes
❑ No (explain) _____
(3) Did you participate in any vigorous physical activity today before the samples were collected (e.g., soccer practice, swimming)?
❑ Yes (explain) _____ At what time? _____ a.m./p.m.
❑ No
(4) Did you experience an emotional event today before sampling (such as fighting with sibling)? ❑ Yes (explain) _____ At what time? _____ a.m./p.m.
❑ No
(5) Did you eat or drink anything with caffeine today before sampling?
❑ Yes (explain) _____ At what time? _____ a.m./p.m.
❑ No
(6) Did you use the sugarless gum supplied just prior to sampling?
❑ Yes
❑ No, no gum used
❑ No, used something else (explain) _____
(7) Did you have anything to eat in the 30 minutes prior to sampling?
❑ Yes (explain) _____ At what time? _____ a.m./p.m.
❑ No
(8) Did you have milk products in the 30 minutes prior to sampling?
❑ Yes (explain) _____ At what time? _____ a.m./p.m.
❑ No
(9) List the medications you are currently taking taking. If there are no medications, please indicate.
(10) Is there **anything** else we should know that you feel may be relevant?

Appendix 14: Procedural Timing Protocol for Stress Study

Timing of Procedures, including stressor and cortisol sampling, by Condition

Time (PM)	Consolidation Group	Reconsolidation Group
3.00	Overview & Consent	Overview & Consent
3.10	Baseline measures: **Cortisol Time 1**	Baseline measures: **Cortisol Time 1**
	*First cortisol sample to be taken **immediately** upon arrival at lab (baseline measure)	
	***BASELINE must be 30 minutes long at least**	
3.15	Pre-assessments	Pre-assessments
3.40	Rest phase	Rest phase
	Rest Phase: Read neutral material in a relaxing environment (to take place in Developmental Lab – before 3.30pm as booked up until the foreseeable future from 3.30-5.30pm)	
3.40	**Cortisol Time 2**	**Cortisol Time 2**
	*Second cortisol sample must be taken **immediately** after rest phase	
3.45	Anticipation period	Anticipation period
3.55	**Cortisol Time 3**	**Cortisol Time 3**
	* Third cortisol sample to be taken immediately after anticipation period	
4.00	**Stressor:** (1) Arithmetic Task (2) Serial Subtraction Task (3) 'Presentation'	**Stressor:** (1) Arithmetic Task (2) Serial Subtraction Task (3) 'Presentation'
	***__END__ OF STRESS PHASE: THIS MUST BE MADE CLEAR TO PARTICIPANTS: We are **NOT** evaluating their performance from this point forward	
4.15	**Cortisol Time 4**	**Cortisol Time 4**
	*Fourth cortisol sample to be taken **immediately** after stressor	
4.20	Distractor Task: **no** context reinstantiation: 0-back Task	Distractor Task: **context reinstantiation**
	***Using Distractor Task & Test-Block as Stress **Recovery Period** (10 mins)	
4.30	**Cortisol Time 5**	**Cortisol Time 5**
	*Fifth cortisol sample to be taken **immediately** before test-block	
4.25	VPA test-block	VPA test-block
4.45	RAVLT: delayed	RAVLT: delayed
4.45	**Cortisol Time 6**	**Cortisol Time 6**
	*** **FINAL** cortisol sample at end of test-phase	
5.15	Post-assessments	Post-assessments

5.20	Debriefing	Debriefing

***Debriefing: **MUST** make sure participants are **FULLY** debriefed as to the nature of the task: we do **not** want this task to be in any way aversive to the participant

---

Note: RAVLT = Rey Auditory Verbal Learning Paradigm VPA = Visual Paired Associates Task Attention Task = 0-back task

Appendix 15: Time Record Sheet (Salivary Cortisol)

- Participant #

- Date

- Time of participant arrival at lab

- Saliva sample # 1
- Time taken (TT)
- Time salivette removed for use (TR)
- Time sample #1 frozen (TF)

- Time taken by participant to complete questionnaire battery

- Rest & preparatory area time length

- Saliva sample # 2
- TT
- TR
- TF

- Anticipation period time length

- Saliva sample # 3
- TT
- TR
- TF

Stressor total time taken:
Arithmetic Task: time started (TS)
time finished (TFI)
Serial Subtraction Task:
TS
TF
Presentation Task:
TS
TF

- Saliva sample # 4
- TT
- TR
- TF

- Time taken to complete Distractor Task
- TS
- TFI

- Saliva sample # 5
- TT
- TR
- TF

- Time taken to complete VPA test-block
- Time taken to complete RAVLT delayed

- Recovery period (time taken – 30 mins)

- Saliva sample # 6
- TT
- TR
- TF

- Time participant leaves lab:

Appendix 16: *Informed Consent Form* **Behavioural paired-associate tasks**

In agreeing to participate in this research I understand the following:

- Jennifer Moore, a postgraduate student at the Department of Psychology, National University of Ireland, Maynooth, is conducting this research.
- It is the responsibility of Ms. Moore to adhere to ethical guidelines in her dealings with participants and the collection and handling of data. If I have any concerns about participation I may refuse to participate or withdraw my data at any stage.
- I have been informed as to the general memory nature of the study and agree voluntarily to participate.
- I am **not** currently taking **prescription medication** that **may affect cognitive processes**. I have also **not** taken **alcohol** or other **recreational drugs** within the **preceding 24 hours**.
- All data from the study will be treated confidentially. The data will be compiled, analysed and submitted in a report to the Department of Psychology, NUI Maynooth. No participant's data will be identified by name at any stage of the data analysis or in the final report.
- At the conclusion of my participation, any questions or concerns I have will be fully addressed.
- I may withdraw from this study at any time, and may withdraw my data at the end of the experiment if I still have concerns.

If during your participation in this study you feel that the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact the Secretary of the National University of Ireland Maynooth Ethics Committee at pgdean@nuim.ie of 01 7086018. Please be assured that your concerns will be dealt with in a sensitive manner.

Signed:

_____ Participant

_____Researcher

_____Date

Appendix 17: *Informed Consent Form:* **ERP Study 1: Chapter 4**

Participant:

I …… consent to participate in an experimental psychology study being run by Jennifer Moore and supervised by Dr. Richard Roche in the Department of Psychology, National University of Ireland, Maynooth (Tel: ++ 353 1 708 4765). I understand and consent to the following:

- I understand that during the experiment my brain activity will be monitored by attaching electrodes to my scalp. Electrode gel will be used to ensure high-quality electrode contact with the scalp (given that hair presents a major problem in keeping electrodes attached optimally with the scalp).
- There are no known risks associated with this experimental procedure. **However**, it has been explained to me that slight irritation to the electrode gel and alcohol wipes used may occur however the chance of this occurring is very small. Further, it has been explained to me that mobile phones or any other form of electronic device should NOT be taken into voltage-gated experimental room.
- It has been explained to me that in order to reduce artefacts during recording I have been instructed to blink only during the intervals between trials provided this does not impose too heavy an attentional burden.
- The experiment will last approximately 3 hours maximum
- I have completed attached risk assessment and criteria screening form
- If I have any concerns about participation I may refuse to participate or withdraw my data at any stage.
- All data from the study will be treated confidentially.
- No participant's data will be identified by name at any stage of the data analysis or in the final report. Participant's data will be identified throughout the experimental research process by an alphanumeric code only.
- Your data is available to you at your discretion.
- The data will be compiled, analysed and form part of Jennifer Moore's doctoral thesis which will be submitted to the Department of Psychology, NUI Maynooth. The resultant data may also be presented at various conferences and may be included in published scientific journal articles produced during the course of the doctoral degree.
- All data will be retained in the Department of Psychology for a minimum of 3 years, after which it will be discarded.
- At the conclusion of my participation, any questions or concerns I have will be fully addressed.
- I may withdraw from this study at any time, and may withdraw my data at the end of the experiment if I still have concerns.
- If during your participation in this study you feel that the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact the Secretary of the National University of Ireland Maynooth Ethics Committee at pgdean@nuim.ie of 01 7086018. Please be assured that your concerns will be dealt with in a sensitive manner.

Signed:

- Participant _____
- Date _____

Experimenter:

As primary experimenter, I accept full responsibility for the care of all experimental participants and I confirm that all the necessary safety precautions have been taken:

- Researcher _____
- Date _____

Appendix 18: *Informed Consent Form*: ERP Study 2 (Chapter 5)

In agreeing to participate in this research I understand the following:

- Jennifer Moore, a PHD candidate at the Department of Psychology, National University of Ireland, Maynooth, is conducting this research.
- It is the responsibility of Ms. Moore to adhere to ethical guidelines in her dealings with participants and the collection and handling of data.
- I have been informed as to the **general memory aspect of the study** as well as the expected **3 hour maximum duration** and agree voluntarily to participate.
- I understand that during the experiment my brain activity will be monitored by attaching electrodes to my scalp. Non-abrasive electrode gel will be used to ensure high-quality electrode contact with the scalp (given that hair presents a major problem in keeping electrodes attached optimally with the scalp).
- It has been explained to me that **slight irritation to the electrode gel and alcohol wipes used may occur** however the chance of this occurring is very small. Prior allergies to alcohol will be noted by the experimenter prior to participation in this research. Also, a swab test has been carried out with the electrode gel prior to experimentation.
- Slight irritation may also occur due to impedance checking during the course of the experiment. Furthermore, participants may experience slight discomfort due to long duration of the experiment.
- It has been explained to me that mobile phones or any other form of electronic device should NOT be taken into voltage-gated experimental room.
- It has been explained to me that in order to reduce artefacts during recording I have been instructed to blink only during the intervals between trials provided this does not impose too heavy an attentional burden.
- I have **normal vision** or indeed **normal vision with correction.**
- I am **not** currently taking **prescription medication** that **may affect cognitive processes**. I have also **not** taken **alcohol** or other **recreational drugs** within the **preceding 24 hours**.
- If I have any concerns about participation **I may refuse to participate or withdraw my data at any stage.**
- **All data from the study will be treated confidentially.**
- No participant's data will be identified by name at any stage of the data analysis or in the final report. Participant's data will be identified throughout the experimental research process by numbers only.
- The data will be compiled, analysed and submitted in a PHD thesis to the Department of Psychology, NUI Maynooth. The resultant data may also be presented at various conferences and may be included in published scientific journal articles produced during the course of the doctoral degree.
- All data will be retained in the Department of Psychology for a minimum of 3 years, after which it will be discarded. Any data will ONLY be viewed by the experimenter.

At the conclusion of my participation, any questions or concerns I have will be fully addressed.

I may withdraw from this study at any time, and may withdraw my data at the end of the experiment if I still have concerns.

If during your participation in this study you feel that the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact the Secretary of the National University of Ireland Maynooth Ethics Committee at pgdean@nuim.ie of 01 7086018. Please be assured that your concerns will be dealt with in a sensitive manner.

- Participant signature _____ Date _____

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

- Researcher _____
- Date _____

Appendix 19: *Informed Consent Form*: Stress Induction (Chapter 6)

In agreeing to participate in this research I understand the following:

- Jennifer Moore, a PHD candidate at the Department of Psychology, National University of Ireland, Maynooth, is conducting this research.
- It is the responsibility of Ms. Moore to adhere to ethical guidelines in her dealings with participants and the collection and handling of data.
- I have been informed as to the **general nature of the study** as well as the expected **120 minute total duration** and agree voluntarily to participate.
- I **have not** been previously diagnosed with any learning and/or memory impairments (e.g., dyslexia)
- I am a **fluent** English speaker.
- I am **not** currently taking **prescription medication** that **may affect cognitive processes**. I have also **not** taken **alcohol** or other **recreational drugs** within the **preceding 24 hours**. If currently taking prescription medication and you are unaware as to its cognitive effects please report the medication being used (in complete confidence) to the experimenter.
- I am **not** currently taking beta-blockers, steroids, or any medication which may affect central nervous system functioning or endocrine systems.
- In accordance with stipulated guidelines I have refrained from strenuous physical exercise, heavy meals, alcoholic beverages and low PH soft drinks **at least 1hr prior to testing**, in order to avoid a low PH with devices used.
- In accordance with stipulated guidelines I have refrained from brushing my teeth at least 1 h prior to taking part in the experiment.
- In accordance with stipulated guidelines I have refrained from using any possible salivary stimulants such as chewing gum, lemon drops, granulated sugar, drink crystals, and so on within 1 hour prior to the experiment.
- In accordance with stipulated guidelines I have refrained from acidic or high sugar foods within the 20 minutes preceding the experiment.
- I **do not** suffer from Cushing's syndrome, Syndrome X or any other metabolic syndromes.
- I **have not** been recently diagnosed with depression or anxiety related disorders
- I **do not** have a history of head injury.
- I have **refrained** from strenuous physical exercise, large meals, cigarette smoking, and coffee for at least 1 h prior to the experiment given the known effects of these variables on HPA functioning.
- I am a **non-smoker** or I have **not smoked a cigarette within the past 24 hours.**
- Please tick if you currently use oral contraceptives: **yes** ____ **no** ____
- If you ticked yes to the above, please note the name of oral contraceptives used: _____
- I am a: **smoker** [ ] **non-smoker** [ ]
- Are you currently taking any form of steroid medication? **yes** ____ **no** ____
- If you ticked yes to the above, please note the name of steroid medication used: _____
- Please list what you have eaten/had to drink within the past 24 hours: _____ _____
- If I have any concerns about participation **I may refuse to participate or withdraw my data at any stage.**
- **All data from the study will be treated confidentially.**
- **No** participant's data will be identified by name at any stage of the data analysis or in the final report. Participant's data will be identified throughout the experimental research process by numbers only.
- The data will be compiled, analysed and submitted in a PHD thesis to the Department of Psychology, NUI Maynooth. The resultant data may also be presented at various conferences and may be included in published scientific journal articles produced during the course of the doctoral degree.
- All data will be retained in the Department of Psychology for a minimum of 3 years, after which it will be discarded.

At the conclusion of my participation, any questions or concerns I have will be fully addressed.

I may withdraw from this study at any time, and may withdraw my data at the end of the experiment if I still have concerns.

NB If during your participation in this study you feel that the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact the Secretary of the National University of Ireland Maynooth Ethics Committee at pgdean@nuim.ie of 01 7086018. Please be assured that your concerns will be dealt with in a sensitive manner.

I understand that taking part in this study is voluntary and that I may withdraw from the study at any time. I understand that my participation in this study is confidential and that no material, which could identify me, will be used in any reports on this study.

I _____ (full name) hereby consent to take part in this study which involves a cognitively challenging task.

Signed: _____ Date: _____

As a representative of this study, I have explained the purpose and the procedures involved in the current study:

- **Researcher:** _____
- **Date:** _____

Publications and Presentations emanating from the Present Thesis

Publications

Refereed Abstracts

Moore, J.L., & Roche, RAP (2008). Context and stress effects for human memory reconsolidation in hippocampally-based memory. *International Journal of Psychology, 43.*

Moore, J.L., Rawdon, C., & Roche, RAP (2007). Electrophysiological correlates of memory consolidation and reconsolidation. Abstract to be published in *Proceedings of the Australian Neuroscience Society (ANS),* July 2007.

Moore, J.L., Rawdon, C., & Roche, RAP (2007). High-density ERPs may differentiate consolidation from reconsolidation processes in humans during associative learning. *Neural Plasticity, 64.*

Moore, J.L., Cassidy, S., Boll, S., Joyce, E., & Roche, RAP (2007). Behavioural and electrophysiological correlates of local versus global contextual processing in episodic memory. *British Neuroscience Association Abstracts, 19*, 102.

Moore, J.L., Cassidy, S., Boll, S., & Roche, RAP (2006). Role of context in episodic memory: Evidence of selective facilitation in congruent environmental contexts in humans. *The Irish Journal of Medical Science, 175*(3), 86.

Publications

Moore, J.L., & Roche, RAP (2007). Reconsolidation revisited: A review and commentary on the phenomenon. *Reviews in the Neurosciences, 18*(5), 365-382.

Conference Presentations

Moore, J.L., & Roche, RAP (2008). Context and stress effects for human memory reconsolidation in hippocampally-based memory. Poster presented at the International Congress of Psychology, Berlin, July 2008.

Moore, J.L., Rawdon, C., & Roche, RAP (2007). Electrophysiological correlates of memory consolidation and reconsolidation. Poster presented at International Brain Research Organisation (IBRO) Conference, Melbourne. July 2007.

Moore, J.L., Rawdon, C., & Roche, RAP (2007). High-density ERPs may differentiate consolidation from reconsolidation processes in humans during associative learning. Poster presented at European Brain and Behaviour Society (EBBS) Conference, Trieste. September 2007.

Moore, J.L., Cassidy, S., Boll, S., Joyce, E., & Roche, RAP (2007). Behavioural and electrophysiological correlates of local versus global contextual processing in episodic memory. Poster presented at the British Neuroscience Association Conference, Harrogate. April 2007.

Moore, J.L., Cassidy, S., Boll, S., Joyce, E., & Roche, RAP (2007). Behavioural and electrophysiological correlates of contextual processing in episodic memory. Poster presented at the Cognitive Neuroscience Society Annual Meeting. New York, USA. May 2007.

Moore, J.L. & Roche, RAP (2006). The Role of Context in Episodic Memory: Evidence of Selective Facilitation in Congruent Environmental Contexts in Humans. Poster presented at the Neuroscience Ireland Conference, Cork. September 2006.

Moore, J.L., Scanlon, P., Murphy, J., Commins, S., Dockree, P.M., Jacoby, L..L. & Roche, RAP (2006). High Density ERPs Reveal Neural Correlates of Disrupted Source Memory in Humans. Poster presented at the Cognitive Neuroscience Society Annual Meeting. San Francisco, USA. April 2006.

Symposium Presentations

Moore, J.L. (2009). The role of context and stress in human memory reconsolidation: Implications for drug addiction. Invited Presentation at the National Institute of Drug Abuse (NIDA). Baltimore, Maryland, USA, May 2009.

Moore, J.L. (2007). Electrophysiological Correlates of Consolidation & Reconsolidation. Presentation given at the 1st Annual Irish Research EEG symposium, August 2007.