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Evaluating sleep and circadian rhythm disturbances and symptoms of impulsivity and inattention: Implications for adult attention-deficit/hyperactivity disorder

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Summary of thesis

Reports of sleep disturbances and delayed sleep timing in attention-deficit/hyperactivity-disorder (ADHD) are common however the aetiology of such features is poorly understood. There is substantial evidence pointing to dysfunction of the circadian timing system in ADHD, and individual differences in human chronotype and diurnal preference have been linked with impulsivity and attention problems in adults. In the work presented here we examined associations between a later circadian phase of entrainment, impaired sleep quality, and circadian misalignment and how they relate to core symptoms of ADHD distributed among the general population. We report novel evidence which suggests that 'social jetlag' – an index of circadian misalignment arising from discordance between endogenous circadian timing and the timing of the social clock – is a consistent predictor of poorer ADHD-like symptom outcomes. Furthermore, objective assessment of the rest-activity rhythm and sleep intervals of subjects show that a failure to precisely entrain to the 24 h circadian period is associated with ADHD-like symptom severity which was in turn predicted by delayed circadian phase/sleep phase, sleep quality, and duration. Candidate gene approaches did not replicate previous findings linking symptoms of impulsivity, inattention, and later chronotype with elements of the core molecular clock. However, we did find differential susceptibility to the previously identified risk factors; poor sleep quality and social jetlag which were both modified by genotype. Preliminary data from an exploratory study examining the neurophysiological correlates of response inhibition and selective attention revealed interesting patters of ERP elicitation in individuals with high levels of social jetlag. The current findings highlight how examination of sleep and circadian rhythm disturbances associated with ADHD may inform our understanding of the disorder risk and might in the future be factored into interventions designed for better symptom management.

Publications arising from this thesis:

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McGowan, N.M., & Coogan, A.N. (June, 2014). Chronotype and circadian rhythms of sleep in the symptomatology of adult attention-deficit-hyperactivity-disorder in the general population. Poster presented at the Sleep and Circadian Neuroscience School, University of Oxford, United Kingdom.

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Chapter 1

Theoretical background and literature review

1.1 Biological rhythms

The principal characteristic of life's propagative success lies in its adaptation to its environment and the natural selection of traits that are advantageous for survival. Similar to the manner in which an organism will express phenotypes suited to its habitat and environmental niche, evolution has conserved rhythmic patterns of biology and behaviour in many different species honed to respond to changes within a dynamic and predictable temporal ecology (Dunlap, Loros, & DeCoursey, 2003).

Examples of these rhythmic changes are both manifold in nature and obvious even without scientific interrogation. Among several animal species that have for centuries been domesticated by humans such as sheep, horses, and other livestock, seasonal breeding patterns exist such that population birth is most prevalent in the portion of the year when the ambient temperature and the availability of food and water are most favourable for offspring weaning (Prendergast, 2005). Migratory patterns of several temperate climate dwelling bird species and flying insects exist – the most magnificent of which might be represented by the journey of the Monarch butterfly *Danaus plexippus* from the Rocky Mountains to their Mexican overwintering sites – which occur during seasons where the climate becomes colder and the length of day shortens (Gwinner, 1996; Kyriacou, 2013). Likewise, in animals that hibernate or undergo torpor temporal changes in the environment lead to adaptive thermoregulatory state economising energy conservation and ensuring survival over the winter months (Darrow *et al.*, 1988).

In a similar fashion, marine life dwelling in our planets oceans and coastal areas has developed important time-keeping mechanisms involving behavioural responses synchronised to the recurring movement of the tides. The Mangrove cricket *Apteronemobius asahinai* for example predicts the time of high-tide to escape submergence by the sea by synchronising its activity patterns to that of the tidal period (Satoh, Yoshioka, & Numata, 2008). Furthermore, these rhythmic operations found in biology can be so complex in their nature that they may even involve the calculation of the monthly moon phase as demonstrated in the European Atlantic Coast dwelling midge *Clunio marinus* – a sea creature for which the entire survival of

the species has evolved to predict the synchronised low spring tide and the full moon phase during which time they live, mate, and perish all within a 1 – 3 h lifespan (Kaiser & Heckel, 2012; Reinberg, Smolensky, & Touitou, 2016).

In broad terms, the aforementioned programmes of biology and behaviour may be defined as *circannual*, *circatidal*, or *circalunar* rhythms respectively, where biological timing adapted in response to recurring and relatively reliable environmental changes present throughout evolution derived from orbital constants: namely the Earth's orbit around the Sun, or the Moon's orbit around the Earth. In such cases, these patterns represent *infradian* rhythms where the period involved exceeds that of one day. Other biological rhythms such as those involved in the blinking of the eye, breathing, nasal dilation and pulse rate are *ultradian* in nature and cycle in period several times within the day. The most important evolutionarily conserved system of biological time-keeping for most life and indeed the most ubiquitous found in nature however are those which track the twenty-four hour day – these types of biological rhythms which occur with a periodicity of approximately 24 h are termed *circadian* (derived from Latin: *circa*- around; *dies*- day).

1.2 Circadian rhythms

The reliable, reoccurring, and predicable transition between night and day has presented an environmental constant which evolution has exploited. The ability to anticipate important changes in the environment such as the availability of food, mating potential, and predation risk, all over a recurring 24 h period, imbues the organism with an important survival advantage. Consequently, anticipatory changes in animal physiology and behaviour in preparation for circadian changes in the environment have become integrated in biology spanning from a molecular level to a system wide operation. Circadian rhythms unsurprisingly are found to be a ubiquitous feature present in virtually all eukaryotic organisms studied to date (Merrow, Spoelsta, & Roenneberg, 2005).

The circadian system provides a temporal architecture for the expression of various biological and behavioural parameters about a day. In diurnal organisms such as humans where the day is the normally active phase, these rhythms produce a catabolic physiological profile prioritising energy expenditure and physical preparedness; whereas during the night-time the physiology is primarily anabolic promoting rest and recovery (Arellanes-Licea *et al.,* 2014). Circadian rhythms are apparent among several homeostatic biological parameters including blood pressure (Hastings, Reddy, & Maywood, 2003), core body temperature (Refinetti & Menaker, 1992), hormonal secretion (Czeisler & Klerman, 1999; Buijs et al., 1997; Hastings, O'Neill, & Maywood, 2007), as well as renal (*e.g.* electrolyte excretion, urinary production) and pulmonary function (*e.g.* expiratory volume, lung capacity) (Stow & Gumz, 2011; Hetzel, 1981). Moreover, rhythms of appetite (Costa *et al.,* 1987), alertness, and sleepiness (Rosenthal *et al.,* 2001; Natale & Cicogna, 1996), as well as cognition (reviewed in Schmitt *et al.,* 2007) all show pronounced circadian features.

An important aspect of the circadian time-keeping system is that the rhythms it generates are innate and endogenously produced evidenced by the fact that they persist under constant environmental conditions where no environmental cues are made available for the system to respond to (Vitaterna, Takahashi, & Turek, 2002). Data described in Hastings *et al.* (2007) for example show rhythmic cycling of hormones such as melatonin, cortisol, as well as core body temperature and other physiological functions that are maintained about a 24 h cycle in individuals kept under constant conditions (Figure 1.1). In order to function as a useful biological clock however the endogenously generated circadian rhythm must synchronise appropriately to match the period and phase of the temporal signal of the environment; a process known as 'entrainment'. To achieve this outcome the circadian system utilises external stimuli, referred to as '*Zeitgebers*' (from the German *Zeit* – time; *Geben* – to give), which communicate the relative time of day to system. Several zeitgebers of the system exist such as food availability, ambient temperature, exercise, and social interaction, however the most potent zeitgeber to which the circadian rhythms of mammalian species, including humans, entrain is the photic signal produced by the recurring cycle of night and day (Vitaterna *et al.,* 2001).

Knowledge of the circadian clock and how it integrates with its environment can be understood both from a biological perspective (reviewed in section 1.3) and also by a close examination of the characteristics involved in its entrainment (reviewed in section 1.4).

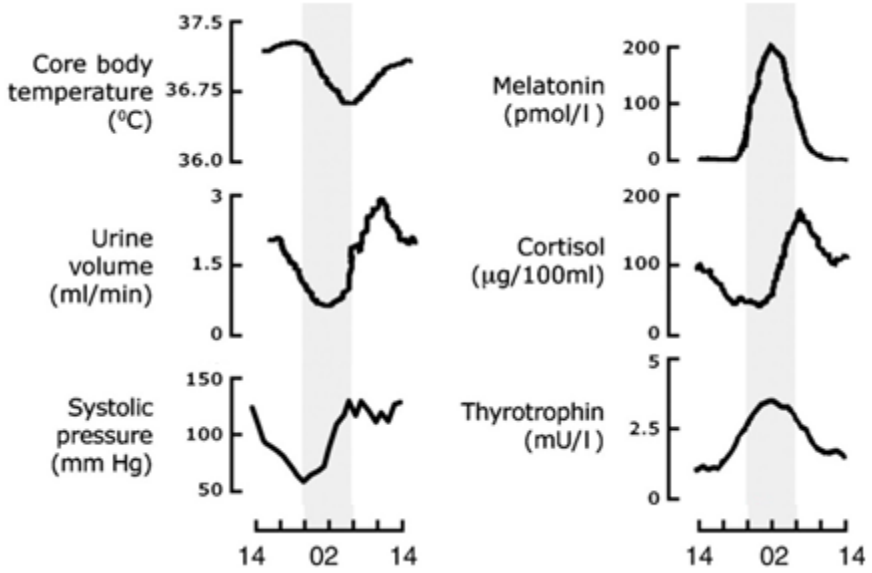

Figure 1.1 Circadian oscillations of physiological and endocrine parameters in humans held under constant environmental conditions.

Left panel depicts circadian rhythmicity in vital physiological parameters; right panel depicts 24-h hormonal profiles. Shaded area represents normal quiescent interval of human activity. Throughout the routine subjects remained awake, were held in dim light, and temporally isolated from external time-cues. Figure adapted from Hastings et al. (2007). Original data adapted from Czeisler & Klergman (1999), Hastings et al. (2003), and Conroy et al. (2005).

1.3 The anatomy of the internal clock

The operation of the internal clock in mammals is known to be regulated by a complex machinery of biological oscillators distributed throughout the brain and peripheral tissues. This programme is comprised of both bottom-up and top-down features. Twenty-four hour rhythmic oscillations begin as cellular clocks, which collectively form cellular networks, tissues, and build up to constitute organs, each oscillating with their own intrinsic circadian properties (Roenneberg & Merrow,

2016). These elements culminate in a hierarchical system governed by a central pacemaker that synchronises circadian rhythms to each other internally, a process known as internal coupling, and synchronises these rhythms to oscillate in tune with the external environmental signal.

The molecular clock

Beginning at a molecular level, cell autonomous circadian oscillations (Figure 1.2) are generated by rhythmic processes controlled by transcriptional-translational feedback loops (TTFLs) whose complete cycle oscillates with a period of approximately one day forming the substrate of system-wide circadian time-keeping (Ko & Takahashi, 2006; Reppert & Weaver, 2001). Central among the factors regulating this TTFL are the canonical core *'clock genes',* circadian locomotor output cycle kaput protein (*CLOCK*) and brain-muscle-arnt-like protein 1 (*BMAL1*) which belong to the basic helix-loop-helix (bHLH)-PER-ARNT-SIM (PAS) family of transcription factors. The translational products of *CLOCK* and *BMAL1* together form heterodimer complexes which act as transcriptional activators upon E-Box sequences in the promoter regions of the Period genes (*PER1, PER2,* and *PER3*) and the Cryptochrome genes (*CRY1* and *CRY2*). In turn the PER and CRY proteins translocate to the cytoplasm where they are subject to post-translational modifications relating to their localisation and degradation (Gallego & Vishrup, 2007). Importantly, PERs and CRYs heterodimerize and form a complex with caseine kinase I ε and δ (CKIε/δ) and are phosphorylated which leading to changes in their stability and aided nuclear entry (McClung, 2007; Kurabayashi *et al.,* 2006). The PER:CRY complex undergoes nucleo-cytoplasmic translocation and acts as the transcriptional repressor on *CLOCK*/*BMAL1,* thereby PER and CRY proteins inhibit their own expression via this negative limb of the TTFL. (Nader, Chrousos, & Kino, 2010; Ko & Takahashi, 2006). The aforementioned process constitutes the main TTFL of the cellular circadian oscillation and is accompanied by an additional auxiliary loop where *CLOCK*/*BMAL1* stimulate the expression of other clock-related proteins such as Rev-erbα and retinoic acid receptor-related orphan receptor α (RORα) the function of which is to stabilize the

main regulatory loop of the molecular clock (Nader *et al.,* 2010). Finally, elements from both the main and auxiliary loops act on numerous clock-responsive elements which influence several downstream biological activities (Ko & Takahashi, 2006). This cycling of the positive and negative limbs of the TTFL's perpetually renews itself each circadian day in virtually all mammalian tissues that oscillate with a 24-h rhythm.

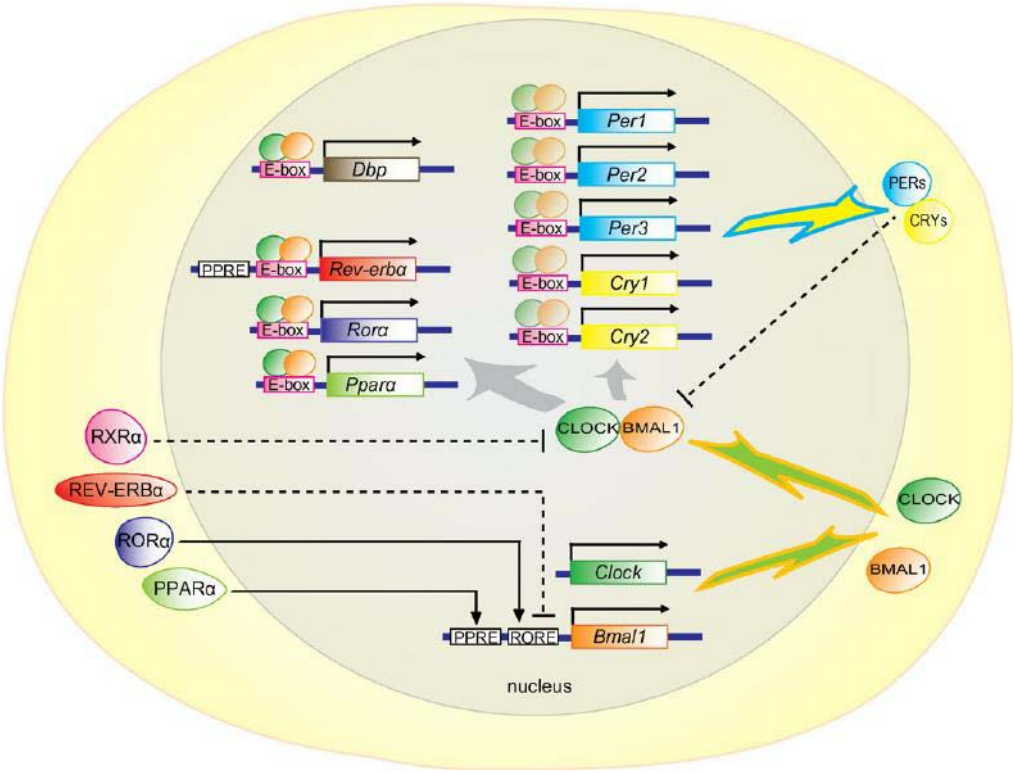

Figure 1.2 Molecular circadian transcriptional-translational feedback loop

Diagram depicts the manner in which CLOCK and BMAL1 proteins act as transcriptional activators (indicated by arrows) on the Period and Cryptochrome family of genes. PER and CRY proteins dimerise in the cytoplasm and undergo a number of post-translational modifications including phosphorylation and binding with CKIε/δ. The PER-CRY product enters the nucleus and acts as a negative repressor (indicated by broken line) of its own expression by inhibiting expression of CLOCK and BMAL1. A secondary transcriptional loop exists between CLOCK-BMAL1 and the genes Rev-erbα and Rorα which negatively or positively drive BMAL1 activation respectively. Figure from Laposky et al. (2008) adapted from Kohsaka & Bass (2007).

The central pacemaker

In order to function in a coordinated fashion, the autonomous rhythms of the cells distributed throughout the system must achieve a state of uniform synchrony such that the oscillating internal biology of the organism produces a circadian rhythm that is coherent, robust, and importantly, in phase with both itself as well as the environment. This operation is orchestrated by a hierarchical system which includes a central pacemaker of the internal clock that signals to peripheral tissues the appropriate phase at which to perform their daily functions (Storch *et al.,* 2002; Yamamoto *et al.,* 2004).

The central pacemaker which governs this system is situated in the suprachiasmatic nuclei (SCN) (Figure 1.3A), a paired cluster which consists of approximately 20,000 neurons located in the anterior hypothalamus of the mammalian brain (Dibner, Schibler, & Albrecht, 2010; Reppert & Weaver, 2002). The importance of this site was highlighted by early ablation studies in experimental animals in which circadian rhythmicity in several parameters was eliminated with destruction of the SCN (Moore & Eichler, 1972; Raisman & Brown-Grant, 1977). This condition was later shown to be rescued in hamsters by grafted tissue implants from the intact SCN of another *tau* mutant animal, a hamster whose internal circadian period was dramatically shorter than the wild-type animal (Ralph *et al.,* 1990). In these experiments it was noted that the recipient animal expresses the period and the phase of entrainment of the mutant donor (Ralph *et al.,* 1990; Sollars, Kimble, & Pickard, 1995). Other studies demonstrated that the restoration of rhythmic behaviours in animals rendered arrhythmic via lesioning of the SCN could be achieved following intact foetal SCN tissue grafts (Aguilar-Roblero *et al.,* 1992; Aguilar-Roblero *et al.,* 1994; Griffioen *et al.,* 1993).

The SCN may be separated into two anatomically and functionally distinct portions: the ventrolateral "core" region and the dorsomedial "shell" region (Figure 1.3B+C). Neurons in the SCN core mainly contain vasoactive intestinal polypeptide (VIP), calretinin (CalRet), and gastrin releasing polypeptide (GRP), while the partially enveloping shell consists of mainly of arginine vasopressin (AVP)

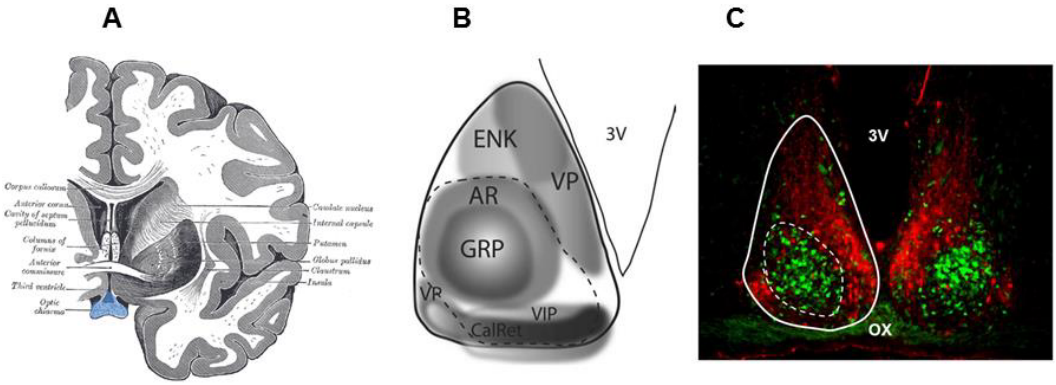

Figure 1.3 Location and structure of the suprachiasmatic nucleus (SCN) site of the mammalian master circadian pacemaker

(A) *Depicts location of the SCN in brain exposed via coronal cross section. Paired cluster of SCN highlighted in blue situated in the anterior hypothalamus, superior to the optic chiasm, ventrolateral to third ventricle.* ***(B)*** *Topographical organisation of the SCN into 'core' region characterised by the presence of androgen receptor (AR), vasoactive intestinal polypeptide (VIP), gastrin releasing peptide (GRP), and calretinin (CalRet), and the 'shell' region mainly containing vasopressin (VP) cells.* ***(C)*** *Immunoflurescent labelling of mouse SCN delineating core (GRP labelled in green) and shell (VP labelled in red). OX; optic chiasm, 3V; third ventricle. Figure adapted from Gray (1918), Silver & LeSauter, (2008), and Welsh et al. (2010).*

expressing neurons. In both regions neuropeptides are colocalised with γ-aminobutyric acid (GABA) with most synaptic activity in the SCN neurons being GABAergic (Welsh, Takahashi, & Kay, 2010; Moore & Speh, 1993; Strecker, Wuarin, & Dudek, 1997).

SCN cells differ from other oscillators in a number of unique ways. Physically isolated neurons of the SCN have been shown to demonstrate pronounced circadian rhythms in their electrical spike activity both *in vivo* (Inouye & Kawamura, 1979) and *in vitro* (Green & Gillette, 1982; Welsh *et al.,* 1995) indicating the presence of a circadian clock in each neuron. In order to function as an accurate pacemaker however SCN cells must synchronise to one another, a process known as 'coupling', thus creating a network of oscillators enabling the generation of a coherent output signal (Welsh, 2009).

Unlike independent oscillations of dissociated cells in peripheral tissues, SCN neurons remain tightly coupled to one another in circadian period and phase

through distinct topographically organised coupling mechanisms (Moore, Speh, & Leak, 2002; Aton & Herzog, 2005). Synaptic transmission between SCN cells appears to be the principal mechanism by which neurons are coupled to one another (Welsh, 2009). Candidate neurotransmitters through which intercellular coupling is achieved are via GABA and the core neuropeptide VIP as application or disruption of each promotes or compromises circadian rhythm coherence respectively (Liu & Reppert, 2000; Colwell *et al.*, 2003). Evidence suggests that the two nuclei are also coupled with one another as unilateral lesions will perturb the rhythmic patterns in circadian rhythms of behaviour (Pickard & Turek, 1982) and projections from either core or shell sub-nuclei run contra-laterally to innervate the other nucleus (Leak, Card, & Moore, 1999).

Another important manner in which the SCN complex is unique in its function concerns its ability to receive external zeitgeber signal input through afferent neural projections and how this signal is communicated to other areas of the brain and peripheral nervous system to entrain the dispersed oscillators of the host to function in a coherent manner. In broad terms the prevailing model which can be applied to the functional organisation of the SCN purports that circadian signal input moves from core to shell (Moore, Speh, & Leak, 2002). It is understood that the retinorecipient SCN core receives and organises pacemaker inputs through an assembly of neural afferents while the shell is responsible for the outgoing circadian signal which synchronises extra-SCN targets and peripheral oscillators to the master clock (Rosenwasser, 2009).

Sensory input and afferent pathways

The manner in which external time-cues are integrated within the circadian system primarily involves afferent projections to the SCN core. Neurons projecting from the optic nerve which terminate in the SCN core relay photic signal information from the environment acting as the principal zeitgeber to the system. The retinorecipient core receives photic signal input via an afferent pathway distinct from the primary visual

pathway known as the retinohypothalamic tract (RHT). Downstream, retinal ganglion cells located in the inner retina of the eye transmit photic information through the optic nerve and RHT (Welsh, 2009). This photoreceptor system is comprised of intrinsically photosensitive retinal ganglion cells (ipRGCs) which project to areas involved *in 'non-image forming'* (NIF) functions such as the olivary pretectal nucleus (OPN) which controls the pupillary light reflex and to the SCN where photoentrainment to circadian rhythms begins (Hattar *et al.,* 2006).

Until recently it was thought that classical rod and cone photoreceptors were the only two to exist in mammals however a number of clinical and laboratory findings cast dispersions on this line of thought. Czeisler *et al.* (1995) first reported cases of behavioural circadian rhythm entrainment and attenuated circadian rhythms of melatonin secretion in response to light in visually blind people. These individuals had no faculty for conscious light perception as a result of severe degeneration of rods and cones yet unconscious responses to light somehow remained intact. Later studies on a genetically modified knockout strain of blind mouse in which rods and cones were completely absent showed that circadian and endocrine responses to light and the pupillary reflex response were still present (Lucas & Foster, 1999; Freedman *et al.,* 1999; Lucas, Douglas, & Foster, 2001) thus implicating the involvement of a separate class of receptor system in the NIF response to light.

It is now understood that ipRGCs of the inner retina express a unique photoreceptor known as 'melanopsin', named so after having first been identified in the photosensitive melanophores of the African clawed frog *Xenopus laevus* – an amphibian whose skin pigmentation adapts to ambient light levels (Provencio *et al.,* 1998). Melanopsin plays a crucial role in the ability of the internal clock to entrain to the light/dark cycle (Hatori & Panda, 2010; Schmidt *et al.,* 2011). Distinct from classical rod/cone opsins in the outer retina, melanopsin is maximally sensitive to short-wavelength light (~480 nm) which lies in the blue shifted range of the visual spectrum, closely resembling the peak spectral frequencies emitted by sunlight, and it is in this frequency band that NIF responses to light are the most pronounced (Hatori & Panda, 2010). Photic input into the system excites the melanopsin pigment

leading to transduction of the photic signal via synaptic transmission of the axons in the RHT which is then converted into chemical information that alters the phase of clock gene expression in neurons in the SCN core (Dibner *et al.*, 2010).

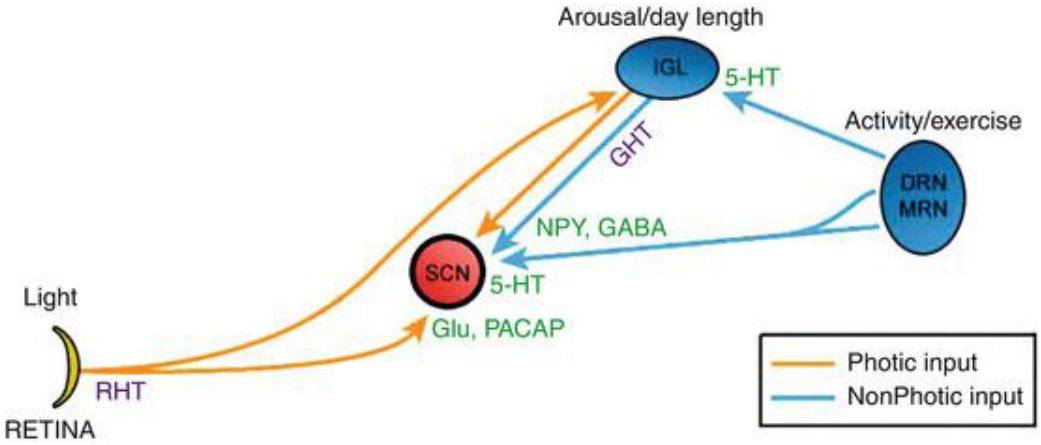

Figure 1.4 Major afferent projections to the SCN core

Retinal projections directly target the SCN transducing the photic signal (orange arrows) from the optic nerve via the retinohypothalamic tract (RHT). Additionally, the RHT projects to the intergeniculate leaflet (IGL) which provides a secondary route for photic input via the geniculohypothalamic tract (GHT). Non-photic inputs (blue arrows) are also communicated from the IGL to the SCN via the GHT as well as via the dorsal (DRN) and median raphe nuclei (MRN). The following neurotransmitters have been implicated in signal transduction from these brain regions to the SCN: glutamate (Glu), pituitary adenylate cyclase-activating peptide (PACAP), neuropeptide Y (NPY), γ-aminobutyric acid (GABA), and serotonin (5-HT). Figure from Silver & Rainbow (2016) adapted from Dibner et al. (2010).

Other major afferents which innervate the SCN core exist (Figure 1.4) that also relay zeitgeber signal information to the master pacemaker. The intergeniculate leaflet (IGL) situated in the retinorecipient region of the thalamus between the dorsal lateral and ventral lateral geniculate complex innervates the SCN via the geniculohypothalamic tract (GHT). The signal passed from the IGL to the SCN appears to involve both secondary indirect photic input from the axons via a separate limb of the RHT and also non-photic zeitgeber signals which entrain the clock (Harrington, Nance, & Rusak, 1985; Pickard, Ralph, & Menaker, 1987; Morin and Pace, 2002). IGL lesions produce an altered photic circadian response leading to a

change in circadian period length (Edelstein and Amir, 1999; Rosenwasser, 2009). The entrainment signals of non-photic zeitgebers such as the novel wheel locomotion or benzodiazepine treatment have also shown to be compromised following IGL lesions (Janik & Mrolovsky, 1994; Wickland & Turek, 1994; Meyer, Harrington, & Rahmani, 1993; Schuhler *et al.,* 1999). Finally, the midbrain raphe nuclei (MRN) are linked with serotonergic (5-HT) signalling to the SCN involved with non-photic zeitgeber signals. Ablation to the 5-HT afferent pathways to the SCN consequently results in a diminished entrainment response to several non-photic cues (Challet, Pevet, & Malan, 1997; Edgar, Reid, & Dement, 1997).

Integration of rhythms down the hierarchy and efferent pathways

Entrainment of the entire organism to perform its circadian operation in a synchronised and coherent fashion involves signal output from the SCN to oscillators in the periphery. In normal conditions peripheral organs and tissues adopt a phase relationship close to that of the SCN (Izumo *et al.,* 2014; Husse *et al.,* 2014). Non-SCN tissues in the periphery are entrained through neural and endocrine signals transmitted from the master pacemaker to peripheral oscillators (Bartness, Song, & Demas, 2001; Dibner *et al.,* 2010). Twenty-four hour cycles of glucocortisoids and temperature for example are capable of synchronising cellular clocks *in vitro* (Kiessling, Eichele, & Oster, 2010; Balsalobre *et al.,* 2000; Buhr, Yoo, & Takahashi, 2010; Cuesta, Cermakian, & Boivin, 2015) and melatonin has been shown to be a powerful synchroniser of circadian rhythms at various levels of the circadian system (Pevet et al., 2006). SCN activity also influences organismal sleep and feeding cycles and thereby in doing so in an indirect manner also entrain peripheral oscillators such as those found in the liver and kidneys – organs which are entrained by the timing of feeding and other behaviours which occur only during the organism's active phase (Izumo *et al,* 2014; Stokkan *et al.,* 2001; Damiola *et al.,* 2000; Oosterman *et al.,* 2015).

Many of these physiological and endocrine signals, which in and of themselves may be considered endogenous 'eigen-zeitgebers' to peripheral oscillators

(Roenneberg & Merrow, 2016), originate from the efferent pathways of the SCN. From the SCN complex a major efferent pathway projects in an arc dorsally and caudally to the ventral (vSPZ) and dorsal (dSPZ) subparaventricular zones on to the dorsomedial nucleus of the hypothalamus (DMH) (Saper, Scammell, & Lu, 2005). Neurons projecting to the dSPZ are crucial for controlling the circadian rhythm of body temperature, an important system wide circadian signaller, through their connection to the medial preoptic region (MPO) (Figure 1.5A). Lesions to the dSPZ severely attenuate or eliminate specifically the circadian rhythm of body temperature while leaving other circadian outputs intact (Lu *et al.,* 2001).

The projection from the SCN to the dorsal parvicellular paraventricular nucleus (PVHd) (Figure 1.5B) is thought to be an important signalling pathway to neurons in the intermediolateral column of the upper thoracic spinal cord and the preganglionic neurons responsible for controlling pineal melatonin secretion (Vrang, Larsen, & Mikkelsen, 1995; Teclemariam *et al.,* 1999). The vSPZ also sends outputs from the SCN to the DMH which relays this signal to the medial parvicellular paraventricular nucleus (PVHm). The PVHm regulates neurons containing corticotrophin releasing-hormone (CRH) which signal the rhythmic secretion of corticosteroids from the pituitary (Figure 1.5B). Disruption of these circuits compromises the endocrine signalling which maintains coupling between the master pacemaker and peripheral oscillators (Saper *et al.,* 2005).

Concerning indirect entrainment of peripheral oscillators by sleeping and feeding patterns exhibited by the host, the SCN-dSPZ-DMH efferents exert their influences on these behavioural outputs through a series of neural outputs governing arousal and appetite. Projections from the DMH to the ventrolateral preoptic nucleus (VLPO) promote sleep via GABAergic signalling whereas DMH outputs to lateral hypothalamus (LHA) containing orexin and melanin concentrating hormone (MCH) producing neurons contain glutamate and thyrotropin-releasing hormone (TRH). The orexin-containing and MCH-containing neurons are among the important components required to maintain rhythms of wakefulness and feeding (Saper *et al.,* 2005) (Figure 1.5C.). Chou *et al.* (2003) showed that lesions to the dSPZ and DMH

resulted in near total loss of rhythms of the sleep/wake cycle, feeding, locomotor activity, and corticosteroid secretion.

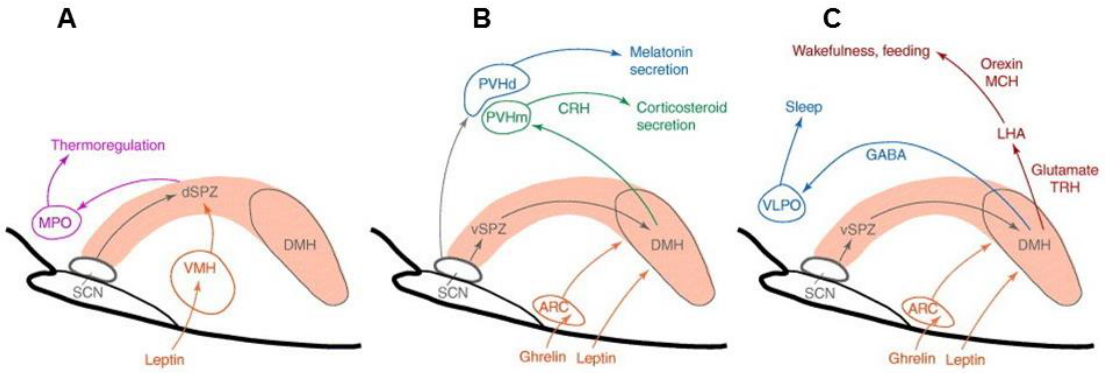

Figure 1.5 Circadian signalling via efferent projections from SCN to hypothalamus

(A) *Circadian rhythms in core body temperature are controlled via SCN signalling to the medial preoptic area (MPO) of the hypothalamus via projections to the dorsal sub paraventricular zone (dSPZ).* ***(B)*** *Hormonal factors under circadian control such as melatonin and cortisol are controlled via SCN efferents to the dorsal paraventricular nucleus (PVHd) and dorsomedial nucleus of the hypothalamus (DMH) respectively. PVHd communication runs to the superior cervical ganglion in the upper spinal cord and innervates the pineal gland which secretes melatonin. Cortisol secretion is under pituitary control the circadian rhythm of which is gated via corticotrophin releasing-hormone (CRH) neurons in the PVHm.* ***(C)*** *Sleeping and feeding patterns are influenced by SCN-vSPZ-DMH projections to the ventrolateral preoptic nucleus (VLPO) and the lateral hypothalamus (LHA). Neurotransmitters involved in these circuits are γ-aminobutyric acid (GABA), thyrotropin-releasing hormone (TRH), glutamate, melanin concentrating hormone (MCH), and orexin. Figure adapted from Saper et al. (2005).*

1.4 Principles of circadian rhythm entrainment

While much of the work involved in describing the neuroanatomy of the circadian clock and the molecular mechanisms which underpin its operation have only relatively recently been described, a comprehensive understanding of how the clock entrains to its environment has arisen years before from behavioural studies of model organisms in laboratory conditions. Much of our contemporary understanding about the circadian system arises from experimental studies in which the zeitgeber signal is manipulated or restricted and the outputs controlled by the

clock are carefully monitored (Aschoff, 1981; Daan & Pittendrigh, 1976; Pittendrigh, 1967, 1981; Pittendrigh & Daan, 1976). In similar terms to the properties seen in physical oscillators a circadian rhythm may be described by three parameters: period, phase, and amplitude.

Period

Period refers to the rate at which an oscillator completes one oscillation generally measured by the time from crest to crest or trough to trough. As previously mentioned the internal clock is an endogenous, innate, and self-sustaining program and therefore it generates its own oscillations with its own internal period or τ (*tau)*. The circadian clock has evolved to fine tune biological functions to times within the 24 h solar day and therefore it oscillates with a period close to 24 h but does not quite fill the 24 h day (τ < 24 h) or in many cases oscillates with a period longer than it (τ > 24 h) such as in humans (Czeisler *et al.,* 1999). For the clock to adequately function however it depends on the successful synchronisation of internal period to that of the external environment (T) – an optimal condition known as entrainment, where an organism's internal circadian period matches that of its temporal environment (τ = T).

Under normal circumstances the rhythms generated by the circadian clock are synchronised (Figure 1.6A) to the recurring 24 h cycle of night and day, however when placed in temporal isolation the circadian rhythm of an organism will begin to *'free-run'* with its own period or free-running τ (Roenneberg & Merrow, 2005). In this state the temporal organisation of parameters under circadian control such as core body-temperature, hormone secretion, feeding times, and the rest-activity cycle deviate from a precise 24 h arrangement (Figure 1.6B). The most straightforward example of such is the expansion and contraction of free-running τ which emerges when an animal is released into constant light (LL) or constant darkness (DD) (Aschoff, 1979; Pittendrigh & Daan, 1976; Winfree, 1980). Depending on the species and the environmental condition the free-running τ will be slightly longer or shorter

than the 24 h light-dark cycle. In nocturnal species this period has a propensity to be less than 24 h in DD and in diurnal species (humans inclusive) it has a propensity to be greater than 24 h (Roenneberg & Merrow, 2005). Importantly the free-running τ is found to be an incredibly precise phenotype deviating only slightly in an individual over the course of observation (Richter, 1968) and has been shown to be a heritable trait in avian model organisms (Helm & Visser, 2010). The adaptive advantage that the near 24 h intrinsic oscillation generated by the pacemaker confers is highlighted by findings showing that a greater deviation of free-running τ from 24 h inversely correlates with lifespan in several animals (Wyse *et al.*, 2010).

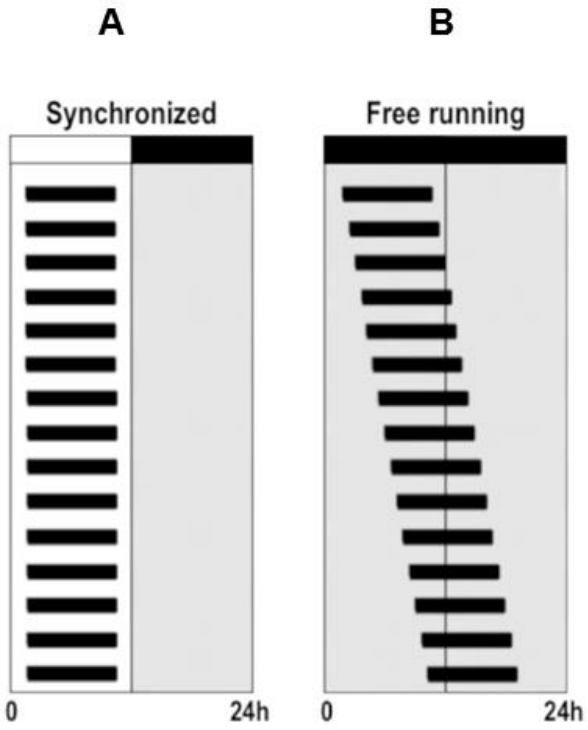

Figure 1.6 Schematic representation of entrained and free-running activity profile of a typical diurnal organism

(A) *Actogram showing normally entrained behaviour where activity (represented by black bars stacked to represent each successive day) co-occurs with the onset of the light phase of the LD cycle.* ***(B)*** *Actogram represents a diurnal organism placed in DD (humans for example) where, without a photic time-cue to entrain to, the circadian period expands to a period of greater than 24 h and therefore drifts out of phase with each day. White bar on top represents light phase, black bar on top represents dark phase. Adapted from Arellanes-Licea et al. (2014).*

Individual differences exist in the length of τ with some individuals running slightly shorter than 24 h and some individuals slightly longer. The process of entraining the oscillator to synchronise to the solar day depends on the action of zeitgebers which act upon the endogenous oscillator in a discriminate manner. In order for entrainment to occur the endogenous circadian rhythm must be compensated by adjustments to the oscillation known as phase shifts (Δϕ). An output rhythm shifts to accommodate the changes in the phase of zeitgeber onset (ΔΦ) where it may occur later known as a '*phase delay*' (+Δϕ) – or earlier – known as a '*phase advance*' (-Δϕ)(Remi, Merrow, & Roenneberg, 2010).

The phase shifting potency of the zeitgeber depends on both its intensity and at what internal time the signal connects with the endogenous circadian rhythm. Importantly an identical zeitgeber can produce both a phase advance and a phase delay depending on what time in the relative biological day exposure occurs. Light, being the most potent zeitgeber that entrains the clock, can elicit a phase delay in an individual when exposure occurs during the early part of the individual's subjective normal dark period (*i.e.* in the late evening/early night which might typically occur at around 22:00 h). Conversely, if light exposure occurs during the late part of the subjective normal dark period (*i.e.* very early morning before sunrise which might typically occur at 06:00 h) a phase advance is elicited shifting activity to occur earlier in the day. The relationships between light (or any other zeitgeber) and the phase shifting potential of the stimulus may be summarised by phase response curves (PRCs) which are depictions of the action of the circadian clock in response to time cues extrapolated from experimental studies where light pulses are administered to free-running animals at different internal time-points. There also exists time-points in the 24 h day when light exposure has a very minimal impact on the entrained phase of the circadian rhythm also known as the so called 'dead-zone' of the PRC.

The period of circadian clocks become accurately adjusted to the temporal environment within the limits of a light-dark cycle that closely resembles a 24 h day. While entrainment may still occur in circumstances where the day is shortened or elongated, there are limits of entrainment outside of which the circadian program

cannot accurately tune itself to and will begin to run-free. Examples of this can be seen in the *'forced desynchrony protocol'* (FDP) experiments where the human endogenous circadian rhythm can be observed to be dissociated from the external T when subjects' rest-activity pattern is forced occur under a 28 h period (Dijk & Czeisler, 1994, 1995) or under 20 h period (Hiddinga, Beersma, & Van den Hoofdakker, 1997). While these FDP approaches have been useful in disentangling the intrinsic influences on circadian outputs such as core body temperature, rest-activity cycle, and sleep variables, such forced periodic conditions are not a representation of any naturalistic environment humans are ordinarily exposed to. Exceptions exist however as in individuals that do not receive photic zeitgeber signals such as people that are totally blind (Lewy *et al.,* 2001). In such subjects the photic zeitgeber is eternally abolished as if placed in DD and consequently the endogenous τ runs free with a period > 24 h (Lewy & Newsome, 1983; Nakagawa, Sack, & Lewy, 1992), though during FDP the sleep/wake cycles of visually intact people remain synched to the circadian cycle. The result of this period differential produces a pattern of perpetually delaying circadian rhythm onset relative to the stable 24 h external environment as the free-running τ drifts out of phase with T. In normal conditions individual differences exist in the internal τ which can differ between subjects. By slightly deviating from exactly 24 h however the system compensates the internal clock's operation through discrete alterations which set the phase of the circadian rhythm relative to the external environment (Vitaterna *et al.,* 2002).

Phase

Phase refers to the position of a timepoint within an oscillation. In entrained conditions circadian oscillations establish a predictable phase relationship to their temporal environment. The '*phase of entrainment'* (Ψ) refers to the difference between the given phase marker of a circadian output and that of the zeitgeber (*i.e.* Φ - ϕ) (Aschoff *et al.,* 1965; Remi *et al.,* 2010; Roenneberg, 2015). Many examples of circadian rhythm phase markers exist such as the nadir in core body temperature or the time

point at which plasma melatonin levels begin to increase (dim-light melatonin onset; DLMO), the positions of which are determined relative to zeitgeber signals such as the onset of daylight (dawn) or waning of light in the night (dusk). When successfully entrained, zeitgeber signalling equalises the internal and external day in each of us to match T = 24 h, however the phase of the circadian rhythm may still differ between individuals and between conditions (Roenneberg & Merrow, 2016). The phase of entrainment is not fixed but is rather a malleable factor which depends on a number of parameters such as the endogenous τ of an individual, the period of the external zeitgeber signal T, the ratio of light to darkness in a cycle (photoperiodic changes), the intensity of the zeitgeber strength and its position of exposure along an individual's PRC (Roenneberg, Daan, & Merrow, 2003).

In nature, the phase of entrainment phase delays and advances along the PRC of an organism occur gradually over time allowing the circadian system to manoeuvre to a changing temporal environment such as the seasonal expansion and contraction of the photoperiod. In modern times however humans are presented with more abrupt circadian challenges as a result of societal and technological changes. The most apparent examples of phase shifts that occur in the human circadian system are those elicited by travel between different time-zones and occupations that involve shift-work. Westward trans-meridian flight, where for example a passenger might travel from the Central European Time-zone to the Eastern Coast of America results in an advance of the light/dark cycle to an earlier time-zone to which the circadian system must appropriately advance in phase also (Figure 1.7B). Similarly, Eastward travel from the same point of origin to Eastern Asia for example delays the light/dark cycle and as a result the circadian clock must phase delay in order to synchronise to the new time-zone (Figure 1.7A). The realignment between internal time to a shifted external time is not an instantaneous one but occurs over a number of circadian cycles (days) in which the underlying circadian rhythm adjusts in phase in order the establish a stable Ψ once again with the external time. Importantly the process of becoming re-synchronised to the external environment takes longer depending on the severity of the phase shift and also the directionality of the phase shift as

evidence shows that entrainment is better re-attained following phase delays compared to phase advances (Saksvik *et al.,* 2011; Deacon & Arendt, 1996).

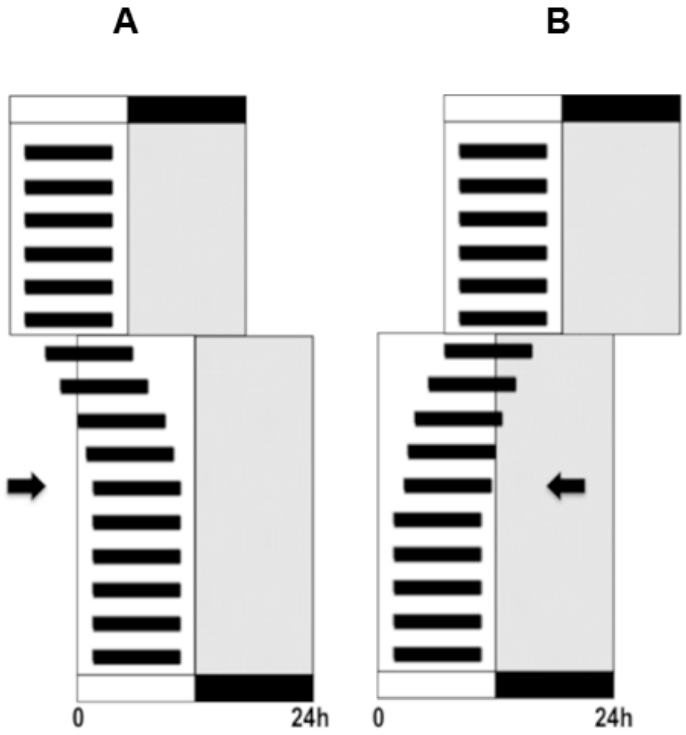

Figure 1.7 Schematic representation of a behavioural rhythm in response to a phase delays and a phase advance

(A) *Actogram showing a shift in the LD cycle to a later point in the subjective day (phase delay) where the circadian rhythm of behaviour gradually delays to re-entrain to the new zeitgeber onset.* ***(B)*** *Actogram showing a shift in the LD cycle to an earlier point in the subjective day (phase advance). Similarly the onset of behaviour gradually advances as it re-entrains to the earlier zeitgeber. White bar on top represents light phase, black bar on top represents dark phase. Adapted from Arellanes-Licea et al. (2014).*

In the interim these periods of circadian desynchrony between internal time and external time is known to produce many deleterious health effects. Short-term consequences such as the aptly named 'jet-lag' which appears especially after long-haul trans-meridian flight refers to a transient syndrome which includes symptoms such as: difficulties initiating and maintaining sleep, general fatigue and malaise, poor attention and concentration, loss or change in appetite and metabolism, and a weakened immune system (Winget *et al.,* 1994; Tsai *et al.,* 1998; Redfern, 1989;

Waterhouse, Reilly, & Atkinson, 1997; Cho *et al.,* 2000; Waterhouse *et al.,* 2002; Castanon-Cervantes *et al.,* 2010). While these symptoms usually resolve after the circadian clock has re-entrained to its new environment longer-term consequences of repeated circadian desynchrony are gleaned from studies investigating shift-work which produces a condition analogous to jet-lag where individuals experience frequent and chronic phase advances and delays over alternating workdays. Shift-work is estimated to impact up to 20% of the workforce in the western world and has been linked to several morbid outcomes including an increased risk of cancers, diabetes, metabolic syndrome, and obesity, as well as cognitive dysfunction and mood disorders (Schernhammer et al., 2006; Kubo *et al.,* 2006; Conlon, Lightfoot, & Kreiger, 2007; Knutsson & Kempe, 2014; Canuto, Garcez, & Olinto, 2013; Karlsson, Knutsson, & Lindahl, 2001; Kim *et al.,* 2013; Bara & Arber, 2009; Driesen *et al.,* 2010).

The central hypothesis explaining shift-work as a risk factor for these conditions focuses on circadian misalignment that occurs between the internal clock and the environment. The likelihood for internal desynchrony to emerge where the peripheral and central oscillators drift out of phase within the organism is also a realistic consequence of repeated circadian rhythm desynchrony. While the light signal within a day is of prime importance to the entrainment of the clock in the SCN, peripheral oscillators, especially those that are food entrainable can disconnect from the master clock – a condition known as *'internal desynchrony'* – and adopt different phases of entrainment in comparison to the global oscillator under turbulent feeding schedules such as those commonly found in shift-workers (Damiola *et al.,* 2000).

Amplitude

The amplitude (AMP) of a circadian rhythm refers to the differences between the peak and the trough of a circadian parameter. In order for a circadian system output to oscillate in a robust manner an appropriate rhythmicity should be present such that the peak and nadir of the biological process in question be suitable relative to the

time of day. The strength of a circadian oscillator is therefore reflected by its amplitude (Aschoff & Pohl, 1965). It is suggested that the weaker a circadian oscillator the more susceptible rhythms are to phase shifting stimuli (Baehr, Revelle, & Eastman, 2000), the argument being that robust circadian rhythms are the result of a strong endogenous pacemaker operation and require strong zeitgebers to exert a phase shifting effect upon them.

Studies investigating circadian rhythm amplitude have linked a weakening rhythmicity of circadian patterns of core body temperature and rest-activity pattern in older age (Weitzman *et al.,* 1982; Vitiello *et al.,* 1986; Czeisler *et al.,* 1992; Hofman & Swaab, 2006). These findings are accompanied by evidence from animal studies which show suppression in the amplitude of clock proteins CLOCK and BMAL1 in the brains of older mice (Wyse & Coogan, 2010). In neurodegenerative disorders too such as Alzheimer's disease, Parkinson's disease and Huntingson's disease, circadian rhythm disturbances are believed to be part of pathological characteristics of such illnesses with individuals showing attenuated rest-activity profiles, problems with sleep consolidation, and more fragmented patterns of activity (Coogan *et al.,* 2013; Morton *et al.,* 2005; Witting *et al.,* 1990; Hatfield *et al.,* 2004).

In such examples the reduction in circadian rhythm amplitude is thought to be linked to the operation of internal clock. However, the external environment too can have a profound effect on the circadian rhythm amplitude. Importantly the amplitude of the zeitgeber signal which entrains the circadian clock must also be sufficient to facilitate a coherent circadian rhythm and alterations in the zeitgeber signal can contribute to suppression or promotion of a correct circadian oscillation. Examples of circadian rhythm attenuation occur as a result of light pollutants and less exposure to photic signals during the normal light phase of an individual. Artificial light at night has been shown to significantly reduce the rhythm amplitude of the circadian hormone melatonin (Zeiter *et al.,* 2000; Gooley *et al.,* 2011). Furthermore, short wavelength light which the circadian system is maximally responsive to is known to be a chief agent in this regard and is readily deliverable with the proliferation of televisions, computer screens, and tablet devices, in the

home and domiciliary environment in the late evening (Figueiro *et al.,* 2011; Smolensky, Sackett-Lundeen, & Portaluppi, 2015). Similarly, during the day the shielding from the natural solar light dark cycle in dimly lit workplaces and homes reduces exposure to the alerting and cognitive enhancing effects of light (Cajochen *et al.,* 2005; Lockley *et al.,* 2006) and reduces the overall circadian drive to wakefulness.

Interestingly, pronounced sex differences exist concerning the peak amplitude of a number of parameters under circadian control and behaviours that exhibit circadian features. Peak plasma levels of hormones cortisol and melatonin, both of which oscillate in a circadian manner, have been demonstrated to be greater in females compared to males (Gunn *et al.,* 2016; Cain *et al.,* 2010; Santhi *et al.,* 2016). Furthermore the circadian rhythm of slow wave activity appears to be greater in women compared to men around the crest of the melatonin rhythm under constant routines (Santhi *et al.,* 2016). Independent of the effects of slow-wave activity and plasma melatonin amplitude it has also been shown that circadian modulation of cognitive performance involving the component accuracy is also differentially expressed depending on sex (Santhi *et al.,* 2016). Such experiments that employ constant routine or forced desynchrony protocols allow for a separation of the effects of sleep restriction and circadian effects upon behaviour and unmask the endogenous circadian phase from the effects of sleep deprivation.

Strictly speaking cases where the external environment perturbs or enhances the amplitude of a circadian parameter are examples of *'masking'* or acute amplitude change and do not reflect the underlying function of the internal clock (Mrosovsky, 1999). However, from an operational perspective and as highlighted in the aforementioned examples both internal and external factors can have powerful effects on the successful operation of the circadian clock and are pertinent within the framework of understanding how the circadian clock functions in the normal environment. Importantly, the circadian rhythm characteristics reported and discussed here are separated for the purpose of clarity however in the real-world circadian entrainment is an integrative phenomenon involving complex interactions between the period, phase, and amplitude of the circadian rhythm. A reduction in

the amplitude of the circadian rhythm for example normally accompanied by a weaker zeitgeber signal and therefore a tendency for the circadian rhythm to rely more on its internal oscillator rather than synchronise adequately with the environment. Individuals with a shorter circadian period are biased towards an early phase of entrainment which is accompanied by more exposure to the advancing zone of the PRC while the opposite is true for those with longer periods (Wright *et al.*, 2001). In sum these characteristics give rise to pronounced individual differences in the circadian phase of entrainment of which there is considerable variation and a normal distribution among the broad population.

1.5 Measuring individual differences in human rest-activity rhythms in situ

Much of the knowledge the field of chronobiology has attained about the operation of the circadian clock comes from laboratory conditions that are removed from the natural environment. In many studies model organisms such as mice and the common fruit fly *Drosophila melanogaster* are the subjects with the experimental manipulations involving artificial movement or complete removal of the LD cycle. Similarly, while human circadian experiments that take place in temporal isolation or under FDP are scientifically interesting for investigating circadian rhythms in their free running state, they do not adequately represent the biological clocks function in the environment in which it adapted to or exists in everyday life (*i.e.* when the clock is entrained) (Roenneberg *et al.*, 2015). Furthermore, the classical (and most faithful) measurements of circadian phase that are used to determine the phase of entrainment, such as rectally measured core-body temperature and salivary or plasma derived DLMO, do not lend themselves practically to continuous recording over long periods of time or for use *in situ* circumstances either because of their invasive nature or financial cost. As a result, the behavioural analogue of human circadian rhythms preferred in everyday circumstances is the pattern of rest and activity. Sleep, and especially so the timing of its onset/offset, being perhaps the most conspicuous output that is under circadian control can be used to observe and characterise individual differences in the human circadian phenotype. Both objective

measures such as the monitoring of daily profiles of activity and subjective measures such as questionnaires examining daily habits of sleep can be used to estimate the entrained phase of the circadian rhythm in everyday circumstances.

A cursory yet reliable estimation of the individual circadian phase of entrainment exists in the concept of circadian typology which is often synonymously referred to as 'chronotype'. Individual differences in the population exist distributed along a continuum ranging from early-types (sometimes referred to as 'morning-types' or 'larks') compared to extreme 'late-types' (sometimes referred to 'evening-types' or 'owls') (Adan *et al.,* 2012). 'Morning-types' on one tail-end of an approximate Gaussian distribution, refer to individuals who are early to rise, prefer early bedtimes, and have their peak performance earlier in the day, while 'evening-types', occupying the other end of the spectrum, refer to individuals that prefer to stay awake late, sleep later into the morning, and perform at their best in the later parts of the day (Horne & Östberg, 1976). Several studies have validated such a typological approach in describing individual chronotypes. Most notably early or morning types are shown to have an earlier sleep schedule compared to late or evening types (Robilliard *et al.,* 2002; Taillard *et al.,* 2004; Foret *et al,.* 1982, 1985; Mecacci & Zani 1983; Kerkhof 1991; Kerkhof & Lancel 1991; Carrier & Monk, 1997). Morning types also exhibit an earlier circadian temperature phase relative to evening types (Kerkhof 1991; Lack & Bailey 1994; Kerkhof & Van Dongen 1996; Duffy et al., 1999; Vidacek et al. 1988; Kerkhof and Lancel 1991; Neubauer 1992; Gupta and Pati 1994). The extent of this contrast was about a 2 h phase difference in core body temperature between the morning and evening types (Baehr *et al.,* 2000). Hormonal rhythms too have been the focus of much of the research concerning circadian typologies. The canonical circadian hormone melatonin, both a predictor of sleep onset and circadian rhythm phase (Arendt, 2006; Rossenwasser, 2009; Benloucif *et al.,* 2005), has been found to secrete approximately 3 h earlier in morning types in both salivary and plasma measurements (Gibertini, Graham, & Cook, 1999; Griefahn *et al.,* 2002; Mongrain *et al.,* 2004). Similarly, salivary and blood concentrations of cortisol show an advanced phase onset of almost one hour in morning types and the peak amplitude of cortisol occurring in the morning is also observed to be greater than in evening types (Bailey

& Heitkemper, 2001; Griefhan & Robens, 2008) and phase differences in clock gene expression is also noted between individual chronotypes (Brown *et al.,* 2008; Novakova *et al.,* 2013). Fundamentally the basis of chronotyping individuals relies on an inspection of the typical rest-activity pattern, or as the case may be the sleep-wake cycle, by objective or subjective (self-report) means. The remainder of this section therefore introduces the reader to the state of the art of the chronobiologist's toolkit to enable a familiarity with the instruments widely used in the literature and in the experimental content of this thesis.

Actigraphy

Actigraphs (or 'actimeters' in some texts) are accelerometer devices generally worn on the user's wrist which passively record movement throughout the day. The technology is used to quantify daily rest-activity profiles of the user and can be used to estimate sleep-wake schedules based on the observation that there is greater motoric activity during periods of wakefulness compared to periods of sleep. Modern actigraphs sample movement at a fine temporal resolution that differs depending on manufacturer specifications and study population in question. Generally accelerometers use a bandpass filter in the .25 – 4 Hz range eliminating very slow movements and very fast involuntary movements such as shivers or tremors typically exceeding 5 Hz (Redmond & Hegge, 1987). In younger populations however a broader sampling range is recommended in the region of .5 – 11 Hz to detect faster and spontaneous movement (Van Someren, Lazeron, & Vonk, 1995). Once the device detects movement an activity count is measured commonly derived from the 'time above threshold' or 'zero-crossing method' where the signal is considered pertinent if it exceeds a threshold level or crosses the zero mark respectively (Ancoli-Israel *et al.,* 2003). Activity counts are then stored typically in 60 s intervals or another shorter specified epoch length.

Actigraphy is most commonly used in sleep medicine to objectively assess characteristics of an individual's sleep pattern over a number of days. While the

microarchitecture of sleep is best quantified by polysomnography (PSG) the current 'gold standard' measure in seep research, the 'macroarchitecture' of sleep, that is how sleep varies in an individual over a number of days, can be assessed by actigraphy where recording can take place *in situ* and for longer than one or two nights. A number of algorithms exist which calculate sleep actigraphy sleep variables such as the estimated onset/offset of sleep, total sleep time (TST), sleep onset latency (SOL), sleep efficiency, and wake after sleep onset (WASO) (Ancoli-Israel *et al.,* 2003). Actigraphy compares favourably with PSG for the valid and reliable detection of sleep (Jean-Louis *et al.,* 1996).

As well as measuring night-to-night differences and within night disturbances in the estimated sleep period of an individual actigraphy can also be used to objectively record the rest-activity circadian rhythm even if no attempt is made to examine sleep. Raw activity counts recorded by actigraphs may be analysed to produce a faithful 24 h rest-activity patterns that exhibit a robust circadian rhythm. The consinor method involves fitting the data to a cosine curve with a period at or near 24 h from which the acrophase (time of peak activity) may be used as a phase marker of the circadian rhythm and the amplitude (peak-to-nadir difference in activity count) can be used to measure the strength of the rhythm (Youngstedt *et al.,* 2001; Binkley, 1995; Glod *et al.,* 1997; Sakurai & Sasaki, 1998). Non-parametric methods which make no *a priori* assumptions about the fit of the data are also used to estimate circadian phase, amplitude, and within (stability) and between (variability) day differences in rest-activity patterns (Van Someren *et al.,* 1997, 1999; further described in Chapter 4).

Actigraphy derived phase markers such as sleep-onset time, sleep mid-point time and acrophase are all found to be significantly correlated with salivary or urinary metabolite secretion (6-sulphatoxymelatonin) measures of melatonin phase (Youngstedt *et al.,* 2001, Carskadon *et al.,* 1997, 1998). Furthermore, evidence supporting the utility of actigraphy derived sleep rhythms being a good proxy measure of central pacemaker phase comes from one study which used FDP to dissociate sleep and circadian patterns of activity. The authors found that in free-running subjects when sleep was attempted at an unfavourable circadian phase TST

was lower suggesting that the actigraph-identified sleep was not entirely masked by exogenous factors outside of the circadian pacemaker's control (Blagrove *et al.,* 1998, Ancoli-Israel *et al.,* 2003). It is recommended that at least seven nights of actigraphic recording is required to obtain 5 nights of useful data for the estimation of sleep parameters such (Sadeh, 1996; Acebo *et al.,* 1999). In order to determine differences between workday and free day patterns of activity over two weeks of data may be necessary. Similarly, the power of actigraphy to depict an accurate representation of an individual's typical rest-activity rhythm depends on an adequate amount of free and workdays to sample from (Roenneberg *et al.,* 2015).

Morningness-Eveningness Questionnaire (MEQ)

The Morningness-Eveningness Questionnaire (MEQ; Horne & Östberg, 1976) was the first self-report scale of circadian typology which is considered to represent underlying individual differences in circadian function. The scale allows participants to indicate their preferred timing for activity, bedtime and rising time, and optimal timing for mental alertness and physical exercise according to what is described as their subjective *'feeling best rhythm'*. The circadian phenotype in this manner is expressed on a spectrum ranging from morningness to eveningness with a preference for timing activity at either time of the day revealing individual differences between so-called morning-types and evening-types. The scale score ranges from 16 to 86 and the original authors prescribe cut-off scores that are used to discriminate between morning, intermediate, and evening types. Due to the limitations of extrapolating the cut-off reliability of the original study to independent samples however other groups have suggested revising the scoring procedure using different cut-off scores or median/percentile splits to distinguish between typologies (Taillard *et al.,* 2004; Natale & Lorenzetti, 1997; Caci *et al.,* 2009). The MEQ is one of the most widely used instruments in probing individual differences in circadian typology and its validity has been demonstrated using objective measures of circadian phase such as timing of body temperature, cortisol secretion, and melatonin secretion (Di Milia *et al.,* 2013; Bailey & Heitkemper, 2001; Griefahn *et al.,*

2002; Horne & Ostberg, 1976; Neubauer, 1992). Several derivatives of the MEQ exist based on a similar premise such as the reduced Morningness-Eveningness Questionnaire (rMEQ; Adan & Almirall; 1991) and the Composite Scale of Morningness (CSM; Smith, Reilly, & Midkiff, 1989).

Although the MEQ is the oldest and most cited instrument used to measure self-reported individual differences in circadian rhythm function limitations pertaining to its quantitative ability exist. Firstly, concerns the discrepancy between how the MEQ measures behaviour compared to other more objective markers of circadian phase which are recorded by their position they occur in the 24 h day. The MEQ produces a score with a range of 71 points (16-86) which cannot be readily transformed linearly into a time on the clock and therefore the entrainment characteristic of the individual cannot be measured in temporal terms (Roenneberg, 2015). Secondly, because of the subjective nature of choosing ones preferred time of activity rather than ones precise behaviour the MEQ has been likened to a dimension of personality rather than a measure of the underlying biological rhythm function (Di Milia *et al.,* 2013). Thirdly, MEQ measurements do not differentiate between behaviour on workdays and free days, nor do the parameters determining whether one is a morning type versus an evening type account for differences in age, sex, or cultural background (Kuehnle, 2006). For these reasons and the due to the questionnaires focus on individuals considering their 'feeling best' rhythm the MEQ might be considered a measure of a more suitable measure of psychologically based diurnal preference rather than a biologically determined phase of entrainment *per se* (Di Milia *et al.,* 2013).

Munich Chronotype Questionnaire (MCTQ)

The Munich Chronotype Questionnaire (MCTQ; Roenneberg *et al.,* 2003, 2007) is a measure which uses the midpoint of an individual's sleep on free days as a phase marker of circadian entrainment and therefore an indicator an individual's chronotype. The questionnaire asks respondents to report their bedtime, sleep latency, and wake times from which the midpoint of sleep ('midsleep') is computed

differentially for workdays and free days. According to the authors, the MCTQ overcomes limitations associated with self-report measures of circadian typology however the questionnaire is itself still a self-report instrument though an important distinction is made between the actual time one goes to bed reported in it, and their diurnal preference as recorded by measures such as the MEQ.

Further, because of social pressures arising from standard working hours, later chronotypes are found to accumulate a greater sleep debt over the working week which masks the phase of sleep on free days when individuals oversleep (Figure 1.8A) (Roenneberg *et al.,* 2004). As a result an algorithm is applied taking into consideration an individual's average sleep duration which corrects the mid-point of sleep to produce the questionnaire's principal measure of chronotype the sleep corrected mid-sleep on free days (MSF_{sc}) (Ronneberg *et al.,* 2012). Similar to the MEQ score, MSF_{sc} is approximately normally distributed among the population though a slight negative skew is present illustrating modern lifestyle factors (Figure 1.8B). As the questionnaire collects information about mid-sleep on workdays (MSW) and the normal phase of entrainment on free days (MSF) the instrument also allows for a broad interrogation into discrepancies between circadian phase changes normally experienced throughout one's educational/working life. Consequently, the *'social jetlag'* (SJL) – a functional jetlag arising from mismatching social schedules – can be reliably measured in normal working/school attending populations (Wittman *et al.*, 2006), a phenomenon which is of central importance to the study of humans in chronobiology and will be discussed further in the introduction to this thesis.

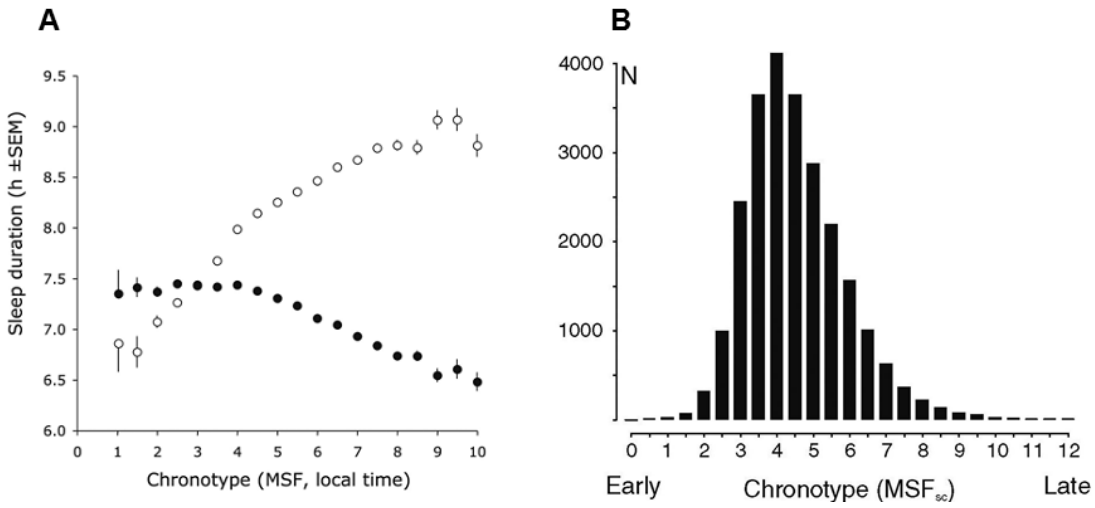

Figure 1.8 The epidemiology of the mid-sleep on free days (MSF), a phase marker of circadian rhythm entrainment

(A) *Illustration of sleep duration on workdays (filled circles) and free days (unfilled circles) as a function of chronotype (MSF). Note the chronic sleep restriction that occurs in later chronotypes on workdays and the resultant elongation of sleep duration on free days in which this sleep debt is dissipated.* ***(B)*** *Demographic distribution of sleep-corrected MSF shows an approximately Gaussian distribution among the general population (N ≈ 25,000). Data from the MCTQ database; figures from Roenneberg & Merrow (2007) and Roenneberg et al. (2004), respectively.*

Numerous studies support that mid-sleep time derived from the MCTQ is a suitable proxy measure of circadian phase as it is a strong predictor of DLMO (Burhess & Eastman, 2005; Crowley *et al.,* 2014; Kitamura *et al.,* 2014; Simpkin *et al.,* 2014; Terman *et al.* 2001). Wrist actigraphy and sleep-log studies have shown mid-sleep correlates strongly with objectively and subjectively estimated sleep patterns (Kantermann *et al.,* 2007; Kuehnle, 2006). Mid-sleep on free days also compares favourably with the MEQ score (correlation: - .74) but this association becomes weaker (- .66) as the MCTQ is corrected for sleep debt reflecting the MEQ not overcoming confounds associated with recurring weekly sleep restriction (Roenneberg *et al.,* 2007). Kantermann and colleagues (2015) additionally showed that MSF_{sc} may be a better predictor of DLMO than MEQ score and therefore a better phase marker of the central endogenous timekeeping system. For these reasons it is argued that chronotype expressed as MSF_{sc} might be the best self-reported measure

of the underlying phase of entrainment and the MEQ used to determine diurnal preference (Roenneberg, 2015)[1].

1.6 On the epidemiology of chronotype

The translation into multiple languages and use of instruments such as the MEQ and MCTQ has led to a wealth of knowledge concerning the epidemiology of circadian entrainment in humans. The creators of the MCTQ alone operate a database which as of 2015 has accumulated over 200,000 entries spanning several countries worldwide (Roennenberg *et al.,* 2015). Furthermore, several studies emerging from the literature on personality factors and individual differences have indicated links between specific demographics and domains with circadian typology. As a result a comprehensive picture is emerging pointing to the factors associated with different patterns of diurnal preference and chronotype.

Age and sex

Chronotype and sleeping habits change drastically throughout the development of one's lifespan. Population data from the MCTQ database show that starting in adolescence (approximately 14 years old) chronotype progressively delays throughout adolescence into early adulthood (Carskadon, 2011; Roenneberg *et al.,* 2004; Borisenkov, Perminova, & Kosova, 2010). Studies using the MEQ also show a

[1] There is considerable absence of agreement in the literature over what components of behaviour self-report measures of circadian related traits actually assess. As a result much confusion has arisen in part due to the incorrect characterisation 'chronotype' and 'circadian typology' as synonymous factors. For nomenclature consistency in this research we utilised the following terms as operational definitions of aspects of the human circadian phenotype in agreement with Roenneberg *et al.* (2004) and Roenneberg (2015):

Morningness/Eveningness refers to the circadian typology dimension captured by the MEQ and is a measure of the individual differences in 'diurnal preference'. It is measured on a scale ranging 16 – 86.

Chronotype refers to the MSF_{sc} of an individual which is computed using the MCTQ. All references to chronotype therefore correspond to this phase marker of sleep/wake interval measured in local time. Chronotype assessed in this fashion reliability estimates an individuals' phase of circadian entrainment and it is based on the theoretical assumptions of circadian entrainment.

propensity towards eveningness as age progresses in individuals in the 12 – 20 year old bracket of the population (Achari & Pati, 2007; Kim *et al.,* 2002, Randler, 2011; Tonetti *et al.,* 2008).

At approximately twenty years of age chronotype abruptly starts to advance again, a trend which is found to persist into old age until the end of life (Roenneberg *et al.,* 2004). Likewise, after adolescence, morningness scores increase drastically as age advances (Kim *et al.,* 2010; Merikango *et al.,* 2012; Monk & Kupher, 2000; Paine, Gander, & Travier, 2006; Tonetti *et al.,* 2008). The early adulthood point of inflection in the charting of chronotype/circadian typology over the course of lifespan is so conspicuous it has been even posited as a developmental marker for the end of adolescence (Randler, 2011; Roenneberg *et al.,* 2004).

Several lines of evidence also suggest that the circadian phenotype might be a sexually dimorphic trait in humans (see Figure 1.9). This is especially true concerning its interaction with age related changes in the circadian system. Females for example are found to reach the inflection point between delaying and advancing chronotype associated with the end of adolescence significantly earlier (~19.5 years of age) than males (~20.9 years of age) (Roenneberg *et al.,* 2004). Numerous studies have also shown a later chronotype or more evening shifted diurnal preference in males when compared to females (Adan & Natale, 2002; Borisenkov *et al.,* 2012; Natale & Di Milia, 2011; Randler, 2011; Tonetti *et al.,* 2011). Moreover, Duffy *et al.* (2011) showed that the intrinsic circadian period was shorter in women than in men, and that women were proportionally more likely to have a $\tau < 24$ h which is believed to underpin an earlier chronotype. Interestingly, differences in chronotype among men and women tend to emerge at the onset of puberty close to normal menarcheal age in girls and completely dissipate at close to fifty years of age which coincides with the average age of menopause in women (Roenneberg *et al.,* 2004; Tonetti, Fabbri, & Natale, 2008; Hollander *et al.,* 2001; Greer, Sandridge & Chehabeddine, 2003). A precise reason for this discrepancy in sex is unclear however. Adan and Sanchez-Turet (2001) suggest that due to the coexistence of a circamensual rhythm, endogenous control of rhythmic biological parameters may be less robust in women. According to this

principle it might be reasonable to hypothesise that such sex differences might underpin a different entrainment profile seen between men and women.

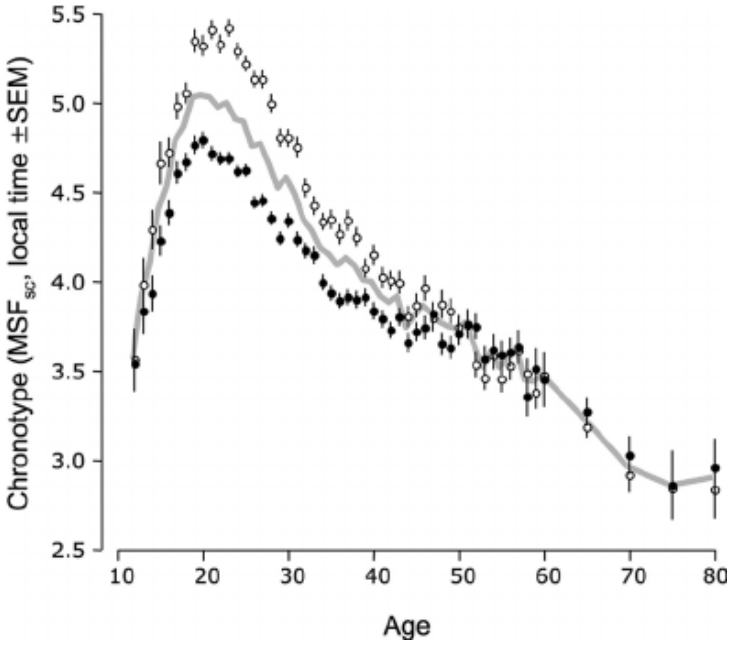

Figure 1.9 Chronotype dependent on age and sex

Data from MCTQ database indicating the change in chronotype is dependent on age and sex. Throughout adolescence, the entrainment of the circadian clock substantially delays in phase until it reaches its inflection point at the end of adolescence and begins to advance as age progresses. Females (indicated by filled circles) reach this inflection point earlier than males (indicated by open circles). The sex dependent differences in chronotype (males, later) present for most of adulthood where they begin to dissipate at around fifty years of age. Figure from Roenneberg & Merrow (2007).

Light exposure

Consistent with what is known about the entrainment characteristics of the clock in response to photic zeitgebers, both the subjective time of exposure and intensity of solar light during the day and the degree of darkness one is exposed to during the night are found to be important determinants of an individual's chronotype.

Epidemiological evidence from the MCTQ-database shows that the amount of self-reported time spent outdoors exposed to daylight negatively correlates with MSF_{sc}, indicating that chronotype advances with an increased amount of time spent outdoors (Roenneberg *et al.,* 2012; Roenneberg & Merrow, 2007). Despite this however adolescents being the latest chronotypes are among the population demographic most likely to report spending the longest times outdoors. One reason for this might involve the timing of exposure as teenagers may prefer to socialise outdoors later in the day and thereby light is administered in the phase delaying zone of the PRC which occurs in the later part of the day (Roenneberg, Hut, Daan, & Merrow, 2010; Roenneberg *et al.,* 2015).

Furthermore, apparent evidence for the entrainment of chronotype to the solar clock is gathered from a close inspection of the distribution of chronotypes within the same time zone. Numerous studies have found that the chronotype/circadian typology of the population delays or advances as longitude moves in a westward or an eastward direction respectively (Roenneberg, Kumar, & Merrow, 2007; Borisenkov *et al.,* 2010; Shawa & Roden, 2015). When examining the distribution of chronotypes within the German population Roenneberg and colleagues (2007) found that this difference is phase equates to 4 min per degree of longitude travelled corresponding directly with position of the sun relative to the local clock time. These findings have been corroborated by others living in Hungary which is further East in the Central European Timezone (CET) with chronotype fitting the German-longitudinal-trendline as expected (Haraszti *et al.,* 2014). Similarly, seasonal changes in photoperiod and cloud cover generally associated with winter months result in a weaker zeitgeber signal and therefore a later chronotype than would be found during summer months (Kantermann *et al.,* 2007) and short photoperiods in northern latitudes, where light exposure is reduced during the day, have been linked to delays in chronotype also (Borisenkov *et al.,* 2010). Accordingly, it has been noted that chronotype assessment is influenced by the season in which measurements are taken and whether the subject's country of origin is currently implementing daylight-saving-time or operating under standard time-zone (Allebrandt *et al.,* 2014).

Comparably, increased light exposure during the night as a result of electric lighting in the home or light pollution in urban environments is associated with later chronotype compared to rural dwellers. Similarly, the effect of short-wavelength light emitting sources such as portable reading devices used before bedtime can significantly alter the circadian drive to sleep suppressing evening levels of melatonin, decreasing sleepiness, and phase delaying the onset of sleep (Chang *et al.,* 2014). Numerous studies therefore have begun to examine the effects on the circadian entrainment profile of individuals removed from sources of artificial light. Wright *et al.* (2013) studied late chronotypes while on a camping trip for two weeks without artificial electrical light and found significant advances in circadian phase corresponding with the time of sunrise. One study examining indigenous traditionally hunter-gatherer communities in Argentina exposed to electrical lighting and those without found significant delays in sleep onset and a shorter sleep duration in the population using electrical lighting (de la Inglesia *et al.,* 2015). In another study conducted in rubber tappers in the Amazon living with and without electricity researchers report shorter sleep times and a delayed DLMO in those exposed to electrical light at night (Moreno *et al.,* 2015). Finally, actigraphy derived measures of rest-activity from modern pre-industrial communities in Papua New Guinea found that circadian patterns in behaviour showed less intradaily variability and synchronised strongly to the light-dark cycle (Siegmund, Tittel, & Schiefenhovel, 1998).

Genetic associations

Several lines of evidence have pointed to a strong genetic disposition underpinning the circadian phase of entrainment in humans. Twin studies examining genetic liability towards circadian typology have found that approximately half of the heritability is accounted for by genetic factors (Vink *et al.,* 2012; Koskenvuo *et al.,* 2007; Toomey *et al.,* 2015; Barclay *et al.,* 2013; Watson, Buchwald, & Harden, 2013). Consistent with the observations that circadian rhythms are generated by a molecular clockwork and that chronotype/circadian typology is derived from other

sleep systems it is to be expected that variation in these genes produce different circadian phenotypes (Adan *et al.,* 2012).

Studies undertaken in extreme early types, for example kindreds with Familial Advanced Sleep-Phase Syndrome (FASPS) a circadian sleep disorder where individuals show a profound phase advance of the sleep-wake cycle as well as measures of underlying circadian phase as a result of an extremely short τ, show overwhelming genetic determination (Brown *et al.,* 2008; Jones *et al.,* 1999; Toh *et al.,* 2001; Xu *et al.,* 2005). FASPS is well characterised with the syndrome phenotype emerging as a consequence of a mutation in the CKI binding site in *PER2* which results in a reduced phosphorylation by CKI and therefore a shorter circadian period (Jones *et al.,* 1999; Toh *et al.,* 2001). Similarly, a missense mutation in the *CKIδ* gene which results in altered expression of the kinase directly impinges on the near 24-h rhythmicity of the TTFL producing a short period and advanced phase of entrainment (Xu *et al.,* 2005). Despite an illuminated understanding of the circadian clock arising from such studies, FASPS is a rare condition and therefore the genetic contributions to this sleep disorder may not be generalizable in terms of describing the genetic contributions towards the normal ranges within which chronotypes fall in the wider population.

Concerning this question recent genome wide association studies (GWAS) have been conducted indicating specific loci which might be of importance in shaping chronotype/diurnal preference (Kalmbach *et al.,* 2016; Jones *et al.,* 2016; Lane *et al.,* 2016). Numerous candidate gene studies have focused on polymorphisms in canonical circadian genes which show associations with chronotype or circadian typology. A single nucleotide polymorphism (SNP) in the *CLOCK* gene (T3111C) was first linked to diurnal preference in a study carried out by Katzenberg *et al.* (1998) showing that the C allele was correlated with eveningness. A number of studies support these findings in alternative populations (Mishima *et al.,* 2005; Bandin *et al.,* 2013) though attempts to replicate findings have failed also (Johansson *et al.,* 2013; Barclay *et al.,* 2011; Chang *et al.,* 2011). Additionally, a variable number tandem repeat (VNTR) polymorphism in the *PER3* gene which consists of a 54 base pair

repeat sequence repeated either four (short allele; *PER3*^{4}) or five times (long repeat; *PER3*^{5}) is among one of the most studied polymorphisms in human circadian candidate gene studies. Studies have shown an association between the long repeat and morning preference while the shorter repeat associates with evening preference and DSPS (Archer *et al.,* 2003, 2010; Ebisawa *et al.,* 2001; Johansson *et al.,* 2003; Jones *et al.,* 2007; Lazar *et al.,* 2012; Pereira *et al.,* 2005). These findings are similarly controversial however as many research groups have failed to replicate these findings (Barclay *et al.,* 2011; Osland *et al.,* 2011). The reason for the failure to replicate this association might emerge as a result of different samples sizes or previously mentioned environmental factors such as the sex distribution of the sample, the latitude/longitude of the study site, or the phenotyping methods used (*ie.* MEQ measuring subjective diurnal preference not phase of entrainment *per se*). Less studied genetic factors such as SNPs located in both the *PER1* and *PER2* genes have been associated with increased morningness preferences too (Carpen *et al.,* 2005, 2006). A more focused review on the genetic associations explored in this programme of research is provided in Chapter 6.

Relationships with dimensions of personality

A number of studies have examined associations between different components of personality and the chronotype/diurnal preference trait. Among the trends previously described in the literature has been an association between morningness and greater levels of agreeableness and consciousness using the Five-Factor Model of personality (Hogben *et al.,* 2007; de Young *et al.,* 2007; Gray & Winston, 2002; Tonetti *et al.,* 2009). Additionally reports have demonstrated associations between higher levels of eveningness with extraversion using the Eysenck Model of Personality (Langford & Glendon, 2002; Mitchell & Redman, 1993). Others however have failed to find a direct relation with the Five-Factor Model when cognate traits such as sensation seeking and impulsiveness are considered above broader features such as extraversion (Russo *et al.,* 2012). Exploration of narrower personality traits have revealed consistent associations between eveningness preference and impulsivity

and novelty/sensation seeking (Adan, Natale, Caci, & Prat, 2010; Tonetti et al., 2010; Kilgore, 2007; Caci, Robert, & Boyer, 2004). Taken together these findings suggest that an individual's tendency to be a morning-type or to express an earlier phase of circadian entrainment might be shaped partially by features such as discipline and achievement orientation captured by the contentiousness domain of personality. Conversely, a pattern of later expressed circadian phase and diurnal preference might be mediated in part by an individual's level of arousal and excitatory gradient as indicated by higher levels of sensation seeking and stimulation from environment typically associated with impulsive personality types. A recent area of research interest in decomposing the interaction between individual traits and the circadian timing system has emerged from exploring the association between an individual's temporal perspective of events and chronotype. A number of studies have investigated individuals' time perspective which is a trait-like feature indicating levels of present orientation and future orientation when recalling events and making decisions (Stolarski, Binter & Zimbardo, 2011). Among several cohorts it has been demonstrated that evening diurnal preference is associated with reliance on present time frames and morningness with future time frames (Stolarski, Ledzinska, & Matthews, 2013; Nowack & van der Meer, 2013; Milfont & Schwazenthal, 2014; McGowan *et al.,* 2017). Patterns of present time perspective and future time perspective have in and of themselves been linked to personality factors associated with chronotype (Kairys, 2015) indicating that both circadian preferences and associated personality domains might be both mediated by individual differences in the appraisal of time perspectives. Recently we demonstrated that the relation between timing of the sleep phase and diurnal preference was moderated by the time perspective psychological construct thus further illuminating the complex interaction between the underlying phase of entrainment of the circadian timing system and an individual's time-of-day preferences (McGowan *et al.,* 2017).

1.7 General and psychiatric health consequences, and cognitive performance among individual chronotypes

Circadian typology and chronotype are often found to be components associated with general and mental health problems (Partonen, 2015). First and foremost as a result of social pressures, eveningness is perhaps unsurprisingly associated with both restricted sleep and a poorer rating of sleep quality (Carrier *et al.,* 1997; Park *et al.,* 1999; Taillard, Philip, & Bioulac, 1999; Giannotti *et al.,* 2002; Gau *et al.,* 2007) and as previously discussed late chronotypes from the MCTQ database are observed to drastically shorten the duration of their sleep to accommodate work schedules leading to a chronic sleep deprivation throughout the work week (Roenneberg *et al.,* 2007). Evening-types also engage in a number of behaviours which are deleterious to health such as consuming more alcohol (Adan, 1994) and smoking more (Negriff *et al.,* 2011; Maukonen *et al.,* 2016) with other reports indicating that irregular and unhealthy diets are commonplace among evening-types (Nakade *et al.,* 2009; Haraszti *et al.,* 2014) as well as reports of less engagement in physical exercise (Urbán, Magyaródi, & Rigó, 2011).

As a result of such unhealthy lifestyle choices and their interaction with sleep and circadian rhythm disruption rife among evening/late types there is a consistent pattern in the literature implicating a late chronotype with metabolic and cardiovascular illnesses. Melinska *et al.* (2012) report a that women with a delayed midsleep and melatonin rhythm were at greater risk of obesity than early-types, an observation recapitulated amongst adolescents and alternative samples with late chronotypes showing increased BMI and rates of obesity (Arora & Taheri, 2015; Baron *et al.,* 2011). Furthermore, sleep deprivation produces a condition of reduced glucose tolerance and insulin sensitivity (Turek *et al.,* 2005) and evening-types have been shown to have poor glycaemic control indicated by higher blood levels of glycated haemoglobin (Osonoi et al., 2014; Iwasaki et al., 2013; Reutrakul et al., 2013). Prevalence rates of type II diabetes are also shown to be elevated amongst adults that are evening-types (Merkikanto et al., 2013; Yu et al., 2015). After controlling for sleep duration and quality evening-types have been shown to have increased risk of

arterial hypertension which is a risk factor for cardiac events (Roeser *et al.,* 2012; Merikanto *et al.,* 2013). Furthermore, population studies show a pronounced circadian rhythm in the time of day of acute myocardial infarction indicating that risk is greatest in the evening and Selvi *et al.* (2011) showed a differentiation in the time of day at which incidences peaks among morning and evening-types.

Sleep and circadian rhythm disturbances are among the most frequently found co-morbidities in many neuropsychiatric and/or mental health complaints (Wulff *et al.,* 2010). Several studies report that circadian timing is significantly delayed in patients with mood disorders such as major depressive disorder and bipolar disorder (Soria & Urretavizcaya, 2009; Giglio *et al.,* 2010; Soeca *et al.,* 2009; Coogan, 2013). The extent to which such disruptions to sleep and circadian rhythms are part of the symptomatology of psychiatric conditions is reflected in the clinical picture of many conditions specified in the *DSM* or *ICD-10* where sleep disruption or irregular sleep timing frequently co-occur though evidence shows that sleep and circadian dysfunction might be an additional aetiological consideration for such conditions as well. Evening/late-types are found to be at increased risk of depression (Konttinen *et al.,* 2014; Kitamura *et al.,* 2010; Merikanto *et al.,* 2013; Drennan *et al.,* 1991) and pre-clinical studies have demonstrated that evening-types are more prone to depressive symptoms, sadness, and pessimism as well as anxiety disorders (Alvaro *et al.,* 2014; Chelminski *et al.,* 1999; Giannotti *et al.,* 2002; Hidalgo *et al.,* 2009; Selvi *et al.,* 2011; Reid *et al.,* 2012; Antypa *et al.,* 2016). In bipolar disorder irregular sleep timing, which is common among late chronotypes, is known to be a trigger for symptoms of mania (McClung, 2007). Moreover, there is also evidence which suggests that regardless of mood state, individuals with bipolar disorder are more likely to show a diurnal preference for evenings (Seleem *et al.,* 2015).

Cognitive performance seems to also be adversely affected in late chronotypes when compared to their early counterparts. There have been several reports indicating that earlier midpoint of sleep is associated with greater academic achievement among school children/adolescents and adults attending university (Arbabi *et al.,* 2015; Kolomeichuk *et al.,* 2016). Morning preference is also found to

predict better grades (Besoluk *et al.,* 2011; Medeiros *et al.,* 2010; Tonetti, Natale, & Randler, 2015) and attention in school (Clarisse *et al.,* 2010). Among working populations, especially those engaged in occupations with irregular schedules, evening-types are less able to cope with adapting to occupational schedules impinging on work performance (Gamble et al., 2011; Martin et al., 2015). One primary reason for this discrepancy between morning and evening-types seems to relate to the time-of-day effects on cognitive ability. Morning-types consistently show a phase advance in peak performance compared to evening-types (Adan, 1991; Natale & Lorenzetti, 1997) and as a result performance of morning-types is more efficient in the context of typical daily work/school schedules which commence in the early morning and conclude in the late afternoon.

1.8 Social jetlag: understanding living against the clock

As previously stated the evolutionary purpose of the circadian system is to maintain a synchronous condition between the endogenously generated biological rhythm and the twenty-four hour day. Individual differences in how these rhythms embed themselves into the environmental light-dark cycle are represented by the distributed nature of chronotypes among the population which until only very recently gave rise to a relatively stable circadian phase of entrainment around which temporal changes in biology and behaviour are structured (Foster *et al.,* 2013). In modern times however, and particularly after the advent of electrical lighting, an additional critical temporal factor has arisen in the form of social timing. The encroachment of the socially determined clock through everyday activities such as work and school schedules presents the circadian system with novel challenges not previously encountered it is development. To accommodate rest and activity to social schedules individuals frequently use stimulants such as caffeine to curb sleep deprivation during the workweek and a growing number use soporific medication at night to align their sleep to a more socially convenient time (Foster & Wulff, 2005). Epidemiological evidence from the MCTQ-database shows that around 80% of individuals rely on alarm clocks to wake up on workdays and thus in doing so halt

their sleep prematurely (Roenneberg *et al.,* 2012). As previously discussed those that are late chronotypes are particularly biased against in that they forego sleep during the workweek to align their schedules with the typical social clock and in doing so accumulate a substantial sleep debt on workdays (Roenneberg *et al.,* 2004, 2007). Similarly, in the evenings and weekends early chronotypes stay awake long into their biological night to facilitate socially normal recreational times (Roenneberg *et al.,* 2007).

There are few individuals that are unaffected by the disparity between the biological clock and the social clock. Data from the MCTQ-database suggests that about 89% of individuals report having to begin work either before or at 09:00 h and consequently 83% must get up on workdays before or at 07:00 h. This is contrasted by data from the same population which shows that using MSF_{sc} as an anchor point the biological sleep window of 77% of the population only ends at 08:00 h or later and in almost 50% of the population only ends at 09:00 h or later (Roenneberg *et al.,* 2015). Consequently, among many individuals this results in different schedules of sleep-wake timing and duration on workdays when compared to free days which can be quantified using the midsleep on workdays (MSW) and the midsleep on free days (MSF) measures derived from the MCTQ. In a sense individuals occupy different timezones on workdays and free days and as a result the natural phase of entrainment of sleep-wake cycle represented by MSF is perturbed by the imposing action of the social clock upon the sleep-wake cycle on workdays represented by MSW. This condition is analogous in character and outcome to the *desynchronosis* observed in those that experience jetlag as a result of flying to a different time-zone. As such the term *'social jetlag'* (SJL) has been coined to describe this manifestation of circadian desynchrony arising from the social clock (Wittmann *et al.,* 2006).

Unlike travel induced jetlag in which symptoms are transient until the circadian clock realigns to an appropriate phase, SJL is a chronic phenomenon which usually persists throughout one's working career (Roenneberg *et al.,* 2015). Among working populations represented in the MCTQ-database, it is found that around 69% of individuals experience at least 1 h of SJL during a typical workweek while

approximately 33% experience 2 hours or more (Wittmann *et al.,* 2006; Roenneberg *et al.,* 2015; Foster *et al.,* 2013). The same data show that only 13% of the population experience or close to 1 in 8 individuals are free of SJL. Additionally, because most individuals have a tendency to restrict sleep on workdays and compensate for this sleep loss on free days by 'sleeping-in', sleep on free days is often longer and delayed in phase compared to sleep on workdays. Even after correcting for the accumulation of sleep-debt however the later the chronotype, the more pronounced the SJL experienced (Figure 1.10A) (Wittmann *et al.,* 2006). Effectively, the differential in circadian phase represented by SJL equates to a dramatic and recurring pressure to phase advance the circadian clock for most individuals on workdays. Moreover, because re-entrainment is not instantaneous but rather takes a number of days to fully adjust (Monk & Folkard, 1976; Nicholson & Stone, 1978; Kantermann *et al.,* 2007) it is unclear whether or not the biological clock ever settles to cope with the pressure from the social clock, thereby leaving the circadian system and social time dissociated to some degree for the majority of one's adult life (Figure 1.10B).

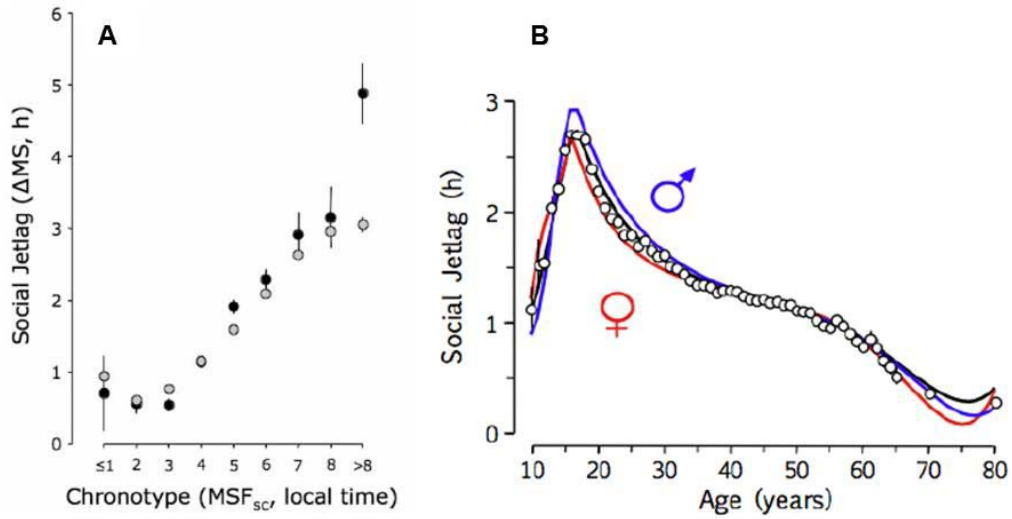

Figure 1.10 Social jetlag, chronotype, and lifetime prevalence

(A) *Data depicting the relationship between chronotype and SJL. Note the positive association between later MSF$_{sc}$ and more severe SJL. Grey circles represent data from MCTQ-database, black circles data from seminal SJL paper by Wittmann et al. (2006).* ***(B)*** *Lifetime prevalence of SJL in males and females. Note the sharp reduction in SJL after the traditional age of retirement when social clock is not so deterministic of behavioural patterns and chronotype naturally advances. Sex differences most life attributable to an average later chronotype among males. Figures from Wittmann et al. (2006) and Roenneberg et al. (2012), respectively.*

Since its articulation and formal quantification, SJL has been shown to be an important predictor for several negative general and mental health outcomes. In many cases SJL is thought to account for the preponderance of deleterious health outcomes that are found in late-chronotype/evening-types. Wittmann *et al.* (2006) for example demonstrated that greater SJL predicts the volume of the population that are smokers over and above the effects of late-chronotype alone. The authors propose that behaviours such as caffeine and alcohol consumption as well as smoking might represent coping strategies for individuals that are sleep deprived or socially jetlagged and thus suggest a reason for the positive correlation between these behaviours and chronotype. Similarly, when the chronotype-obesity association is examined through the same lens, reports show that SJL is a better predictor of BMI than chronotype and this association is independent of sleep deprivation (Roenneberg *et al.,* 2012). The risk associated with SJL in that study is estimated to equate to a 30% increase in the chance of being overweight/obese for each hour of SJL accrued. Parsons *et al.* (2015) corroborated the obesity-SJL association and furthermore reported that SJL was a risk factor for clinical indicators of diabetes and metabolic syndrome, a relationship which was more pronounced if accompanied by overweight. Rutters *et al.* (2014) also showed that greater SJL was associated with elevated cortisol levels, less physical activity, and an increased cardiovascular risk profile.

As well as potentially explaining the relationships between later chronotype and unhealthy behaviour, obesity, and diabetes, SJL has also been associated with psychiatric health and cognitive performance. Findings from a study conducted by Levandowski *et al.* (2011) investigating the association between late-chronotype/eveningness, and depression found that SJL was the variable most strongly correlated with depressive symptoms in a large cross-sectional sample. Additionally, academic performance measured by weekly exams among Hungarian medical students has been found to negatively correlate with SJL – an association that disappears once regular teaching schedules conclude and the exam period begins (Haraszti *et al.,* 2014). Thus irrespective of the outcome measure assessed, accumulating evidence points to the role of SJL as perhaps a mediator in the

association between chronotype and general/mental health consequences, and therefore potentially provides a framework to allow researchers to clarify the reasons why late chronotypes are at elevated risk. In practical terms it is postulated that it is the misalignment between biological and social time reflected by SJL rather than the individual phase of entrainment *per se* that heightens individual risk of illness and other associated deleterious outcomes.

1.9 Adult attention-deficit/hyperactivity disorder: a clinical picture

Attention-deficit/hyperactivity disorder (ADHD) is a widespread neuropsychiatric disorder the core symptoms of which involve excessive and impairing levels of inattention, and/or impulsivity and hyperactivity (American Psychiatric Association, 2013). ADHD is among the most common psychiatric disorders present in childhood populations where it is usually first diagnosed (Spencer, Biederman, & Mick, 2007; Kooij *et al.,* 2010). Prevalence estimates of ADHD in childhood vary considerably, however one of the largest and most recent meta-analyses, spanning multiple languages and revisions in diagnostic criteria, reports a pooled prevalence estimate of 7.2% among children and adolescents (Thomas *et al.,* 2015).

Until recently, a common oversight by clinicians was the belief that ADHD was limited to childhood with symptoms being believed to resolve in young adulthood showing little persistence into adult life (Cuffe, Moore, & McKeown, 2005; Kooij *et al.,* 2010). Several follow-up studies in children with the disorder however have shown that symptoms continue into adulthood in about two-thirds of individuals (Lara *et al.,* 2009; Lie, 1992; Gittelman *et al.,* 1985; Weiss, Hechtman, & Milroy, 1985; Mannuzza *et al.,* 1993; Mannuzza, Klein, & Addalli, 1991; Barkley *et al.,* 2002; Mannuzza, Klein, & Moulton, 2003; Rasmussen & Gillberg, 2000). Of these it is estimated that approximately 15% retain a full ADHD diagnosis by 25 years of age and a further 50% continue in partial remission in adulthood (Kim *et al.,* 2011). Currently, it is understood that the prevalence of ADHD among adults is estimated to be in the range of 2-5% (Simon *et al.,* 2009; Kooij *et al.,* 2005; Kessler *et al.,* 2005b;

Fayyad *et al.,* 2007; Wilcutt, 2012). Despite its common prevalence however the condition is often underdiagnosed and untreated in adulthood.

According to the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)* the condition may be diagnosed predominantly as an inattentive subtype, a hyperactive/impulsive subtype, or a combined presentation where both symptoms are indicated (American Psychiatric Association, 2013). Generally, childhood symptoms of inattention may manifest behaviourally as wandering off task and experiencing difficulty sustaining attention while symptoms of impulsivity or hyperactivity might involve excessive motor activity and fidgeting, interrupting others, and hasty decision making without forethought for future consequences. In adulthood presentations of the disorder the condition is mostly described as a combined type and symptoms are generally more subtle than those observed in childhood (Bell, 2010; Kooij *et al.,* 2010). In adult ADHD symptoms might be expressed as acting without thinking, quickly succumbing to boredom, inner restlessness, distractibility, and making impulsive decisions at work and in personal relationships. Underdiagnosis in adults may in part be due to age-related changes in the presentation of symptoms but also as a result of the frequent presence of other psychiatric syndromes. Co-morbidity with other psychiatric disorders is common with prevalence estimates showing high co-occurrence with anxiety disorders (47.1%), major depressive disorder (18.6%), bipolar disorder (19.4%), and substance use disorders (15.2%; Kessler et al., 2006). Symptoms may therefore often be concealed or diagnosis otherwise obscured by differential primary diagnosis.

The aetiology of ADHD is complex and incompletely understood, although there appears to be a high level of heritability of the condition, indicating a significant genetic component (Matthews *et al.,* 2014). Family studies indicate that the prevalence rate of ADHD among first degree relatives is in the range of 20 – 50% (Faraone, Biederman, & Monuteaux, 2000) and twin studies indicate a heritability of about 76% linked to additive genetic factors (Faraone *et al.,* 2005). A recent meta-analysis of genetic studies on adult ADHD revealed several main effects for the DRD4 48bp VNTR and the *rs4680* SNP in COMT both of which are implicated in

dopaminergic activity in the cortex (Bonvicini, Faraone, & Scassellati, 2016). Candidate gene studies have focused on a number of monoamine circuits in the brain with *dopamine D4 receptor gene (DRD4)*, *dopamine D5 receptor gene (DRD5)*, *dopamine transporter gene (DAT1)*, *dopamine beta-hydroxylase gene (DBH)*, as well as the *serotonergic transporter gene (5-HTT)* variants all associating with increased risk of the disorder (Li *et al.,* 2006; Faraone *et al.,* 2005). Overall these candidate gene studies are thought to account for a small degree of the variance in ADHD symptoms with a model suggesting the syndrome aetiology consists of several genetic factors of small to medium effect size as well as substantial modification from environmental factors and gene-environment interactions (Kuntsi *et al.,* 2006; Hawi *et al.,* 2015).

Consistent with candidate gene studies, dopaminergic and monoaminergic neurotransmission is thought to play a role in the disorder with patients responding well to stimulants such as methylphenidate and amphetamines which are mainstays of treatment in children (Biederman & Faraone, 2005). Among adult ADHD populations treatment with stimulant drugs has been demonstrated as successful with similar clinical benefits as those seen in childhood being observed (Koesters *et al.,* 2009; Meszaros *et al.,* 2009; Prince, 2006; Banaschewski *et al.,* 2004) however stimulant use in adults, more so than in children, is controversial among the general public and practitioners. Kooji *et al.* (2010) suggest that the traditional separation between adult and childhood psychiatry, and the previously common misconception that ADHD symptomatology abates in adulthood, presents an obstacle to the appropriate administration of treatment to adults with ADHD. Coupled with this is the fact that amphetamines, and to a lesser extent methylphenidate, may be considered classical drugs of abuse and therefore prescription among adults may be restricted by practitioners (Kollins, 2003; Volkow *et al.,* 1995) despite evidence showing that appropriate stimulant treatment does not negatively impact drug addiction or in some cases is protective against it among individuals treated for ADHD (Wilson & Levin, 2001; Biederman *et al.,* 1999; Wilens *et al.,* 2003). Consequently, because of the high propensity to underdiagnose, misdiagnose, or even to detect yet not apply adequate treatment due to substance use concerns, ADHD in adults is often not managed effectively.

The burden of ADHD to both the individual and society is high. In young adults and college students with the disorder symptoms contribute to marked impairments and underachievement in social, educational, and occupational domains (Biederman *et al.,* 2008; Faraone *et al.,* 2000). Symptoms such as impulsivity might lead to beginning new jobs or relationships without sufficient forethought and inattention contributes to lateness and disorganisation in the workplace. School and university drop-out rates are higher among adults with ADHD (Mannuzza *et al.,* 1993) and such individuals are more prone to excess days of lost role performance and injuries at work (de Graaf *et al.,* 2008; Kessler et al., 2009). Personal relationships are often interrupted and short in term due to an inability to concentrate on partners' conversation and failure to realise responsibilities (Kooij *et al.,* 2010).

Further, individuals with ADHD tend to lead an unhealthier lifestyle with increased rates of smoking, alcohol use, and drug use (Swensen *et al.,* 2004; Barkley, 2002; Ohlmeier *et al.,* 2007; Wilens *et al.,* 1995; Goossensen *et al.,* 2006; Wilens, 2007). Impulsive behaviours may manifest as a risker sexual lifestyle and a proclivity towards gambling and other behavioural addictions (Fayyad *et al.,* 2007; Breyer *et al.,* 2009). Additionally, as a result of high levels of impulsiveness and distractibility, road traffic accidents occur at a greater rate in young adults with ADHD (Fischer *et al.,* 2007; Barkley, Murphy, & Kwasnik, 1996; Barkley *et al.,* 2002; Barkley & Cox, 2007) and other more minor accidents such as dog-bites and burns have been reported as occurring more often among individuals with the condition (Swensen *et al.,* 2004).

As a result of the disorder symptoms and due to secondary outcomes such as difficulty socialising appropriately or co-occurring drug use, criminality in adulthood is predicted by an ADHD diagnosis. According to one study the prevalence of adult ADHD in a Scottish prison was almost ten times the population rate and prisoners diagnosed with ADHD had higher rates of verbal and physical aggression, assaults, and self-injury (Young *et al.,* 2009). Among those with ADHD in the community dwelling public higher rates of delinquency and other anti-social behaviours have been noted (Brasset-Grundy & Butler, 2004; Satterfield *et al.,* 1994)

and compared to normal controls individuals with ADHD are more likely to be arrested and incarcerated during their lifetime (Foley, Carlton, & Howell, 1996; Young *et al.,* 2003).

1.10 Sleep and Circadian Disturbances in ADHD

Over the past number of years a vast literature has accumulated pointing to the involvement of perturbed sleep and a circadian rhythm dysfunction in ADHD. According to Schredl *et al.* (2007) insomnia among adults with ADHD is estimated at 27% while actigraphy studies report that sleep disturbances occur in approximately 83% of adults with the disorder (Sobanski *et al.,* 2008; Coogan *et al.,* 2016). Decreased sleep efficiency and a lengthening of the sleep onset latency are among the actigraphy ascertained pictures of sleep-wake patterns emerging in adults diagnosed with ADHD or ADHD and comorbid sleep onset insomnia (Boonstra *et al.,* 2007; Van Veen *et al.,* 2010). Similarly, PSG studies consistently show reductions in sleep efficiency and in the percentage of rapid-eye-movement (REM) or 'paradoxical' sleep as well as increases in the number of awakenings after sleep onset in ADHD (Dagan *et al.,* 1997; Picchietti *et al.,* 1998; O'Brien *et al.,* 2003; Sobanski *et al.,* 2008). Furthermore, ADHD is associated with parasomnias and movement disorders in sleep such as periodic limb movement and restless legs syndrome (Walters *et al.,* 2008). The extent to which such sleep disturbances and increases in motor activity/awakenings might represent a general feature of increased arousal underscoring the disorder or wether these features constitude risk factors for the disorder, and might therefore be considered putative causal factors, is presently unclear.

Given that in clinical and normative populations, sleep disruptions negatively exacerbate symptoms such as inattention and impulsively (Corkum, Tannock, & Moldofsky, 1998; Fallone *et al.,* 2001) as well as general cognitive function (Babkoff *et al.,* 1991; Bearpark & Michie, 1987), left untreated symptoms of sleep disturbance in ADHD are expected to have a significant impact on core symptom severity and

daytime functioning in individuals diagnosed with the disorder. Indeed, this is consistent with findings from Mahajan *et al.* (2010) who describe a significant association between symptoms of hyperactivity and impulsivity and sleep quality among adults with ADHD. Other findings suggest that sleep disturbances in ADHD might differentially associate with disorder sub-types with associations being present between hyperactive/impulsive subtype and increased sleep duration, while predominantly inattentive and combined types show increased hypersomnia (daytime sleepiness, napping etc.), insomnia, and snoring (Chiang *et al.,* 2010).

Among the most frequently reported sleep related differences associated with ADHD is the presence of sleep onset insomnia (SOI) which itself is a hallmark of the circadian rhythm driven sleep disorder DSPD (Lack & Wright, 2007; Micic *et al.,* 2016). Numerous studies point to a high prevalence of SOI in ADHD among adults and children ascertained by actigraphy and/or sleep diaries (Van der Heijden *et al.,* 2005b; Van Veen *et al.,* 2010; Hvolby, Jorgensen, & Bilenberg, 2008; Hoebert *et al.,* 2009). Similarly, cross-sectional and retrospective studies have pointed to a high degree of DSPD co-occurring with ADHD or ADHD-like symptoms among undiagnosed individuals (Chiang *et al.,* 2010; Sivertsen *et al.,* 2015; Hysing *et al.,* 2016). While some studies suggest that increased SOI and later bedtimes may be a by-product of methylphenidate treatment (Boonstra *et al.,* 2007; Ironside, Davidson, & Corkum, 2010) other reports, such as that produced by Gruber *et al.,* (2000) suggest a high degree of sleep onset time variability among children with the disorder – reflecting perhaps a deficit in the sleep/wake regulatory aspect of the circadian pacemaker in ADHD.

When the focus is applied to the circadian driven aspects of behaviour opposed to difficulties maintaining sleep and wakefulness *per se* the argument for a circadian dimension as part of the ADHD pathophysiology becomes even more compelling. Studies which examine chronotype (using the MCTQ), or circadian typology (using the MEQ and similar derivatives) - both estimates of behaviourally manifested circadian pacemaker function and system entrainment - have been employed in investigating ADHD. Studies involving adult populations diagnosed with ADHD

have consistently revealed a preponderance of late chronotypes and high eveningness scores (Ryback *et al.,* 2007; Baird *et al.,* 2012; Vogel *et al.,* 2015; Kooij & Bijlenga, 2014; Bijlenga *et al.,* 2013a; Gruber *et al.,* 2012). Furthermore, in non-clinical samples these results have been recapitulated with the same instruments applied to 'ADHD-likely' individuals (suspected of having ADHD or showing high pre-clinical symptoms) who are found to show an enhanced diurnal preference for evenings. Moreover, in each of these reports inattention more so than impulsivity is found to strongly correlate with greater eveningness scores (Susman *et al.,* 2007; Caci, Bouchez, & Bayle, 2009; Bae *et al.,* 2010; Voinescu, Szentagotai, & David, 2012).

Coupled with these findings are data from observational studies which indicate pronounced diurnal variations in behaviour in ADHD relative to controls. Studies have mainly focused on classroom behaviour in children with ADHD with several reaching the same consensus, finding stronger increases in hyperactive/impulsive behaviour and poorer attention in the evenings relative to controls (Antrop, Roeyers, & De Baecke, 2005; Imeraj *et al.,* 2012; Tsujii *et al.,* 2007; Zagar & Bowers, 1983). Given that several cognitive parameters including sustained attention/vigilance (Cajochen *et al.,* 1999; Wright *et al.,* 2002), alertness (Valdez *et al.,* 2005), and arousal (Kraemer *et al.,* 2000) all show distinct circadian patterns (see Schmidt *et al.,* 2007 for a review) it is conceivable that interactions between diagnosis and time-of-day effects might produce a mismatch between behaviour and context that therefore exacerbate adult symptoms of the disorder as well.

Apart from self-report measures of circadian preference and an examination of diurnal rhythms of performance, functional assessments of circadian rhythm parameters provide the most overwhelming evidence of an altered biological clock function in ADHD. Consistent with the aforementioned findings reviewed here, actigraphy studies in ADHD volunteers have indicated significant delays in the rest-activity cycle (Van Veen *et al.,* 2010; Gamble *et al.,* 2013) as well as increased activity amplitude in the later portion of the day (Dane *et al.,* 2000). Furthermore, the study from Gamble and colleagues (2013) found that the extent of this phase delay was positively correlated with symptom severity and predictive modelling data from

Faedda *et al.* (2016) suggest that differences in circadian phase and relative amplitude of the rest-activity rhythm may be specifically characteristic of ADHD as they differentiate the condition from other psychiatric disorders that feature circadian parameter differences (*i.e.* bipolar disorder).

Studies which examine daily endocrine rhythms and physiological functions also support significant circadian phase delays accompanying the disorder. Concerning the circadian hormone melatonin, numerous studies using DLMO as a phase marker of the endogenous circadian clock output have reported significant delays in ADHD patients relative to controls (Van Veen *et al.,* 2010; Van der Heijden *et al.,* 2005b, 2006; Bijlenga *et al.,* 2013b). Evidence also points to genetic variation in the melatonin biosynthesis and downstream binding pathways in individuals with ADHD contributing to a melatonin signalling deficiency phenotype in the disorder (Chaste *et al.,* 2011). Such anomalies occurring in ADHD might be underpinned by aberrant pineal function as suggested by a recent anatomical finding of lower pineal gland volume in a cohort of adults with ADHD (Bumb *et al.,* 2016). Other studies which have noted blunted melatonin secretion, such as in Baird *et al.* (2012), suggest that increased exposure to light at night resulting in acute suppression of the hormone may have a role to play. Furthermore, several positive clinical outcomes have been noted, mainly in the domain of improving sleep quality and reducing SOI, after timed treatment of melatonin is applied to patients with ADHD (Tjon Pian Gi *et al.,* 2003; Weiss *et al.,* 2006; Van der Heijden *et al.,* 2007) and one report describing improvements in symptom severity after application of morning bright light therapy has been noted also (Gruber, Grizenko, & Joober, 2007) again highlighting the circadian basis of the disorder.

Other manners of assaying circadian variations in endocrine parameters have focused on examining cortisol rhythms in ADHD. Both phase delays (Baird *et al.,* 2012) and lower amplitudes (Isaksson *et al.,* 2015) in the diurnal cortisol rhythm have been found in individuals with the disorder. Numerous studies however have failed to find any differences in cortisol pattern between ADHD and normal control subjects however (Hirvivkoski *et al.,* 2009; Personen *et al.* 2011; Imeraj *et al.,* 2012).

Reasons for this may include the method of assessment (*i.e.* salivary vs. plasma), amount time-points used throughout the day, and indeed the manner in which cortisol is secreted in a pulsatile fashion over the 24 h period (Young, Abelson, & Lightman, 2004). Other measures of physiological arousal such as heart rate for example have been shown differences in circadian variation between ADHD and control subjects also (Imeraj *et al.,* 2011; Buchorn *et al.,* 2012).

Candidate gene studies have also examined to what extent common mutations in circadian related genes are related to ADHD. The most frequently examined association concerns the *CLOCK* T3111C SNP where numerous studies have reported a transmission bias of the T-allele associating with ADHD or ADHD-like symptomology in healthy subjects (Kissling *et al.,* 2008; Xu *et al.,* 2010; Jeong *et al.,* 2014). Controversially however, another study conducted by Cao *et al.* (2012) reports instead that the C-allele was the risky variant associated with ADHD. Additionally, other reports have linked reward circuit function to a SNP in the *PER2* gene (Forbes *et al.,* 2012) and neurocognitive function in adults to variations in the previously described *PER3* VNTR (Gonzalez-Giraldo *et al.,* 2015) – both outcomes related to being putative endophenotypes of ADHD. Concerning the rhythmic expression of circadian clock genes *in vivo,* Baird *et al.* (2012) was the first to examine expression of BMAL1 and PER2 mRNA derived from buccal mucosa in individuals with ADHD. Compared to healthy controls the authors found that rhythmic expression of these canonical circadian gene products were completely ablated revealed a potential molecular basis to circadian rhythm disturbance in ADHD.

1.11 Conceptual framework for understanding the pathophysiological contribution of sleep and circadian rhythm disturbances to the symptomatology of ADHD

Considering the multiple associations of disturbances in sleep and abnormal circadian functioning with ADHD, interesting questions emerge pertaining to how a better characterisation these system deficits may enhance our understanding of the aetiopathology of the disorder. Ascertaining to what extent sleep and circadian

rhythm disruption are symptomatic features of mental illnesses compared to what extent they might contribute to symptom severity either by exacerbating existing symptoms or precipitating *de novo* symptom liability has been discussed previously (Foster *et al.,* 2013; Wulff *et al.,* 2010). In several severe psychiatric conditions whose psychopathologies involve impairments in cognition and affect, circadian rhythm abnormalities feature extensively. Such disorders include schizophrenia (Wulff *et al.,* 2012), major depressive disorder (Wirz-Justice *et al.,* 2006), and bipolar disorder (Yang *et al.,* 2009), where circadian rhythm disturbances relating to altered phase and amplitude are frequently noted and sleep duration and quality is severely compromised (Wulff *et al.,* 2010).

In a model proposed by Foster *et al.* (2013) it is purported that psychiatric illnesses and sleep/circadian disruption may share common overlapping mechanisms (Figure 1.11, p. 55). It is hypothesised that the same assembly of neural circuits that affect neurotransmitter systems implicated in psychiatric illness have a parallel effect upon the circadian and homeostatic regulation of the sleep/wake cycle. In both schizophrenia and bipolar disorder for example several putative genetic risk factors for these diseases are also elements found within the molecular clock TTFL, variants of which lead to perturbations of the sleep/wake cycle (Lamont *et al.,* 2010; Roybal *et al.,* 2007; Mukherjee *et al.,* 2010). Furthermore, in animal models with alerted circadian clocks, phenotypes resembling mania are recapitulated such as in the *Clock* mutant mouse, whose behaviours are subsequently rescued after administration of lithium, and it is argued that this case may be analogous to the therapeutic effects seen in clinical populations (Roybal *et al.,* 2007; Landgraf, McCarthy, & Welsh, 2014).

The overlap model suggests also that the behaviours and symptoms associated with psychiatric illness and those that involve the circadian clock are mutually modified by several additional feed-forward and feed-back loops acting on each other (Figure 1.11 overleaf). Acute manifestations of mania and psychosis which result in severe psychological trauma may have a feed-forward impact upon patients sleep and compounded by neuroleptic medication use, substance use, and atypical

social patterns, a disordered circadian pattern of behaviour and abnormal sleep-wake cycle persists. Moreover, disruptions to sleep and circadian misalignment may in turn feed-back to worsen pre-existing psychiatric symptoms and pre-dispose individuals to other comorbidities. Sleep and circadian disturbances also feature highly among many prodromal manifestations of severe psychiatric illnesses and worsen prior to full diagnosis being made (Tijssen *et al.*, 2010; Ritter *et al.*, 2011; Mattai *et al.*, 2006) suggesting that alterations to the circadian clock may precede primary psychopathologies.

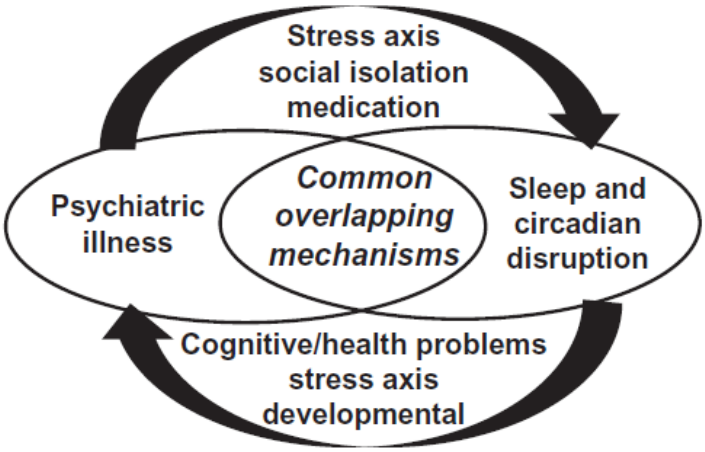

Figure 1.11Possible ways in which sleep and circadian rhythm disturbances underpin psychiatric disorders

It is suggested that psychiatric illnesses and sleep and circadian disruption share mechanistic overlap. Additionally, symptoms of mental illness may interfere with sleep and circadian organisation of the sleep/wake cycle, while sleep and circadian disturbances can feedback to exacerbate such symptoms. Figure from Foster et al. (2013).

Applying this model to the clinical presentation of ADHD in adults makes for a compelling argument. Overlapping mechanisms such as risk predisposing genetic variation, altered molecular clock protein expression and endocrine secretion (reviewed in the previous section) point to a similar aetiological background underpinning both circadian rhythm sleep disorders and ADHD. Furthermore, core

symptoms of ADHD such as impulsivity/hyperactivity and sensitivity to reward are likely contributory factors where SOI and DSPD-like symptoms are concerned. Individual excitability or state-regulation deficits might lead to a delay in sleep onset or due to motivational factors individuals might prefer to stay up late foregoing sleep in favour of immediate reinforcement from the environment. Additionally, pharmacotherpeutic drugs used to treat ADHD such as methylphenidate have been shown to delay the sleep/wake rhythm promoting SOI (Antle *et al.,* 2012) and the non-stimulant drug atomoxetine has been shown to cause altered photic induction of genetic factors in SCN of mice (O'Keefe, Thome, & Coogan, 2012). From a predispositional perspective, circadian rhythm disturbances and sleep restriction are associated with worse symptoms of inattention and impulsivity in ADHD (Baird *et al.,* 2011; Chiang *et al.,* 2010; Mahajan *et al.,* 2010).

In order to attempt to further understand and develop the theoretical basis of the sleep and circadian component associated with ADHD it is important to highlight a number of conceptual positions regarding both the biological clock and the clinical disorder itself. According to the two-process-model of sleep regulation, both circadian (C) and homeostatic (S) drives to sleep are separable mechanisms representing both the homeostatic process and the circadian timing process of sleep regulation (Borbely, 1982). Similarly, this model has been applied to estimate human performance on a number of factors. When examining neurobehavioural or neurocognitive processes and the influences which act upon them it is understood that the circadian system influences cognition and behaviour in both a sleep-independent manner (*i.e.* a primary influence orchestrated by the biological rhythm of the circadian clock) and also through a secondary mechanism involving sleep-modulation and an interaction with the homeostatic drive towards sleep (reviewed in Schmidt et al, 2007). Consequently, this may give rise to a case where a symptom or behaviour related to ADHD might be accounted for by a restriction/deprivation in sleep or a poor quality of sleep while the circadian clock system operates unperturbed. Conversely, an individual might be well rested and feel awake after an adequate duration of sleep though because of an abnormal phase or amplitude in the underlying circadian rhythm, as well as the discordance between rest-activity cycles

determined by the social clock reflected through social jetlag, deficits in neurobehavioral function and cognition might emerge independent of tiredness or fatigue.

Concerning symptoms of ADHD themselves, the traditional clinical view of ADHD involves two qualitatively different behavioural deficits *i.e.* inattention and hyperactivity/impulsivity (Barkely, 1997). It has been argued that the symptomatology of ADHD however might be dissociated and that the separation of inattentive symptoms from those involving impulsivity may lead to a better understanding of disorder epiphenomena (Ustün, 2007). Such a theoretical approach is partially reflected in the DSM method of classifying ADHD separating the condition into two predominant symptom-expressing subtypes or a combined type of the disorder. Barkley (1997) argues however that it is doubtful that the aetiopathological background of the 'predominantly inattentive subtype' overlaps with the symptoms of impulsivity found in the 'hyperactive-impulsive subtype'. Furthermore, it is argued that the combined type of the disorder is not so straightforward a construct insofar as it includes both manifestations of the disorder, rather the attention deficit experienced in the inattentive subtype is thought to be different from the attention deficit experienced in the combined diagnosis (Barkley, DuPaul, & McMurray, 1990). Moreover, considering impulsivity as its own component of the disorder, several lines of research have suggested that impulsivity is not a unitary construct either but rather is better described as a multidimensional trait made up of distinct behavioural phenomena with their own biological bases (see Winstanley, Eagle, & Robbins, 2006 for a review). As a result, the extent to which ADHD as a categorical outcome can be utilised in experiments designed to probe the contributions of risk factors such as interference of sleep and circadian rhythm disturbance to severity of the condition is limited. Therefore, with respect to ADHD, sleep and circadian rhythm research on the condition would benefit from interrogating the contributions of both factors on the separated symptomatology of the disorder *i.e.* by treating impulsivity and attention deficit, and their included neurocognitive sequelae as independent components of a broader diagnostic phenomenon.

The ultimate conceptual position concerning ADHD and its study to be outlined here is the nature in which its symptoms are manifested among the population. The reliance on traditional diagnostic models, whose objective is to nosologically separate psychiatric phenomena into identifiable conditions which represent targets for empirical research has been the subject of recent critical evaluation (Caspi *et al.,* 2014; Lahey *et al.,* 2012). While diagnostic manuals such as the currently ascendant DSM-5 edition or the *International Statistical Classification of Diseases and Related Health Problems – tenth revision* (ICD-10; World Health Organisation, 2010) represent the state of the art in terms of identifying and diagnosing mental illnesses such as ADHD these instruments might be better viewed as taxonomical rather than prescriptive in nature. The suggestion that psychiatric disorders have precise diagnostic cut-offs and can be distinguished from the broader population in terms of discrete clinical presentations is often flawed for models utilised in scientific research.

In the case of ADHD especially, the psychopathology of the disorder is perhaps better understood dimensionally with symptoms of inattention and impulsivity being distributed continuously in a Gaussian manner among the general population (Rodriguez *et al.,* 2007; Martin *et al.,* 2014). It has been postulated that ADHD might be viewed as an extreme manifestation of such traits and behaviours. Given the high degree of heritability of the disorder this view is further spoken to by findings which implicate the same common genetic components with the categorical disorder with those that are found to influence hyperactive-impulsive and attention traits in the general population (Levy *et al.,* 1997; Martin *et al.,* 2004). ADHD-like traits likely exist among normative populations with varying degrees of penetrance sometimes resulting in the emergence of the condition while oftentimes traits remain undetected at the subclinical level.

Furthermore, the use of psychometric scales or objectively assessed neurobehavioural parameters to probe for ADHD-like characteristics in healthy individuals is easily translatable for clinical use. Among the neuropsychological tasks which may be administered an important manner of detecting precursors to symptomatological risks of ADHD resides in the quantification of intermediate

constructs or endophenotypes (Castellanos & Tannock, 2002). Endophenotypes are heritable quantifiable traits that index an individual's biological or behavioural liability to manifest *observable* symptoms of the disorder in question (Gottesman & Gould, 2003). In essence, an endophenotype is not a risk factor to a condition but rather a latent manifestation of the *'full blown'* illness (Lenzenweger, 2013). Numerous behavioural endophenotypes have been suggested for ADHD such as a reduced inhibitory function, reaction time variability, altered sensitivity to reward, shortened delay gradients, and deficits in temporal processing (Castellanos & Tannock, 2002; Henríquez-Henríquez *et al.,* 2014). A closer inspection of these neurobehavioural underpinnings of symptom risk is likely to enhance our knowledge of the pathophysiology of ADHD and the extent to which such intermediate constructs are modified by sleep and circadian rhythm disturbances. This approach is a promising avenue of inquiry, especially given the overlap in genetic elements that are involved in the circadian system and those that are associated with ADHD. In particular given that candidate gene approaches have found associations with common variants in circadian clock genes and ADHD, and discrete diagnoses themselves are poor phenotypes for the quantification genetic association (see Meyer-Lindenberg & Weinberger, 2006), the strategy of interpreting instead separable dimensional traits of the disorder and intermediate phenotypes underlying symptom liability that are grounded in behavioural neuroscience is likely to be a more revealing endeavour.

1.12 Introduction to the current programme of research

The objective of this research thesis is to clarify the role of sleep and circadian rhythm disturbances in the manifestation of ADHD-like symptoms in the general population in an attempt to better understand the aetiopathology of the disorder. Specifically, domains of impulsivity, inattention, and cognitive impairment, will be assessed with respect to previously reported findings in the literature which point to circadian rhythm involvement with these traits. Furthermore, objective assessment of neuropsychological indictors or putative behavioural endophenotypes established in

neuroscience, that are associated with symptom liability are utilised to enhance our understanding of behavioural and genetic circadian clock-related risk factors. We applied a combined exploratory cross-sectional study design, neurobehavioural and actigraphic experimental design, gene association, and brain imaging approaches in order to exhaustively address this research question. This work is divided into three experiments described in five chapters addressing separately themed research questions.

Experiment One (Chapter 2, page 62) addresses the previously described trend among studies pointing to an evening-oriented diurnal preference being present in ADHD and personality traits that are similar to ADHD-like symptoms. We attempt to clarify this association by employing the MCTQ method of measuring mid-sleep on free days as measure of chronotype which is used as an estimate of the circadian phase of entrainment. Further, we assess to what degree sleep quality, sleep restriction and the previously uninvestigated social jetlag concept, associate with ADHD-like traits. We hypothesise that later chronotype, reduced sleep duration, poor sleep quality, and social jetlag would be associated with more severe self-reported ADHD symptoms, dimensional impulsivity, and cognitive failures. This exploratory cross-sectional study utilises a large sample from the general population leading to data-driven experimental approaches to be implemented in further studies.

Experiment Two was performed in another large normative cohort from which objective behavioural data and biological material for genotyping analyses were derived. The experiment is divided into three separate arms of inquiry, each addressing a specific research question. **Experiment Two Part I** (Chapter 3, page 88) uses a data driven approach provided by the first experiment to determine whether diurnal preference, sleep quality, and recurring circadian misalignment captured by social jetlag are associated with objective behavioural indicators of ADHD symptom liability. We utilised two common neuropsychological tests, the Conner's Continuous Performance Test and the Iowa Gambling Task, to assess sustained attention, response inhibition, reaction time performance, and risky decision making. Given

that speed and variability of reaction time are among the most frequently described neurobehavioural correlates of ADHD in clinical populations, we employed an ex-Gaussian analysis to decompose behavioural responding into specific domains of impulsiveness and inattention. We hypothesise that, consistent with results of experiment one, sleep quality and social jetlag would be the most important predictors of neurobehavioural performance.

Experiment Three (Chapter 4, page 93) comprises preliminary results from an electroencephalography study in which performance on two neurobehavioural tasks addressing sustained attention and response inhibition are assessed. Guided by Continuous Performance Task results from the second study showing performance deficits between social jetlag groups we wished to investigate if comparisons between low and high social jetlag groups revealed different patterns of activity potentials during Go and No-Go related trials. We explored the relations between different event-related potentials (ERPs) that have been previously linked to impulsivity and attention deficit in ADHD between individuals experiencing substantial circadian misalignment and those that did not. Furthermore, we examined whether task condition moderated levels of electrophysiological activity in these individuals and performance in these tasks.

Experiment Two Part II (Chapter 5, page 166) utilises actigraphy derived measures of sleep quality and circadian rhythm function in order to objectively assess the contribution of sleep and circadian rhythm disturbances to symptoms of impulsivity and attention deficit. Similar to the goal of Part I where objective behavioural measures are used to provide a clearer picture than is afforded by psychometric testing, the actigraphy component of this research programme brings objective rigour to self-reported measures of sleep quality and chronotype and furthermore allows for probing of circadian rhythm characteristics that are not readily amenable to self-report (*e.g.* circadian rhythm amplitude, daily variability and stability, deviation of τ from 24 h). We hypothesise that later phase of entrainment, less robust circadian rhythm amplitude, a deviation in circadian rhythm period, and more variable and less stable entrainment patterns, would be

associated with worsened symptoms of ADHD and higher levels of trait impulsivity. Furthermore, indicators of poor sleep quality such as sleep onset insomnia, nocturnal wakefulness, and sleep restriction were hypothesised to associate with symptom risk also.

Experiment Two Part III (Chapter 6, page 207) consists of a candidate gene association study in which common variants in the *CLOCK, PER2,* and *PER3* genes, which have been previously associated with both later diurnal preference and risk of ADHD, are investigated. Furthermore, relationships between extreme diurnal preference and reward circuit function in less well studied polymorphisms in other canonical clock components *PER1* and *PER2* addressed also. In this study we attempt to replicate previous findings which link these genes to circadian clock function and ADHD using measures of chronotype rather than diurnal preference, and a dimensional approach to ADHD symptomatology rather than discrete categorical diagnosis. In addition, we hypothesise that if genetic associations are present they may be moderated by factors such as sleep duration, social jetlag, and sex.

Chapter 2

Cross-sectional evaluation of sleep quality, chronotype, and social jetlag, and their relations to symptoms of impulsivity and inattention among the general adult population

The author would like to thank Dr. Bodgan Voinescu for his kind assistance translating questionnaires into Romanian and offering to disseminate survey among collaborating institutions in Romania

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Abstract

Several lines of evidence implicating associations between individual differences in the circadian typology trait with common neuropsychiatric disorders exist. Numerous studies have found an increased proclivity towards eveningness in cases of adult ADHD though a precise reason for this relationship has not been clarified. Given that evening types/late chronotypes experience a substantial degree of sleep restriction, impaired sleep quality, and social jetlag, we conducted an exploratory analysis to investigate whether these factors measured by the MCTQ and PSQI scales predicted symptom risk. The current study examines ADHD symptoms, impulsivity, cognitive failures, sleep quality and chronotype in a cohort of healthy young adults (n = 396). Results show significant, small magnitude associations between the mid-point of sleep on free days, social jetlag, and ADHD symptoms and trait impulsivity. Similarly, poor sleep quality was associated with ADHD symptoms, trait impulsivity, and cognitive failures. Group-wise approaches revealed that later self-reported diurnal preference on the MCTQ was associated with increased ADHD symptoms and poor sleep quality with an inspection of groups stratified by degrees of ADHD symptom risk also showing that ADHD symptom severity was associated with greater social jetlag and poorer sleep quality. Stepwise multiple linear regressions indicated that, when controlling for age and sex, social jetlag and sleep quality but not mid-sleep on free days were significant predictors of ADHD symptomatology and impulsivity. The results indicate that social jetlag and sleep quality may be important factors to consider when exploring chronotype associations with ADHD. Furthermore, social jetlag and impaired sleep quality might be factors which contribute to heightened symptom risk which previous studies focused on other measures of circadian typology in humans have not yet addressed.

2.1 Introduction

Among the several associations between the circadian clock and ADHD that have been described, one of the most frequently reported pertains to the subject of an increased diurnal preference towards eveningness. Utilising items which examine circadian typology such as the MEQ and CSM, numerous studies involving individuals diagnosed with ADHD have found that 'eveningness' is a trait associated with the disorder (Ryback et al., 2007; Baird et al., 2012; Kooij & Bijlenga, 2014). Similar trends have also been observed in non-clinical samples where symptoms of ADHD are repeatedly found to correlate with a preference biased towards eveningness (Caci, *et al.,* 2009; Bae *et al.,* 2010; Voinescu, *et al.* 2012).

While the morningness/eveningness continuum is a valid approach for estimating individual differences in the underlying circadian clock phase and is believed to be in part a behavioural manifestation of the internal clocks operation (and therefore in part biologically determined construct), much of the work investigating circadian typology treats morningness-eveningness in terms similar to that of a personality trait. As such much of the work has focused on its relatedness to other domains of personality. Evening diurnal preference for example has been linked with personality domains such as extraversion and psychoticism among studies which address research questions associated with personality and individual differences (Langford & Glendon, 2002; Tankova, Adan, & Buela-Casal, 1994). Consistent with the reports from ADHD and ADHD-like cohorts, several studies from the personality literature have shown that evening types display higher levels of impulsiveness and dysfunctional impulsivity than morning types (Adan, Natale, Caci, & Prat, 2010) as well as increased risk-taking, novelty seeking, and sensation seeking behaviour (Tonetti *et al.,* 2010; Kilgore, 2007; Caci, Robert, & Boyer, 2004; Prat & Adan, 2013; Muro, Gomà-i-Freixanet, & Adan, 2012; Ponzi, Wilson, & Maestripieri, 2014). By the same token morningness is repeatedly shown to correlate with conscientiousness, agreeableness, persistence, and cooperation with others (Tsaousis, 2010; Diaz-Morales, 2007; Randler & Saliger, 2011), traits which are seemingly oppositional

dimensions to ADHD-like features such as risky decision making and impulsive behaviour.

While several of the aforementioned studies suggest that an evening preference circadian typology and traits such as impulsivity and inattention may be co-precipitating phenotypes, a specific reason for this relationship remains unclear. Insofar as postulating a theoretical basis for this association between symptoms and circadian clock function a number of factors exist that are not adequately captured by the traditional morningness-eveningness expression of the circadian phenotype. Sleep deficit and poor sleep quality for example are co-varying factors that are related to eveningnness and a later chronotype (de Lima *et al.,* 2010; Rique *et al.,* 2014; Roenneberg *et al.,* 2003) and actigraphic studies in ADHD have demonstrated the presence of many indicators of poor sleep quality such as chronic SOI and fewer uninterrupted bouts of sleep (Boonstra *et al.,* 2007; Van Veen *et al.,* 2010). Sleep disturbance in turn has been observed to lead to worsened symptoms of attention deficit and hyperactivity among both non-clinical groups (Gau *et al.,* 2007; Kass *et al.,* 2003) and in individuals with ADHD (Mahajan *et al.,* 2010; Chiang *et al.* 2010) providing support perhaps for the involvement of a sleep disturbance component potentially mediating the links between circadian typology and the aforementioned behavioural outcomes.

Furthermore, due to the psychometric nature in which diurnal preference is measured it is difficult to extract a tangible estimation of the underlying circadian phase expressed in temporal terms using the MEQ (see Roenneberg, 2015). Therefore in order to ascertain whether a delayed pattern of circadian entrainment is a factor which intrinsically influences symptoms of ADHD, a measure that approaches chronotype as an expression of the circadian phase of entrainment, expressed in local clock time, is required (Levandovski, Sasso, & Hidalgo, 2013). The MCTQ which estimates chronotype as the mid-point of sleep on free days (MSF_{sc}), according to its authors, allows for a closer inspection of behavioural rhythms of sleep/wake timing rather than psychological preference towards one circadian typology over another (Roenneberg *et al.,* 2007; Ronneberg, 2015).

Importantly, the MCTQ may be used to examine another factor potentially mediating the relationship between eveningness and ADHD symptoms. As the MCTQ examines the discrepancies between socially imposed sleep patterns on workdays and patterns of behaviour on free days that are thought to be more biologically determined in nature it can be used to compute the phenomena of so called social jetlag (SJL) that individuals accrue throughout the workweek (Wittmann *et al.,* 2006). Several studies have investigated the degree to which SJL may predict many of the negative physical and mental health outcomes traditionally associated with evening typology/later chronotype. In these studies, it has been demonstrated that the recurring circadian misalignment typified by SJL rather than circadian typology or chronotype *per se* is in fact an important risk factor for conditions such as obesity, metabolic syndrome, and depression (Roenneberg *et al.,* 2012; Parsons *et al.,* 2015; Levandovski *et al.,* 2011).

As the psychopathological traits associated with adult ADHD exist upon a normally distributed continuum among the general population (Rodriguez *et al.,* 2007; Martin *et al.,* 2014), it has been suggested that a dimensional approach to understanding symptoms may be more revealing for clinical and research purposes than categorical approaches to diagnosis (Hyman, 2010; Das *et al.,* 2012). Evidence furthermore indicates that individuals with traits/symptoms of the disorder that never meet the diagnostic threshold are still significantly impaired, perhaps expressing a milder sub-clinical variant of the disorder (Faraone *et al.,* 2006a, 2006b). Validated instruments for detecting symptom risk of ADHD in undiagnosed adults exist such as the Adult ADHD Self-Report Scale (ASRS; Kessler *et al.,* 2005a, 2007) which has been employed previously in population based studies (Das *et al.,* 2012; Estévez *et al.,* 2014) and in research specifically examining sleep and circadian rhythm involvement in the disorder (Voinescu *et al,.* 2012). Scales which approach impulsivity as a multidimensional construct such as the Barratt's Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995) are commonly utilised in population based studies as well as in ADHD cohorts (Malloy-Diniz *et al.,* 2007). Similarly, the Cognitive Failures Questionnaires (CFQ; Broadbent *et al.,* 1982) is a frequently used

instrument that probes for common errors in cognition in the general population and clinical populations with adult ADHD (Gray *et al.*, 2015).

The objective of this study is to attempt to clarify the role of circadian rhythm variation and its association with symptoms of adult ADHD in a general, non-clinical population. Here we conduct an exploratory cross-sectional analysis in order to identify targets for future ADHD and circadian rhythm related research. Specifically, we address psychometrically assessed domains of impulsivity and inattention (ASRS, BIS), and cognitive deficit (CFQ) among the general population. We hypothesise that chronotype, that is how early or late an individual's phase of entrainment, and the day-to-day misalignment in rhythms of activity captured by the social jetlag metric, may represent important indicators of symptom risk. Closely linked to this question we draw our attention to individual differences in sleep such as sleep duration and sleep quality which may also cause or exacerbate symptoms of this kind. As a result we aim to expand upon studies limited to investigating the relationship between circadian typology and ADHD and also consider differences in circadian phenotype, sleep duration, and sleep quality in this research focus.

2.2 Materials and methods

Participants

Participants were recruited among undergraduate and master's degree students enrolled in courses at the collaborating institutions, Maynooth University, Ireland and the Faculties of Psychology at universities in Cluj-Napoca, Timișoara, and Bucharest, Romania. The combined cohort consisted of a final sample of 396 respondents (73% female) with a mean age of 24.78 years (*SD* = 8.01, range: 18 – 58). Data were derived from an initial sample of 492 (*n* = 263 recruited in Ireland; *n* = 229 recruited in Romania) from which participants were excluded after having reported shift-work (*n* = 43), psychological/neurological disorder (*n* = 21), diabetes/autoimmune disorder (*n* = 10), or a sleep disorder (*n* = 3). Further to these exclusion criteria an additional nine respondents were removed for having incomplete questionnaire data and another nine removed due to reporting extraordinary atypical sleep durations (*i.e.* workday or free day sleep duration > 13 h or < 3 h; see Roenneberg *et al.,* 2004). All participants gave their electronic informed consent (Appedix A) before participating in this study and were informed that all data collected would be stored anonymously. Participation was voluntary and unpaid. This study was approved by each universities institutional ethical review boards.

Self-reported measures

Adult ADHD Self-Report Scale

The Adult ADHD Self-Report Scale version 1.1 (ASRS) was the principle measure used to examine adult ADHD symptomatology (Appendix B). The ASRS is the official instrument of the World Health Organisation for screening likely undiagnosed cases of adult ADHD (Kessler *et al.,* 2005a, 2007). The questionnaire consists of eighteen questions based on each of the diagnostic criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition* (*DSM-IV*; American Psychiatric Association, 1994). The ASRS is sub-divided into a six-item

screener derived based on its optimal concordance with clinical classification and is estimated to have a sensitivity of 68.7%, a specificity of 99.5%, and a total classification accuracy of 97.9% based on normative survey data (Kessler *et al.,* 2005a). The 6-item screener (Part-A) is recommended over the full questionnaire for case finding purposes (Kessler *et al.,* 2005a, 2007) and therefore was used as our principle measure of ADHD symptomatology. ASRS results were interpreted both as a continuous scale (score range 0-24) and as nominal data according the stratification protocol outlined in Kessler *et al.* (2007). Briefly, based on their scores respondents were assigned to the following four strata: 0-9 "stratum I", 10-13 "stratum II", 14-17 "stratum III", and 18-24 "stratum IV". A score of 14 and above (strata III and IV) indicated a likely case of ADHD.

Barratt's Impulsiveness Scale

The Barratt's Impulsiveness Scale - 11 (BIS) was used to assess general trait impulsivity (Appendix C). The 30-item self-report scale conceptualises impulsiveness as a multidimensional construct which may be separated into three second order factors each measuring different facets of impulsivity (Patton *et al.,* 1995). Likelihood of each statement presented is endorsed on a 4-point Likert type scale ranging from "Rarely/Never" to "Almost Always/Always". We report the total BIS score of participants in this study. An Attentional Impulsiveness subscale addresses the inability to focus attention or concentrate (e.g. "I often have extraneous thoughts when thinking"); a Motor Impulsiveness subscale addresses a tendency to commit action without thinking (e.g. "I act on the spur of the moment"); and a Non-Planning Impulsiveness subscale addresses a lack of forethought and future time perspective (e.g. "I am more interested in the present than the future"). Eleven of the items on the questionnaire are reverse ordered. The sum total score of the 30-item scale and each of the subscales scores were used as self-report measures of impulsivity. It has been shown that clinical adult ADHD populations show enhanced impulsivity on all factors of the BIS-11 (Malloy-Diniz *et al.*, 2007).

Cognitive Failures Questionnaire

The Cognitive Failures Questionnaire (CFQ) is a 25-item questionnaire designed to evaluate participants' propensity towards mistakes or errors in cognition (Broadbent et al., 1982). The scale measures everyday lapses in attention, memory, and motor function. Participants were asked to rate on a 5-point Likert scale the frequency to which minor failures in cognitive function were experienced by them over the past 6 months. The scale ranges from (0 = "Never") to (4 = "Very often"). Examples of questions include "Do you find you forget why you went from one part of the house to the other?", "Do you find you confuse right and left when giving directions?", and "Do you find you forget people's names?" (See Appendix D)

Although several attempts have been made to establish the factor structure of the questionnaire (see Wallace, Kass, & Stanny, 2002; Pollina *et al.,* 1992), results from the CFQ were interpreted as the questionnaire was originally conceived producing a one overall total sum total score reflecting a general cognitive failure factor. Clinical populations of adults with ADHD show increased cognitive failures as measured by the CFQ (*e.g.* Gray *et al*., 2015).

Munich Chronotype Questionnaire

The Munich Chronotype Questionnaire (MCTQ) was used to evaluate individual circadian phenotypes (Roenneberg, Wirz-Justice & Merrow, 2003; Roenneberg *et al*., 2007; Appendix E). The questionnaire askes respondents about how key aspects of their sleep-wake patterns are organised (*e.g.* bedtime, the amount of time taken to fall asleep, wake time, amount of time taken to get up), which are differentially reported for workdays and for free days (*i.e.* days when the schedule is not constrained by the socially imposed clock). The principle measure of the MCTQ is the mid-point between sleep onset and offset for workdays and free days (mid-point of sleep on workdays, MSW and mid-point of sleep on free days MSF respectively). Mid-point of sleep on free days is used as a circadian phase marker of entrainment and therefore a measure of chronotype which is a continuous variable, normally

distributed throughout the general population. It has been demonstrated that individuals accumulate a substantial sleep debt throughout the workweek and therefore compensate for this by over sleeping on free days (see supplement in Roenneberg *et al.,* 2004). Accordingly, an algorithm correcting the mid-point of sleep on free days for sleep debt (MSF_{sc}) is used as an accurate representation of chronotype, given by the formula:

$$MSFsc = MSF - \frac{(SD\text{f} - SD\text{week})}{2}$$

Where SDf = sleep duration on freedays; SDweek = average weekly sleep duration.

The other important measure of the MCTQ reflects the degree of circadian misalignment experienced by individuals in switching between workday and free day schedules, termed social jetlag (SJL). SJL is calculated by examining the difference between uncorrected MSF and MSW, most frequently reported in absolute terms (Wittmann *et al.,* 2006; see supplement in Roenneberg *et al.,* 2012). It is given by the formulae:

$$SJL = |MSF - MSW|$$

$$SJL\text{rel} = MSF - MSW$$

Where SJL_{rel} refers to the +/- prefix representing phase advance/delay respectively. Secondary to the outcome of producing the MSF_{sc} phase marker of chronotype and capturing circadian misalignment via SJL, the MCTQ also quantifies sleep duration, sleep onset latency, and sleep inertia, on workdays and free days via subjective self-report measures. The questionnaire also records individuals' self-rating of chronotype using a 7-point Likert type scale ranging between (0 = "extreme early type") and (6 = "extreme late type").

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) was used to measure self-reported sleep quality (Buysse *et al.,* 1989; Appendix F). The 18-item scale yields a total score attained by finding the sum of the seven PSQI sub-domain component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction respectively). Each sub-domain score ranges between 0-3 which produces a global PSQI ranging between 0-21. According to the authors a global PSQI score of >5 indicates poor sleep quality.

Procedure

Digital versions of questionnaires were presented to participants via online forms. Participants gave their electronic informed consent before commencing questionnaires. Questionnaires were presented in English to participants recruited in Ireland and were translated into Romanian when presented to participants recruited in Romania. Questionnaires were presented consecutively in the order described. The ASRS, BIS, and CFQ were used to screen for symptoms of adult ADHD, general traits of impulsivity, and indicate features of cognitive impairment respectively. The MCTQ and PSQI determined features of sleep timing, circadian misalignment, chronotype, and quality of sleep.

Data analysis

Means and standard deviations were computed for all continuous outcomes. Kolmogorov-Smirnov tests for normality and z-scores for skewness and kurtosis were used to determine distribution of the data. Group comparisons on continuous measures were assessed using independent t-tests and comparisons of nominal data were conducted using Pearson chi-square tests. Pearson product moment correlation coefficients (r) or Spearman rank order coefficients (r_{rho}) were used for normally distributed and non-normally distributed data respectively. Multivariate analysis of covariance (MANCOVA) or Kruskal-Wallis non-parametric ANOVA was used as

appropriate for between group comparisons. Sidak *post-hoc* tests were run for detection of statistically significant pairwise differences where appropriate. Separate exploratory stepwise hierarchical multiple regression analyses using continuous outcomes from ADHD symptom and impulsivity measures as dependent variables. Predictor variables were age, sex, PSQI, average sleep duration, MSF_{sc} and SJL and were entered using a forward selection method. Assumptions of linearity, homoscedasticity, and normality of residuals were confirmed by visual inspection of scatter plots and Q-Q plots. Multicolinearity was assessed via variance inflation factor (VIF) and tolerance scores and no assumptions were found to be violated. Independence of errors was confirmed by Durbin-Watson test statistic proximal to a value of two[2]. All analyses were conducted using SPSS 22 (IBM, Chicago, IL). Results are reported as significant at $p < .05$. Adjusted p-values are presented for *post-hoc* tests.

[2] *Where linear regression is used in other aspects of this research the same assumptions were tested for as listed here.*

2.3 Results

ADHD symptomatology in adulthood

ASRS scores were approximately normally distributed among the final sample with a mean score of 10.53 (*SD* = 3.84). In order to differentiate probable ADHD cases from non-cases the standard dichotomous scoring procedure was applied where a score >13 is associated with ADHD diagnosis. The frequency of probable ADHD cases using this convention was 22.5% which is substantially higher than would normally be expected in the wider population. After applying the stratification protocol outlined in Kessler *et al.* (2007) distribution frequencies for strata I, II, III, and IV, amounted to 41.7%, 35.9%, 18.9%, and 3.5% respectively. Between groups comparisons revealed that males had significantly higher ASRS scores than females, $t(394) = 2.228$, $p = .026$, and that males also scored higher than females on the BIS scale, $t(394) = 2.575$, $p = .010$. Respondents' age was negatively correlated with total ASRS score, $r_{rho} = -.219$, $p < .001$ and BIS score $r_{rho} = -.110$, $p < .001$

Sleep and circadian characteristics of sample

Chronotype was assessed using mid-sleep on free days corrected for sleep debt (MSF_{sc}) which is a measure of circadian phase. The mean MSF_{sc} of the sample was 5:13 AM (*SD* = 1.39 h) and ranged between 1:55 AM and 9:41 AM. The average sleep duration undifferentiated workdays and free days combined was 7.85 hours (*SD* = 1.18 h). Both chronotype and average sleep duration during the week were normally distributed (see Figure 2.1A+B).

Among participants with a later uncorrected MSF there was a negative relationship between circadian phase on free days and hours slept on workdays, $r = -.205$, $p < .001$, and a tendency to sleep longer on free days, $r = .165$, $p = .001$, indicating an accumulation of sleep debt that is dissipated on free days. These associations were not present between MSW and sleep duration on workdays, $r = .038$, $p = .454$, or free days, $r = -.004$, $p = .942$, as participants were constrained by social schedule and as a result their sleep-wake schedules was less biologically determined (Figure 2.2A+B).

Sleep duration was calculated from the average sleep onset and offset for work and free days on the MCTQ.

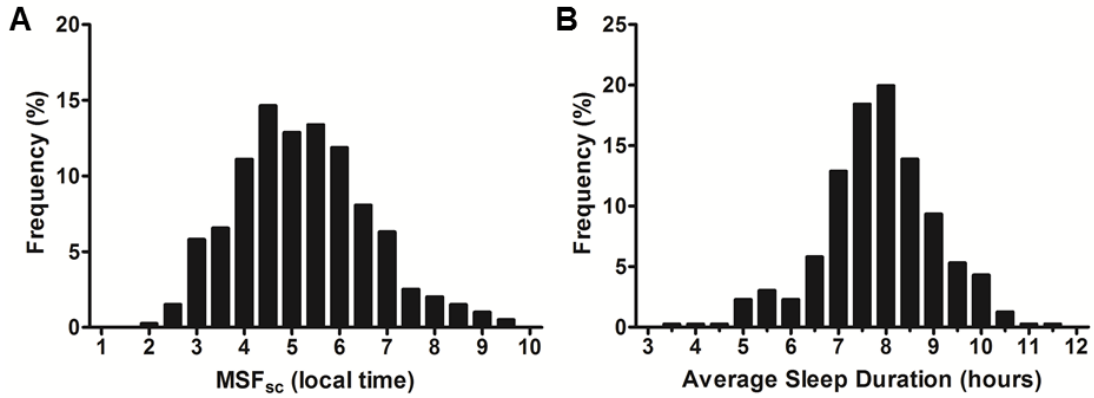


Figure 2.1. Sample demographic of chronotype and average sleep duration

*Histograms depict **(A)** the distribution of chronotypes as measured by MSF$_{sc}$ and **(B)** the average sleep duration in hours of the sample (undifferentiated between work and free days)*

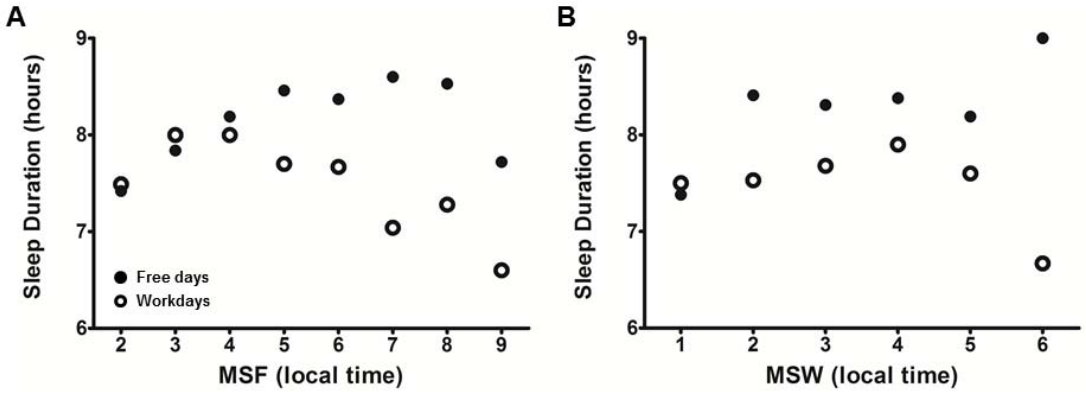


Figure 2.2 Associations between midpoint of sleep and sleep duration on workdays and free days

*The relationship between midpoint of sleep and sleep duration each summarised in 1 h intervals for presentation purposes. Note in panel **(A)** the negative linear relationship between midsleep on free days and sleep duration on workdays indicating restricted sleep experienced by later chronotypes on workdays. This sleep debt is dissipated on free days when late chronotypes tend to sleep longer as demonstrated by the positive relationship between midsleep and sleep duration on free days. These associations are not present in panel **(B)** which depicts the same scatter plot but for workdays.*

The misalignment between workday and free day patterns of the rest-activity cycle known as 'social jetlag' (SJL) was quantified by the difference between MSF and MSW. The amount of SJL accrued in relative terms ranged between -1.5 and 5.98 hours. The large majority of respondents experienced phase advances when switching from their free day schedules to their workday schedules. Only 3.28% of respondents experienced a phase delay when transitioning from free days to workdays (*i.e.* negative relative SJL score). SJL was therefore considered in absolute terms for the remainder of analyses. The mean SJL accrued by individuals was 1.62 hours (*SD* = 1.07 h) with over two-thirds (69.9%) of individuals falling within a SJL range of 0 and 2 hours during their typical work week. A very small minority of participants (2.5%) habitually experienced extreme SJL of greater than 4 hours. SJL distribution in this sample is summarised in Figure 2.3 below.

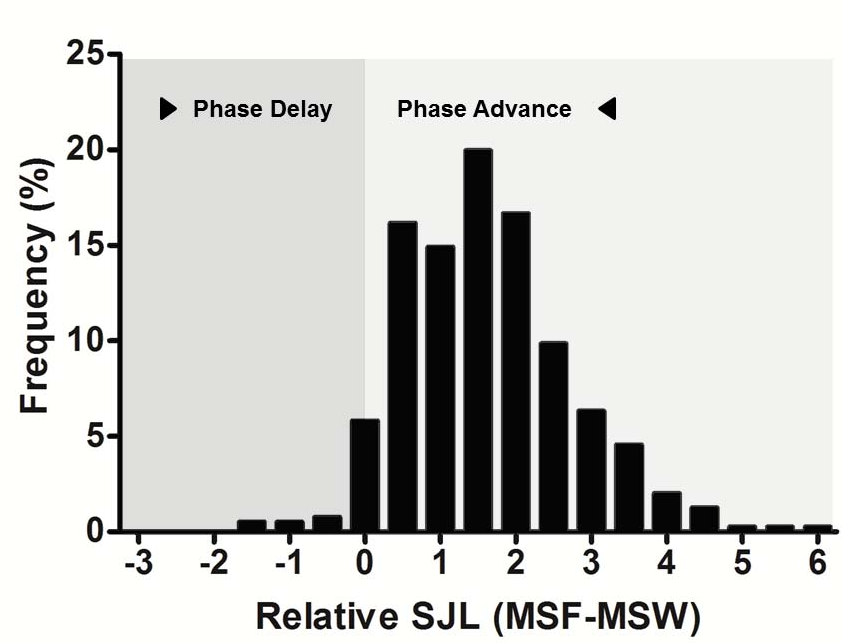


Figure 2.3. Relative social jetlag accrued by sample

Figure depicts the total amount of SJL in hours accrued by individuals during their weekly schedules. Rightward facing arrow indicates phase delays experienced by transitioning between free day and workday schedules (negative SJL score). Leftward facing arrow indicates phase advances experienced by the large majority of individuals when transitioning between free day and workday schedules (positive SJL score).

The mean global PSQI score of the entire sample was 6.56 (*SD* = 3.03) with 58.3% of participants reporting a global PSQI score of greater than 5, indicating a high level of sleep disturbance in our sample. Such a high prevalence was initially unexpected however in line with other studies which implement a cut-off score of >5 in university attending samples (Kabrita *et al.,* 2014). Consequently, as our analyses were exploratory we adopted a more conservative score of > 7 as indicative of poor sleep quality. This approach was justified given recent studies which demonstrate that an adjusted cut-off score might more appropriately distinguish healthy from problematic sleepers. Previous groups have used a cut-off score ranging from > 5.5 to ≥ 8 and have found superior range of sensitivity and specificity for detecting sleep problems among healthy populations (Salahuddin *et al.,* 2017; Manzar *et al.,* 2015; Backhaus *et al.,* 2002; Sun *et al.,* 2014; Zhao *et al.,* 2017). In particular, among a university attending sample such as the one currently under investigation a more conservative cut-off is suggested (Mazar *et al.,* 2015) owing to the younger age and infrequent reliance on sleep medication use compared to the original sample in which the PSQI was validated (Buysse *et al.,* 1989). Later chronotype was associated with greater SJL, r_{rho} = .572, *df* = 395 *p* < .001, as well as poorer sleep quality, r_{rho} = .174, *df* = 395 *p* = .001. SJL and sleep quality were not related however, r_{rho} = .065, *df* = 395, *p* =.197.

Assessing ADHD symptom association with sleep and circadian characteristics

In order to probe associations between chronotype and ADHD symptoms, a series of partial correlations were undertaken between MSF_{sc}, SJL and ASRS, BIS and CFQ scores, controlling for age and sex as important co-variates for both measures of chronotype and of ADHD-related symptoms. These analysis revealed statistically significant, positive, weak associations between MSF_{sc} and ASRS scores and BIS scores, although not with CFQ (Figure 2.4A); statistically significant, positive, weak associations between SJL and ASRS and BIS scores, although not with CFQ (Figure 2.4B); and statistically significant, positive, weak correlations between PSQI scores and ASRS, BIS and CFQ scores (Figure 2.4C). ASRS scores also correlated with total BIS scores (*r* = .53, *df* = 395, *p* < .001) and CFQ scores (*r* = .56, *df* = 395, *p* < .001).

Self-reported chronotype and ASRS, BIS, CFQ, and PSQI scores

We examined the effect of chronotype on ASRS, BIS, CFQ and PSQI total scores by utilising the self-designation of participants in the MCTQ as one of seven chronotypes (extreme early, moderately early, somewhat early, intermediate, somewhat late, moderately late and extreme late) as the independent variable for ANCOVAs, controlling for age and sex. There was a statistically significant, small magnitude effect of chronotype group on ASRS $F(6, 392) = 4.51$, $p < .001$, $\eta_p^2 = .065$; Figure 2.5A). Sidak *post-hoc* tests revealed a significant pairwise difference between the intermediate group and the moderately late group ($p < .001$). There was not a statistically significant effect of chronotype group on BIS total score ($p = .092$; Figure 2.5B), or CFQ scores ($p = .249$; Figure 2.5D), but there was a statistically significant, small magnitude effect of chronotype group on PSQI total score $F(6, 392) = 2.39$, $p = .028$, $\eta_p^2 = .036$; Figure 2.5C).

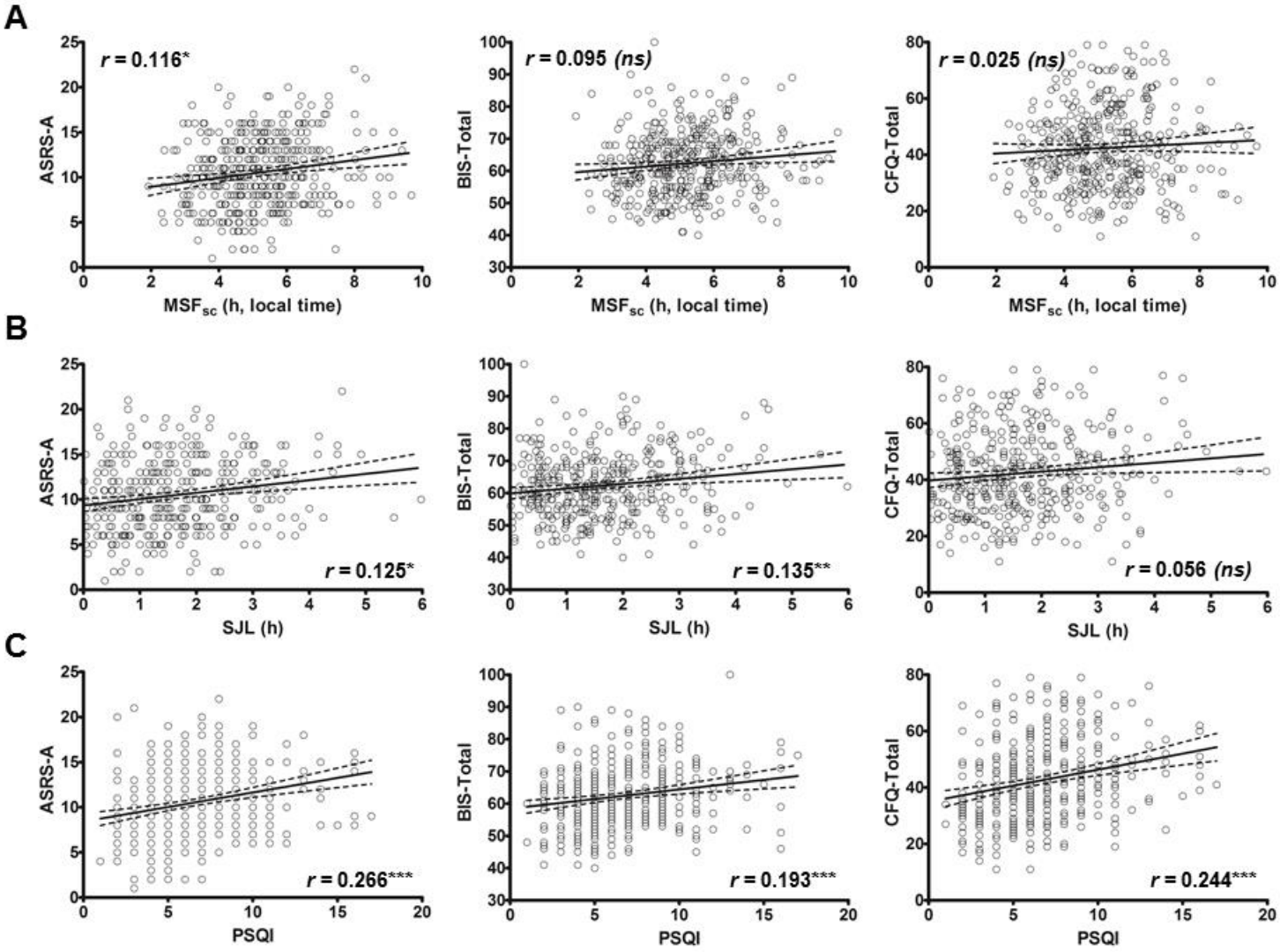


Figure 2.4. Scatterplots illustrating associations of (A) MSF_{sc}, (B) Social Jetlag and (C) PSQI total score with ASRS, BIS and CFQ total scores.

The *r* statistics indicated are those from partial correlation controlling for age and sex. The 95% confidence interval is indicated around the regression line. * indicates $p < .05$, ** $p < .01$ and *** $p < .001$. *ns* indicates no statistically significant difference.

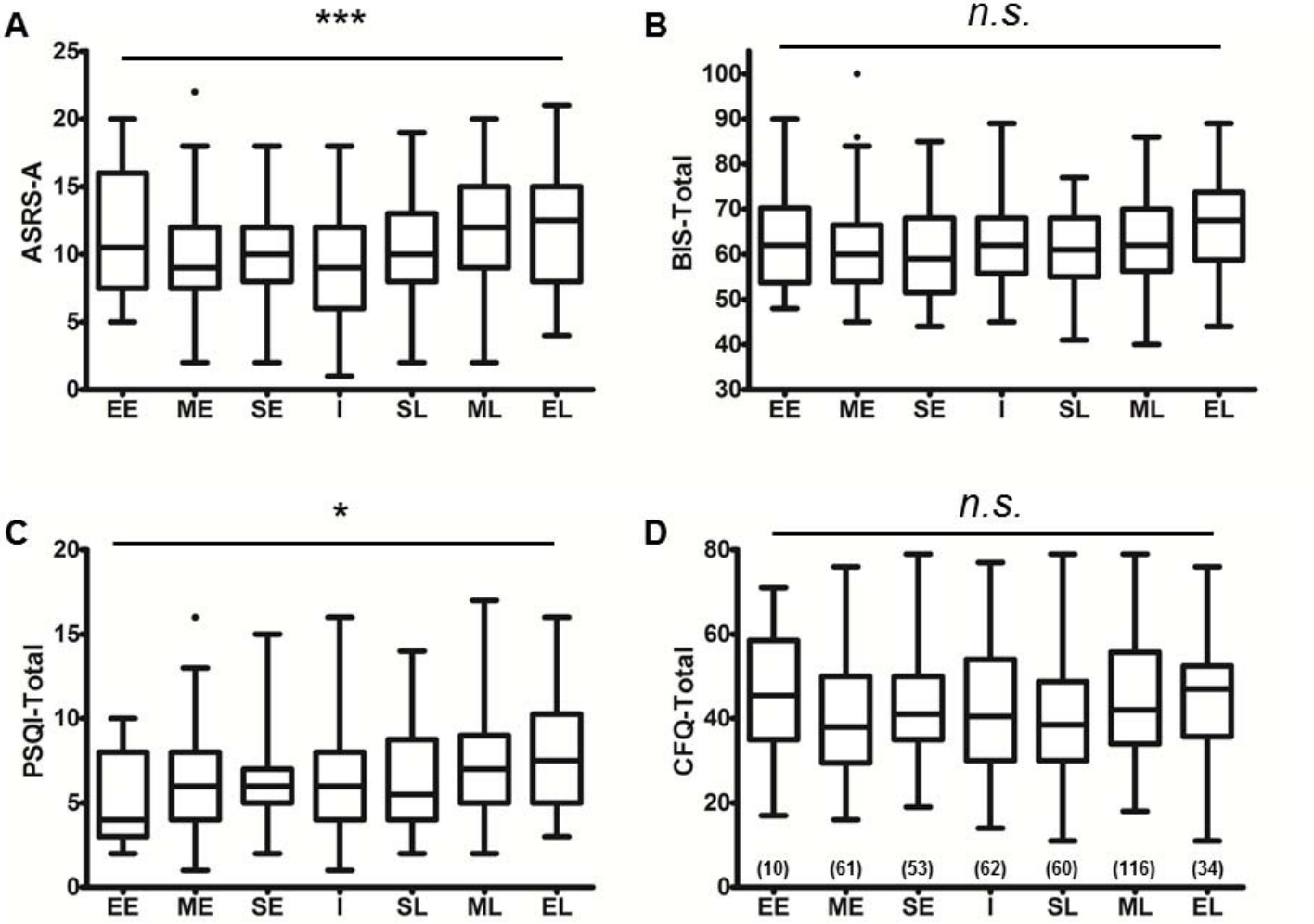


Figure 2.5. Group-wise comparisons of self-designated chronotype (diurnal preference)

*Boxplots showing the distribution of **(A)** ASRS Part-A, **(B)** BIS-total, **(C)** PSQI-total and **(D)** CFQ-total scores across groups of self-indicated chronotype from the MCTQ. The n for each group is indicated on **(D)**. EE=extreme early; ME=moderately early; SE=somewhat early; I=intermediate; SL=somewhat late; ML=moderately late; EL=extreme late. * indicates $p < .05$, *** $p < .001$ and ns indicates no statistically significant difference from ANCOVA controlling for age and sex.*

Predicting symptoms associated with ADHD using measures of sleep and circadian rhythm disruption

As chronotype and SJL are intimately linked (SJL is calculated as the difference in MSW and MSF, and as such there is a moderate-to-strong correlation between MSF_{sc} and SJL in the current data set) multiple regression analyses were untaken to examine the relative predictive properties of MSF_{sc} and SJL on ASRS and global BIS scores. We utilised a forward stepwise regression model as the most unbiased approach, not wishing to influence the results through the order of which predictors are added to the model. A hierachrical method was selected in order to delineate the contribution of each variable independent of the posterior variable entered ito the equation as factors such as PSQI, SJL, and sleep duration account share overlapping features, and, are correlated with age and sex. The aim of doing so was to calculate the contribution of the predictor in the equation model controlling for the variable contributing most to the variance in outcome measure. Age, sex, PSQI score, average sleep duration, MSF_{sc} and SJL were entered as predictors, and the model was run twice, once utilising ASRS score as the dependent variable, and once with BIS as the dependent variable.

The prediction model for ASRS contained four of the six variables, namely, PSQI score, age, sex, and SJL. The final model was statistically significant, $F(4, 391) = 15.258$, $p < .001$, and accounted for approximately 12.6% of the variance of ADHD symptom score ($R^2 = .135$; adjusted $R^2 = .126$). ASRS score was primarily predicted by a higher level of sleep disturbance indicated by total PSQI score, and to a lesser extent by age (the younger, the greater), sex (male), and circadian misalignment through SJL. The raw and standardized regression coefficients of the predictors together with their correlations with each other and their squared semi-partial correlations are shown in Table 2.1. PSQI score received the strongest weight in the final model followed by age, sex and finally SJL. The unique variance explained by each of these dependent variables was approximately 7%, 3%, 2% and 1% respectively.

The model predicting BIS total score ultimately contained three of the six variables; PSQI score, SJL, and sex. The final model was statistically significant, $F(3,$

392) = 10.266, $p < .001$, and accounted for approximately 6.6% of the variance of self-reported trait impulsivity score ($R^2 = .073$; adjusted $R^2 = .066$). BIS score was primarily predicted by a higher PSQI score, followed by SJL, and finally sex (male). The raw and standardized regression coefficients of the predictors together with their correlations with each other and their squared semi-partial correlations are shown in Table 2.2. PSQI received the strongest weight in the final regression model and accounted for 1.2% of the unique variance in impulsivity, followed by SJL and age which accounted for < 1% of the unique variance each. MSF_{sc} and average sleep duration were not significant predictors in either regression models. These results did not differ when variables were entered simultaiously in a hierarchical fashion, with age and sex entered in step 1, and predictor variables entered in step 2, associations between ASRS score and SJL ($\beta = .143$, $p < .05$) and PSQI ($\beta = .265$, $p < .001$), as well as between BIS scores and SJL ($\beta = .116$, $p < .05$) and PSQI ($\beta = .163$, $p < .05$) remained. Chronotype as a predictor in both regressions (MSF_{sc}) failed to achieve a significant status.

Table 2.1. Regression model predicting ADHD symptom rating using self-reported sleep and circadian derived variables

Final Model	Age	Sex	SJL	B	SE_B	β	sr^2
Constant				10.681	.893		
PSQI	-.009	.196	.029	.323	.060	.255	.065
Age	-	-.090	-.202***	-.087	.023	-.206	.003
Sex		-	-.103*	-1.096	.412	-.127	.002
SJL			-	.421	.175	.117	.001

$R^2 = .135$; adjusted $R^2 = .126$, $p < .001$. Predictor variables inserted : age, sex, PSQI score, sleep duration, MSF_{sc}, and SJL. Sleep duration and SJL are measured in hours; MSF_{sc} is measured in local clock time. Sex coded as (0 = males; 1 = females). B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in ASRS score accounted for by variable. $p < .05$ *** $p < .001$*

Table 2.2. Regression model predicting general trait impulsivity using self-reported sleep and circadian derived variables

Final Model	SJL	Sex	B	SE_B	β	sr^2
Constant			58.725	1.554		
PSQI	.029	.043	.600	.157	.186	.035
SJL	-	-.103*	1.296	.448	.142	.02
Sex		-	-2.680	1.074	-.122	.015

R^2 = .073 adjusted R^2 = .066, p < .001. Predictor variables inserted : age, sex, PSQI score, sleep duration, MSF_{sc}, and SJL. Sleep duration and SJL are measured in hours; MSF_{sc} is measured in local clock time. Sex coded as (0 = males; 1 = females). B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in total BIS-11 score accounted for by variable. . p < .05*

Group-wise comparisons of SJL, ADHD symptoms, and trait impulsivity

As the majority of the sample scored within the ASRS range not associated with probable ADHD diagnosis we examined the stratified cut-off scores to determine the existence of a threshold level of symptom severity after which differences became apparent. Due to the low numbers in stratum IV this group was combined with stratum III in our analysis. Preliminary analyses using Kruskal –Wallis tests revealed significant differences in median BIS scores, $\chi^2(2) = 100.7$, $p < .001$, and median CFQ scores, $\chi^2(2) = 119.7$, $p < .001$, between ADHD symptom strata; in both cases the greater the strata order individuals fell within, the greater the their respective overall BIS and CFQ score, adjusted $p_{ALL} < .05$, confirming that classification among ADHD strata was indicative of increased impulsivity and errors in cognition.

A Kruskal-Wallis test was conducted to investigate differences in SJL accrued throughout the week between ADHD strata. Using this group-wise approach there was discovered a statistically significant difference in SJL between groups, $\chi^2(2) = 8.387$, $p = .015$. *Post-hoc* tests revealed statistically significant differences in median SJL between the combined "strata III and IV" group (*Mdn* = 1.75 h) and "stratum I"

(*Mdn* = 1.29 h), p = .012, but not between the borderline "stratum II" group (*Mdn* = 1.5 h) or in any other combination (Figure 2.6A). One-way ANOVA revealed that MSF_{sc} was different between ADHD strata, $F(2, 393) = 3.372$, p = .035; however this effect was not present after controlling for SJL entering the term as a covariate, $F(2, 392) = .673$, p =.526, indicating that phase of entrainment in and of itself was not responsible for this relationship. There was not a significant difference in average sleep duration between strata, $F(2, 393) = .948$, p = .338. Chi-squared test for association was conducted between ADHD strata and poor sleep quality (PSQI score >7) and showed a significant association between symptom strata poorer sleep quality, $\chi^2(2) = 18.534$, $p < .001$ (Figure 2.6B).

Further to examining between group differences on the amount of SJL accrued using ADHD symptom severity as the independent variable SJL was subsequently categorised by means of a sample median split yielding a higher and a lower SJL group (*Mdn* = 1.5 h) in order to determine between groups differences on impulsivity subscales. To address this question a multivariate analysis of variance, adjusted for age and sex as covariates (MANCOVA) was first conducted on the means of the subscales in order to protect against Type 1 error rate. As the BIS scale conceptualises three different scales of impulsivity as components underlying a multidimensional general impulsiveness trait this approach is further warranted. A significantly significant MANOVA effect was obtained, Wilk's Λ = .023, $F(3, 392) = 4.132$, p = .007. The multivariate effect size was estimated at .031 implying that approximately 3.1% of the variance in the canonically derived dependent variable was accounted for by SJL. After adjusting for age and sex as covariates the significant effect significant effect persisted, Wilk's Λ = .980, $F(3, 390) = 2.644$, p = .049. A series of follow-up univariate ANOVAs were conducted to examine the effects of SJL on all three BIS secondary factors and showed significant results on all scales; attentional impulsivity (p = .023), motor impulsivity (p = .032), and non-planning impulsivity (p = .022).

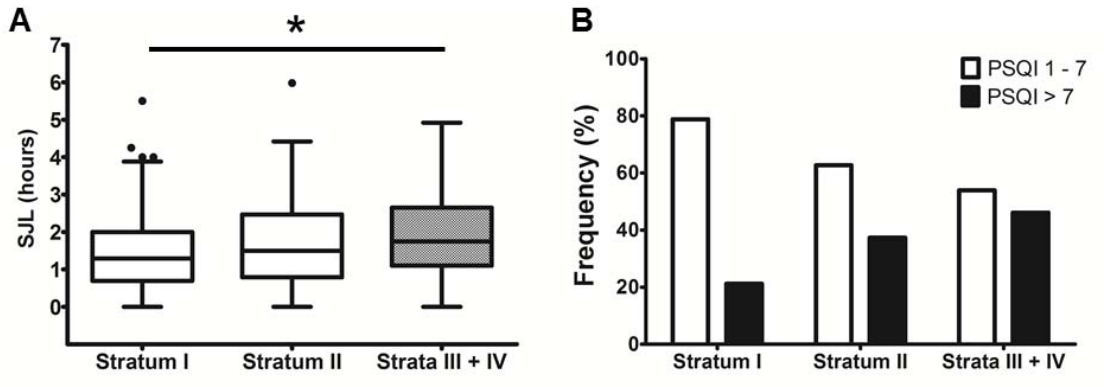


Figure 2.6. Social jetlag and sleep quality among groups at risk of ADHD

*Box plot in panel **(A)** demonstrates differences in median SJL accrued by ADHD strata. Whiskers are created using the Tukey method with outliers appearing outside inner fences greater than the 75th percentile plus 1.5 IQR. Grey cross-hatch design indicates ASRS score > 13. **(B)** Bar chart demonstrates the frequency distribution of poor sleep quality ('bad-sleepers') among ADHD strata using a PSQI score > 7 to designate serious disruption in sleep. * p < .05.*

2.4 Discussion

In this study we report that symptoms of ADHD in adults are associated with measures of sleep and chronotype in a young adult population. Of the measures assessed we found that sleep quality was the most salient with the majority of variance in ADHD symptomatology, impulsivity, and cognitive failures score, uniquely accounted for by this variable alone with group-wise approaches exploring differences between ADHD symptom strata reflecting similar results. We found that social jetlag was also a significant predictor for both measures however MSF_{sc} was not found to be a significant predictor in our analysis, indicating that previous associations between impulsivity-related domains and later chronotype/diurnal preference (Kang *et al*., 2015; Prat and Adan, 2012; Muro *et al*., 2013) may in fact be mediated through social jetlag rather than later entrained circadian phase *per se*. While the associations reported here are modest in magnitude, our findings highlight the subtle yet pervasive effect by which circadian misalignment and disturbances to sleep may aggravate and perhaps precipitate negative psychosocial outcomes in the general population.

Increased evening-preference has been noted in several studies of adult ADHD or suspected-ADHD (Bae *et al.,* 2010; Caci, *et al.,* 2009; Voinescu *et al.,* 2012; Baird *et al.,* 2011). The mechanism through which later diurnal preference or phase of entrainment may impact on attention and impulsivity though has not been elucidated. Later chronotypes/evening types are described as having greater social jetlag and shorter and more impaired sleep (Giannotti *et al.,* 2002; Taillard *et al.,* 2003; Wittmann *et al*., 2006; Roenneberg *et al*, 2012; Allebrandt *et al*., 2014). Given that shortened sleep negatively impacts on attention and impulsivity (*e.g.* Gruber *et al*., 2012), and that poor sleep quality is associated with ADHD in children (LeBourgeois *et al.,* 2004; Dagan *et al.,* 1997), impulsivity and aggression (Kamphius *et al.,* 2014; Ireland & Culpin, 2006), and cognitive dysfunction (Curcio, Ferrara, & De Gennaro, 2006; Peigneux *et al.,* 2001) in adults, it would be plausible that impaired sleep quality could explain the impact of later chronotype with ADHD symptomatic domains.

Indeed, in our results, sleep quality (as assessed by the PSQI) was a significant predictor of scores on the ASRS and BIS. However, with the PSQI accounted for in our regression model, average sleep duration was not a significant predictor, whilst social jetlag was. Further, MSF_{sc} was also not a significant predictor in the regression model or in the between ADHD strata analysis after controlling for SJL, although group-wise analysis did indicate that later diurnal preference (measured by self-assessed chronotype estimates on MCTQ) was associated with more ADHD-like symptoms. While circadian phase might not predict ADHD symptomatology it is interesting to note that other psychosocial factors which shape individuals' self-reported chronotype may underlie this association. We interpret these results as indicating that SJL is (in part at least) mediating the effects of later chronotype on attention and impulsivity/hyperactivity. Previous studies have put forward similar arguments in different scenarios: Wittmann *et al.* (2006) attribute the relationship between chronotype and smoking to a greater accumulation of SJL, Levandovski *et al.* (2011) found SJL to be a more important predictor of depression above the effects of chronotype alone, and academic performance among medical students was found to be negatively associated with SJL but not with chronotype (Haraszti *et al.,* 2014).

The pathways through which social jetlag may negatively impact on ADHD-related symptoms are not currently known. However, given that social jetlag most likely represents a state of chronic circadian misalignment, there are some indicators in the literature of plausible explanations. Dopaminergic neurortransmission is assovciated with impulse control and attention, and is intimately implicated in the pathophysiology of ADHD (Bellgrove & Mattingley, 2008; Bari & Robbins, 2013; Kollins & Adcock, 2014). Interestingly, the dopaminergic system is now understood to be under profound circadian control (Parekh *et al.,* 2015) and circadian changes result in significant changes in dopaminergic neuronal function and animal behaviour (Mukherjee *et al.,* 2010). As such it is possible that the chronic state of misalignment between internal circadian phase and external cycles that are manifest in social jetlag may produce alterations in neural pathways implicated in sustained attention and impulsivity. Whilst there is no current direct evidence to support this hypothesis, it may at least be argued that this represents at least one possible

mechanism through which social jetlag, and maybe late chronotype, impact on ADHD-related cognitive and behavioural domains. It is of interest in our current results that we do not report any significant associations between either social jetlag or MSF_{sc} with CFQ, indicating that there may be domain specificity in the impact of either chronotype or social jetlag on neurobehavioural outcomes.

Given the novel associations between social jetlag and symptoms of ADHD and trait impulsivity, interesting opportunities in managing symptoms might arise by better designing occupational/educational schedules which are better matched to the phase of the internal clock. Recent arguments concerning delaying the school start times to better facilitate later sleep phase during adolescence (Kelley *et al.,* 2014) as well as evidence suggesting that shift-work schedules might be better designed when individual chronobiology is considered (Fischer *et al.,* 2016) support a future movement of social schedules to minimise the burden of circadian misalignment in modern society. Aside from potentially circumventing the symptoms we describe here, improvements to other domains of performance and public health might be achieved by realising the negative consequences of living against the biological clock and taking steps to correct its misalignment.

There are a number of limitations and caveats to this study which should be acknowledged when interpreting its findings. Firstly, our observations are cross-sectional in nature and therefore we cannot infer causal relations between the sleep and circadian measures recorded and ADHD symptoms. It is also possible for reverse causation to apply (if indeed there are any causal relationships underpinning the observed associations). Considering social jetlag for example, it could be argued that greater discrepancy between free day and workday sleep patterns arise as a result of non-planning behaviour which is commonly associated with ADHD. All measures used in the current study are subjective, and future studies should address this through the use of both objectively-derived measures of sleep/wake behaviour (*e.g.* actigraphy) and neurocognitive tests of aspects of attention and impulsivity. Further, sex was not equally distributed in our sample. While a female majority in our sample is reflective of the skewed gender distribution found enrolled in

psychology courses in European universities, and sex was treated as a co-variate in all of our analyses, it may still represent an important confound in the interpretation of the current results. This is especially pertinent given that recent evidence has also suggested that social jetlag might have different outcomes for cognitive performance in females compared to males (Diaz-Moralesa & Escibanoa, 2015). Further, the current study did not examine social jetlag in a population with clinically confirmed ADHD where diagnosis (more extreme symptoms) might moderate the effects seen in the current cohort. This is likely to be an interesting topic for future work to address, as although adult ADHD is associated with evening preference, and as such would be expected to be associated with increased levels of social jetlag, ADHD in adults is also associated with altered social outcomes (*e.g.* increased levels of unemployment; Kupper *et al.*, 2012) which may serve to lessen the extent of social jetlag.

In conclusion, the current results of this chapter show that social jetlag is a factor which should be taken into consideration when possible links between circadian timekeeping, ADHD, and more generally impulsivity and attention, are explored. Whilst the overall magnitude of the observed associations between social jetlag and ADHD-related symptoms were modest, it may be that in individuals with genetic and other pre-dispositions to ADHD and related disorders that the impact of social jetlag could be more pronounced. Future observational and experimental work is needed to further understand these issues.

Chapter 3

Assessing relations between circadian dysfunction, sleep quality and neuropsychological indexes of impulsivity and attention

Abstract

Attention deficit/hyperactivity disorder is associated with a number of notable executive function deficits including response inhibition impairments and shortened delay gradients for reward. Importantly, these traits can be measured objectively on neuropsychological tasks and can be used to index individual liability towards the heterogeneous symptoms of ADHD. In this study we assessed the degree to which individuals with later self-reported chronotype, social jetlag, and diminished sleep quality performed on neuropsychological tests designed to measure impulse control, attention, and risky decision making. A cohort of healthy young adults (n = 189) completed the Conner's Continuous Performance Task (CCPT) and the Iowa Gambling Task (IGT) as well as questionnaires which probed individual differences in sleep and circadian rhythm disturbances. We report that higher levels of social jetlag were associated with shorter mean reaction times on the CCPT which encouraged pre-potent motor responding and required participant response inhibition. Ex-Gaussian analysis of reaction time frequencies revealed that a faster *mu* component of the frequency distribution was predictive of inhibitory dysfunction (increased commission error rate) and was significantly lower in intermediate and high social jetlag groups. This finding was stable across performance conditions with no moderating effect of time-on-task or inter-stimulus interval detected. Furthermore, these effects seem to be specific for social jetlag as no associations between CCPT performance indictors and either self-reported chronotype or sleep quality score were noted. On the IGT we detected differences in deck selection strategy among individuals with self-reported sleep disturbances such that higher win ratios were preferred at the expense of long-term monetary gain. These effects were not present for MCTQ derived self-reported chronotype or social jetlag. Taken together these findings suggest that sleep and circadian rhythm disturbances measured by subjective sleep quality score and the social jetlag metric might differentially confer risk toward worsened symptoms of motor impulsivity and risk taking in healthy young adult populations. We suggest therefore that sleep and

circadian rhythm disturbances might increase liability towards ADHD-like features in the general population and may exacerbate or even precipitate symptom risk in clinically diagnosed patients.

3.1 Introduction

One of the difficulties in assessing traits and behaviours that may be of dimensional relevance to psychiatric illnesses is clearly deciding on measures which reliably target psychopathologies of interest. In the previous chapter we explored the relatedness between sleep and circadian disruption with behavioural constructs associated with ADHD by means of self-report. While numerous scales have been shown to accurately predict symptoms of impulsivity and inattention this approach is susceptible to the reliability pitfalls associated with subjective self-assessment. This is especially problematic in ADHD with a literature demonstrating that across all stages of lifespan development, individuals with the disorder are less valid reporters of symptomology with suspected self-perception biases leading them to under-report their symptoms (Lober *et al.,* 1991; Fischer *et al.,* 1993; Barkley *et al.,* 2002; Sibley *et al.,* 2010; Owens *et al.,* 2007). It is plausible therefore that among the general population too that an impulsive/inattentive individual's behaviour does not match their own self-evaluation on scales designed to probe such traits. In the context of the current research strategy we suggest that our methodology would benefit from incorporating measures of ADHD-like traits that are operationally defined, can be measured by objective means, and are firmly rooted in neuropsychological research.

As discussed previously, ADHD is comprised of a complex and heterogeneous symptomatology and therefore selecting specific traits and behaviours which index liability towards the condition or the epiphenomena surrounding it is of importance for experimental interrogation. Individuals with ADHD are characteristically found to have a variety of executive function deficits, with inhibitory deficits and sustained attention dysfunction being considered primary problems associated with the disorder (Barkley, 1997; Castellanos & Tannock, 2002; Sergeant, Geurts, & Oosterlan, 2002; Nigg, 2001; Pennington & Ozonoff, 1996; Sonuga-Barke, 2005). Another stable finding in individuals with ADHD is that they demonstrate greater delay aversion and show pronounced deficits on tasks involving reward sensitivity. Individuals with ADHD demonstrate greater future discounting on temporal discounting tasks meaning that they are more likely to favour smaller immediate rewards and to

discount delayed rewards that are larger in magnitude and similarly also show more pronounced sensitivity to reinforcement implicating a role for differential reward circuit functioning (Sonuga-Barke, 2002; Luman, Oosterlaan, & Sergeant, 2005; Tripp & Alsop, 1999, 2001).

Importantly, it has been suggested that these neurocognitive components may be mechanistically distinct from one another and therefore might be of causative importance predicting the separate symptomatic domains of the disorder. According to the 'dual-pathway model' of ADHD heterogeneity (Sonuga-Barke, 2002, 2003), it is suggested that the inhibitory deficits and the shortened delay reward gradients that typically characterise ADHD symptomatology comprise two dissociable psycho-pathophysiological pathways. Consequently, the question emerges whether delimiting behavioural performance on tasks measuring the two putatively separable components might further our understanding of symptoms and how they might be moderated by interruptions to sleep quality and timing. As such the current study intends to examine sleep and circadian related variables and outcomes related to ADHD such as response inhibition, sustained attention, and integration of future consequences on risk decision making, and reward responsivity.

Impulsive action has been described as the inability to withhold from making a response, and response inhibition refers to the ability to successfully supress an action where it interferes with a contextually related goal-driven behaviour (Winstanley *et al.,* 2006; Mostofsky & Simmonds, 2008). Response inhibition can be measured by using common neuropsychological tasks such as the Go/No-Go paradigm, start-stop reaction time task, and the continuous performance task. The premise of these tasks involves test subjects continuously responding to a frequently occurring 'GO' stimulus, while requiring that they withhold this pre-potent response on a subset of 'NO-GO' stimuli that are presented concurrently in an intermittent and unpredictable fashion. Failures to successfully inhibit a response are known as errors of commission and are thought to be indicative of impulsive responding (Hwang-Gu *et al.,* 2013). Conversely, instances in which the 'GO' stimuli are not adequately responded to with a hit are known as errors of omission and are thought

to reflect attentional lapses or problems with sustained attention (Barkley, 1991; Halperin *et al.,* 1991). Studies involving individuals with ADHD show increased rates of both omission and commission errors compared to normal controls (reviewed in Losier, McGrath, & Klein, 1996; Epstein *et al.,* 2013). While the precise nature of what each of these parameters actually translates to in terms of symptomatology has largely been informed by behavioural assumptions and the face validity of the measures (Epstein *et al.,* 2013), factor analytic approaches support the assumption that omission and commission errors in ADHD are linked to behavioural counts of inattention and impulsivity respectively (Bezdjian *et al.,* 2009).

Several studies have also looked at differences in participants' reaction time (RT) on such tests. Studies examining individuals' mean reaction time (RTm) have found that generally individuals with ADHD respond slower compared to controls (Klein *et al.,* 2006; Nigg *et al.,* 2005; Willcutt *et al.,* 2005) which is surprising given their propensity towards impulsive responsivity. Numerous studies also demonstrate greater variability (RTSD) within an individual's response pattern (Klein, Castel, & Pratt, 2006; Johnson *et al.,* 2007; Rubia *et al.,* 2001; Uebel *et al.,* 2010; Vaurio, Simmonds, & Mostofsky, 2009) which is thought to be indicative of deficits in attentional processing (Tamm *et al.,* 2012). Closer examination of RT in a trial-by-trial manner in ADHD however reveals a more complex picture suggesting that individuals may simultaneously show extremely fast RTs and also RTs that are extremely slow, thus pointing to a high intra-individual variability (IIV) of RT which characterises the disorder from other psychiatric conditions (Castellanos *et al.,* 2006; Tarantino *et al.,* 2013).

Tamm *et al.* (2012) articulate a number of difficulties with using conventional measures of central tendency such as RTm and RTSD when examining performance in ADHD. Separating the means from the standard deviations of RT data is often problematic because of high degree of correlation that exists between the two variables (Desman, Petermann, & Hampel, 2008; Adams *et al.,* 2011; Tamm *et al.,* 2012). Rather some studies have instead used the coefficient of variation (CoV) of RT in an effort to normalise within-subject variability (Wagenmakers & Brown, 2007;

Antonini, *et al.,* 2013). Another problem which persists however pertains to the assumptions surrounding the distribution of RTs. In both normal controls and clinical populations RT is not normally distributed but rather its distribution has a shape which is highly positively skewed (Luce, 1986). Numerous studies have instead investigated IIV of RT in ADHD using an exponentially modified normal curve or '*ex-Gaussian'* frequency distribution which is found to be a better model fit for reaction time data (Leth-Steensen, Elbaz, & Doughlas, 2000; Tarantino *et al.,* 2013; Epstein *et al.,* 2011; Hervey *et al.,* 2006; Metin *et al.,* 2014; Gmehlin *et al.,* 2014; Biscaldi *et al.,* 2016; Henriquez-Henriquez *et al.,* 2015; Lin, Hwang-Gu, & Gau, 2015; Hwang-Gu *et al.,* 2013; Vaurio *et al.,* 2009; Buzy *et al.,* 2009). The ex-Gaussian model decomposes RT into three separate parameters which reflect the shape of the data distribution; μ (*mu*) and σ (*sigma*), represent the mean and the standard deviation of the normally distributed component of the curve, while τ (*tau*) represents the exponentially distributed long tail-end of the curve which accounts for its positive skew (see Figure 3.1) (Burbeck & Luce, 1982; Tarantino *et al.,* 2013).

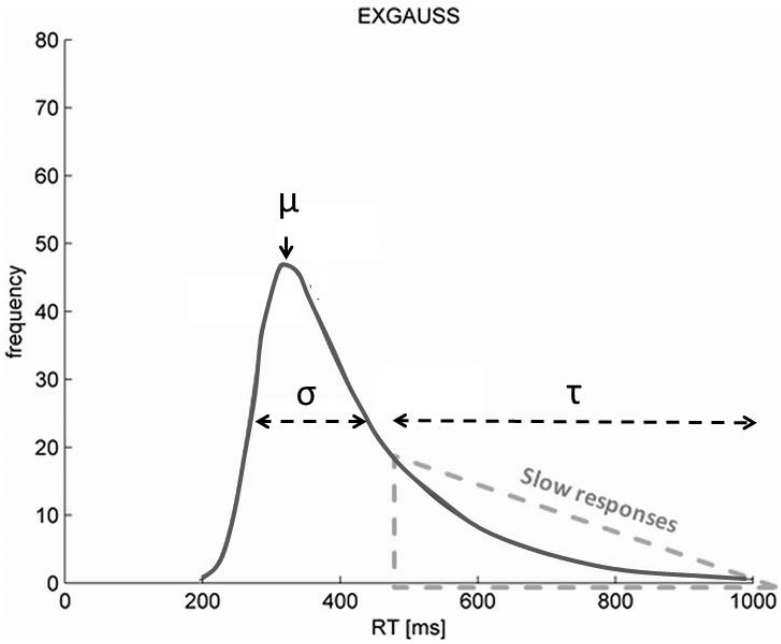


Figure 3.1. Sample ex-Gaussian frequency distribution

The ex-Gaussian frequency distribution is characterised by three parameters: μ and σ represent the mean and the standard deviation of the normally distribution and τ represents the infrequent slow responses in the exponential component of the function. Individuals with ADHD have been characterised as showing a faster leading edge of the curve (smaller μ) while at the same time demonstrate a longer tail-end of the distribution (larger τ) which are respectively suggested to indicate generally impulsive responding and also occasional lapses in attention. Figure adapted from Gmehlin et al., 2014.

Among the most consistent findings in the ADHD RT literature is that the high IIV shown by subjects is due to the presence of a greater number of infrequent excessively long RTs indicated by a larger *tau* which differentiates the individuals with the condition from normal controls (Tarantino *et al.,* 2013; Hwang-Gu *et al.,* 2013; Gmehlin *et al.,* 2014; Leth-Steensen *et al.,* 2000; Hervey *et al.,* 2006). Long RTs are interpreted as reflecting occasional lapses in attention and are thought to be part of the same cognitive mechanism surrounding errors of omission (Epstein *et al.,* 2010; Tamm *et al.,* 2012). Other studies, albeit with less consistency and pronounced effect size as those which demonstrate differences in *tau*, have found that ADHD subjects are separately characterised from controls by showing a shorter *mu* which is indicative of a faster more impulsive responding style (Hervey *et al.,* 2006; Hwang-Gu *et al.,* 2013; Williams *et al.,* 2007; Vaurio *et al.,* 2009). As short RTs typically coincide with errors of commission the two processes are thought to be part of the same mechanistic process reflecting cognitive control. Indeed it has been shown previously that omission errors and commission errors are predicted by a larger *tau* and a smaller *mu* respectively (Hwang-Gu *et al.,* 2013).

Furthermore, IIV in ADHD has been shown to be a construct modified by both genetic and contextual factors. Sibling studies have pointed to stair-like distributions of ex-Gaussian components particularly for an increased *tau* component between controls, unaffected siblings, and those with ADHD, forming a potential intermediate construct for symptom liability (Lin *et al.,* 2015; Henriquez-Henriquez *et al.,* 2015). Such endophenotypes putatively constitute a more direct path of association between gene and symptom and importantly are considered quantitative markers of particular symptomatic domains in behavioural neuroscience. It is thought that among the general population shorter RT latency and increased IIV may represent intermediate phenotypes which index an individual's liability towards exhibiting traits/symptoms that are clinically relevant in conditions such as ADHD. Other studies have found that RT latency and IIV are moderated by energetic effects within the task as well as time-on-task effects themselves. Consistent with the cognitive-energetic theories of ADHD (Sergeant, 2005; Van der Meere, 2002) which suggest that ADHD arises fundamentally due state regulatory deficits,

Hervey *et al.* (2006) found that *tau* became enriched as the momentum of the task slowed. It is further thought that longer inter-stimulus intervals (ISIs) disproportionately produce a non-optimal state in individuals with ADHD during which distractibility and the likelihood towards errors of omission increases. Tarantino *et al.* (2013) also show steep increases in *tau* as a function of time-on-task in ADHD indicating that propensity towards extremely long RTs increase as the task progresses which the authors interpret as an increased motivational burden on sustained attention in the disorder, and such performance markers differentiate normal controls from individuals diagnosed with the disorder.

Propensity towards risky decision making is another well described facet of impulsivity (Daruna & Barnes, 1993; Winstanley *et al.,* 2006) and individuals with ADHD are found to make more disadvantageous choices compared to normal controls on tasks designed to probe risk taking (Matthies, Philipsen, & Svaldi, 2012; Dekkers *et al.,* 2016). Evidence suggests that these differences have less to do with deficits in general risk assessment ability but rather are closely related to the previously described delay aversion phenomenon which is believed to underpin the pathphysiology of disorder (Sørensen *et al.,* 2016). Moreover, children and older individuals with ADHD may also show abnormal responses to reward and punishment as poorer performance on extinction tasks and reversal learning tasks are frequently noted (Sagvolden *et al.,* 1998; Kempton *et al.,* 1999; Itami & Uno, 2002). These tasks involve no longer responding to a previously reinforced stimulus or switching response strategies to choose stimuli which were not previously reinforced respectively, and thus indicate abnormalities in goal directed behaviour involving rewards. It may be the case that individuals with ADHD therefore make riskier decisions than controls as they are led by immediate reinforcement and are less likely to deviate from such choices even after such behaviours become maladaptive.

The Iowa Gambling Task (IGT; Bechara *et al.,* 1994) is a neuropsychological test designed to assess real-life risky decision making. The test examines individuals presented with initially uncertain outcomes and assesses their ability to integrate monetary rewards and losses into decision making processes with the expectation

that they will aim to maximise long-term gain. The standard version of the IGT presents individuals with four decks labelled A, B C, and D, two of which are considered advantageous (C, D) producing an average net gain of $250 over 10 trials, and two of which are considered disadvantageous (A, B), producing an average net deficit of -$250 over 10 trials. Volunteers are asked to make 100 choices from any of the decks with decks differing with respect to the amount and the frequency of token monetary gains/losses produced by each selection. Choices from the disadvantageous decks produce a long-term net loss over time whereas choices from the advantageous decks result in greater net gains being accumulated over time. The test was originally conceived to assess decision making processes in patients with orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) lesions that showed pronounced decision making deficits compared to normal controls that generally learn to choose more from the 'good' decks rather than from the 'bad' decks as the task progressed (Bechara *et al.*, 1994; Bechara, Tranel, & Damasio, 2000). The original authors of the study theorised that the deficits revealed by the IGT could be characterised as a short-sightedness for future outcomes (Bechara, Dolan, & Hindes, 2002). Other studies utilising the IGT however have found that deck preference is not entirely motivated by a strategy which attempts to maximise long-term gain but rather by the reward frequencies associated with each deck (see Horstmann, Villringer, & Neumann, 2012). Indeed several studies question the underlying assumption of the original IGT authors and instead find what has become known as a 'prominent deck B' effect in which participants are lead to select from the high reward frequency deck B in which wins occur on average 90% of the time, despite it being a disadvantageous deck to choose from in the long-run (Lin *et al.*, 2007; reviewed in Dunn, Dagleish, & Lawrence, 2006) which is consistent with findings which point to a shortened delay reward gradient in ADHD (Sonuga-Barke, 2002). Studies which examine IGT performance in individuals with ADHD and normal controls have found differences in deck selections over time (Garon, Moore, & Waschbusch, 2006; Hobson, Scott, & Rubia, 2011). Others have also shown using the IGT that those with ADHD are more sensitive to the frequency of rewards given by decks rather than their magnitude of outcome (Luman *et al.*, 2008; Toplak, Jain, &

Tannock, 2005) consistent with findings of a the lengthened behavioural extinction interval and reversal learning deficits noted in the disorder.

There have been few studies addressing the impact of individual differences in sleep and circadian related variables and outcomes assessing response inhibition, reaction time, and IGT performance. Kang *et al.* (2015) compared morning-types and evening-types on a version of the Go/No-Go paradigm and found that evening-types performed significantly faster and showed a trend towards a greater amount of commission errors. These findings are consistent with the prevailing literature which clusters eveningness with measures of trait impulsivity (Adan *et al.,* 2010). Most studies however are more often concerned at looking at inhibitory control decrements between chronotypes at optimal and non-optimal times of day in order to demonstrate performance synchrony effects (*e.g.* Hahn *et al.,* 2012; Lara, Madrid, & Correa, 2014) rather than focusing on stable trait deficits as is the case in ADHD and none have so far examined social jetlag as a potential causative factor. Kim *et al.* (2011) reported that increased 'catch-up sleep' on weekends was associated with greater omission and commission error rates in a sample of adolescents attending school in Korea. As sleep restriction during the work/school day and the compensatory oversleep during the weekend is a large part of the phenomena described in social jetlag it is possible that such effects might be mediated by conflict between the rhythms of the social and biological clocks. Several studies have shown also that IGT performance is negatively impacted by sleep restriction (Killgore, Balkin, & Wesensten, 2006; Killgore *et al.,* 2007; Killgore, Grugle, & Balkin, 2012) and IGT performance deficits have been described among individuals with sleep disorders (Delazer *et al.,* 2012; Daurat, Ricarrère, & Tiberge, 2013). Olson *et al.* (2016) report that daytime sleepiness was specifically related to reduced integration of long-term outcomes on the IGT. Furthermore, sleep restriction has been shown to amplify the reactivity of reward related networks of the brain in response to positively reinforcing stimuli (Gujar *et al.,* 2011; Mullin *et al.,* 2013) thereby potentially leading to increased reward sensitivity on tasks such as the IGT.

In an attempt to explore the links between sleep and circadian rhythm disturbances and behavioural traits manifested in ADHD, the current study examined whether self-reported chronotype, social jetlag, and sleep quality were important predictors of neuropsychological performance in a non-clinical sample of adults that were independent from the previous sample. Our primary focus was to evaluate if these characteristics contributed to errors of omission and commission as well as mean reaction time and intra-individual variability assessed by the CCPT with the purpose of linking sleep and circadian rhythm disturbances with intermediate neuropsychological phenotypes associated with ADHD. Furthermore, our secondary analyses aimed to decompose RT using an ex-Gaussian approach and to investigate the mediating role of task momentum and time-on-task as these factors have been found to influence performance in ADHD cohorts. We also conducted regression analyses to investigate to what degree performance accuracy on the CCPT was predicted by *mu*, *sigma*, and *tau*, components of the ex-Gaussian frequency distribution. Finally, as delay aversion is thought to be a component separate from primary inhibitory response deficits in ADHD we examined if overall IGT performance was associated with independent measures of sleep and circadian dysfunction in a differential manner to outcomes assessed by the CCPT.

3.2 Materials and methods

Participants

A total of 195 participants were recruited among undergraduate university students attending Maynooth University. From this initial cohort a total of six individuals returned incomplete questionnaire data and were excluded from the remainder of analysis. The final sample consisted of 189 participants (52.1% male) and had a mean age of 22.34 years (*SD* = 3.62; range 18 – 38). Exclusion criteria were shift-work, any psychiatric or neurological conditions, or any other clinical condition likely to affect sleep (*e.g.* autoimmune disorder, diabetes *etc.*). Where possible all participants were tested between 11:00 h – 14:00 h to minimise time of day effects on performance on neuropsychological tests. All participants gave their written informed consent before commencing the experimental protocol (Appendix A). Ethical approval for this study was granted by the Biomedical and Life Sciences Committee at Maynooth University.

Sleep quality and chronotype measures

The Pittsburgh Sleep Quality Index (PSQI) and the Munich Chronotype Questionnaire (MCTQ), both previously described in Chapter 2, were completed by participants. A global PSQI score was derived from the PSQI measuring a participant's level of self-reported sleep disturbances over the previous month. A PSQI score >5 was used to differentiate 'disturbed sleepers' from 'normal sleepers' according to the standard scoring convention of the questionnaire. From the MCTQ individuals' sleep debt corrected mid-point of sleep on free days (MSF_{sc}) was derived as a marker of circadian phase of entrainment. Self-reported chronotype was reported by participants on a scale of 0-6 (extreme early type" to "extreme late type"). Social jetlag (SJL) was calculated as a typical measure of recurring circadian misalignment as previously described and average sleep duration was computed from workday and free day sleep duration (assuming a 5-day workday and 2-day free day schedule).

Stanford Sleepiness Scale

The Stanford Sleepiness Scale (SSS) is a self-rating scale which progressively ranks sleepiness in incremented levels (Hoddes *et al.,* 1973; Appendix G). The scale consists of seven statements describing stages of sleepiness of which participants are asked to endorse the statement that best describes their current state of sleepiness and a specific point in time. The statements and their scale values are as follows: 1 – "Feeling active and vital; alert; wide awake", 2 – "Functioning at a high level, but not at peak; able to concentrate", 3 – "Relaxed; awake; not at full alertness; responsive", 4 – "A little foggy; not at peak; let down", 5 – "Fogginess; beginning to lose interest in remaining awake; slowed down", 6 – "Sleepiness; prefer to be lying down; fighting sleep; woozy", and 7 – "Almost in reverie; sleep onset soon; lost struggle to remain awake". The SSS was applied to participants immediately before commencing tests of neuropsychological performance to attain a measure of their alertness/sleepiness levels. The SSS chosen over other common sleepiness inventories as it generated a momentary, rather than continuous, appraisal of sleepiness.

Measures of neuropsychological performance

Conners' Continuous Performance Test (CCPT)

The Conners' Continuous Performance Test (CCPT; Conners *et al.,* 2003) was used to measure response accuracy and reaction time in our sample. The test was administered as computerised "Go/No-Go" visual performance task in which participants must repeatedly respond to stimuli appearing on-screen. The test consists of 360 trials during which an individual is required to respond by pressing the SPACEBAR key whenever any letter of the alphabet appears with the exception of the letter 'X' (Go target) and withhold their response where they see the letter 'X' (No-Go stimulus). Stimuli were coloured white and appeared against a black background in the centre of the screen for a period of 250 ms. The inter-stimulus interval (ISI) between trials varied between blocks of 1000 ms, 2000 ms, and 4000 ms. Each ISI condition block was presented consecutively for 20 trials before randomly

and without warning switching to another. Further, the test is structured such that the 360 trials are made up of six blocks consisting of 60 trials each during which all ISI condition blocks have appeared (*i.e.* 6 blocks containing 3 sub-blocks of 20 trials). Figure 3.2 illustrates the consecutive test progression.

Instances where participants fail to respond to a letter presentation (Go target) are recorded as omission errors whereas occasions where participants respond to a presentation of 'X' (No-Go target) are recorded as commission errors. The No-Go target 'X' is infrequently presented occurring in only 10% of cases (36 trials) and therefore the test encourages a pre-potent response style. Participants were asked to respond as quickly and as accurately as they could. Along with accuracy parameters mean reaction time (RTm) and the standard deviation of reaction time (RTSD) were also recorded in the test summary statistics. The test takes approximately 14-minutes to complete which allows adequate time for observing changes in performance over time.

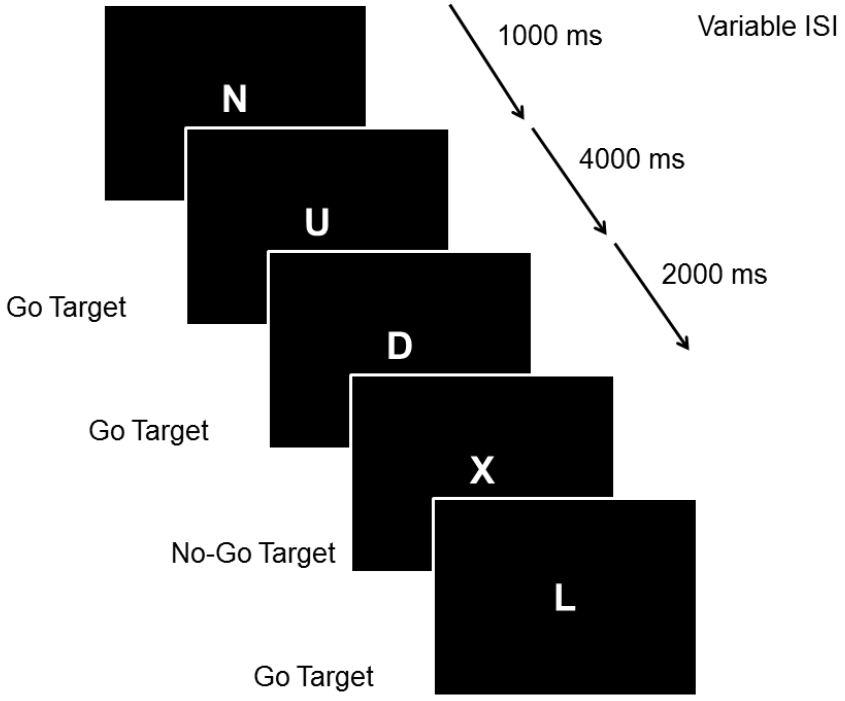


Figure 3.2. Schematic demonstrating CCPT trial structure.

Letters are consecutively presented to participants. All letters except the letter 'X' constitute 'Go' targets. Stimuli are presented in 20 trial sub-blocks, each sub-block with a variable ISI: 1000 ms, 2000 ms, or 4000 ms.

Iowa Gambling Task (IGT)

The Iowa Gambling Task (IGT) is a neurobehavioural test used to measure decision making processes under risk which relies on contingencies of reward and penalty as well as initial uncertainty of test premises and outcomes (Bechara *et al.,* 1994). Participants completed a computerised version of the task in which four decks of cards (labelled 'A',' B', 'C', and 'D') are presented and participants are asked to freely choose a card from one of the decks each turn. Decks differ in respect to the amount and the frequency of monetary gains/losses produced by each card selection. The average gains and losses over the course of each block of 10 trials are presented in Table 3.1. The test was administered using the Psychology Experiment Building Language (PEBL v0.13) program (Mueller & Piper, 2014).

Briefly, decks A and B produce high rewards but also more severe penalties at points which are not predicable by participants. Decks C and D on the other hand produce smaller monetary gains but also even smaller loses. Therefore in the long run selections from decks C and D are more advantageous than selections from decks A and B. Over 10 trials selections from the advantageous 'good' decks (C and D) produce an average net gain of $250, while selections from the disadvantageous 'bad' decks (A and B) produce an average net loss of -$250. On decks A and C the win/loss ratio is equal (5:5) whereas on decks B and D there is a high frequency of reward to losses (9:1). As the test progresses, participants usually begin to show a preference for advantageous decks. Participants began the game with a starting balance of $2000 and were given the standard IGT instructions, instructed to earn as much money as they could and minimise losses during the test. The test lasted for 100 trials with each trial consisting of a single card selection. After each trial, feedback was presented to participants indicating reward, penalty, and net gain status of their selection. Net profits were represented as green while net losses were in red. A progress bar indicated the change to the total balance after each trial. Figure 3.3 depicts a still frame example of the test. In the version of the IGT used decks A, B, C, and D were labelled 1, 2, 3, and 4 respectively.

Table 3.1 Reward and penalty contingencies from standard version of the IGT.

	DECK A	DECK B	DECK C	DECK D
Gain	$100	$100	$50	$50
Loss	$150 - $350	$1250	$50	$250
Gain/loss frequency per 10 trials	5:5	9:1	5:5	9:1
Number of net losses per 10 trials	5	1	0	1
Long-term net outcome	- $250	- $250	$250	$250

Table shows decks A/B produce large rewards but also relatively larger penalties compared to decks C/D. The pay-out frequencies of decks A and C are equivalent while decks B and D produce loses 10% of the time. All things considered, decks C and D produce the largest net profit over time. Adapted from Horstmann, Villringer & Neumann (2012).

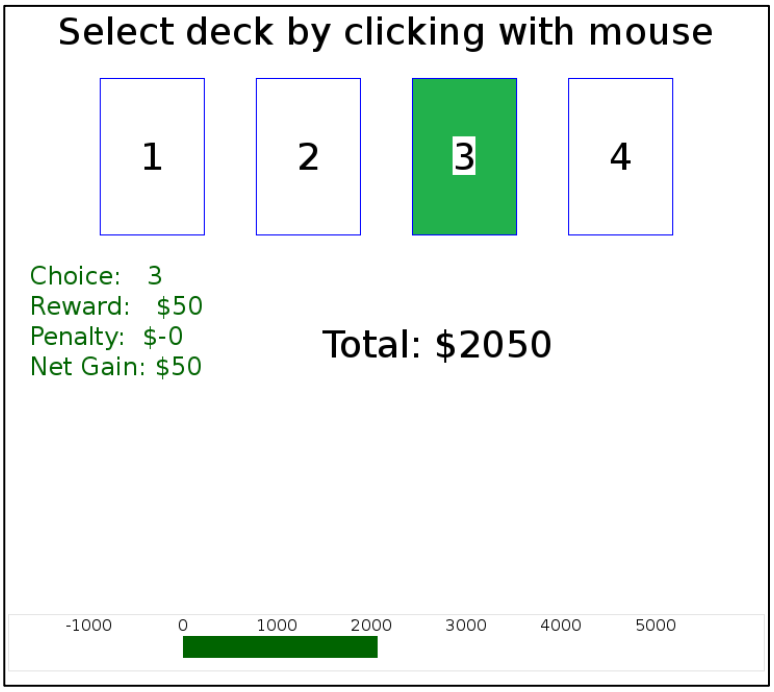


Figure 3.3 Screenshot of test screen shown to participants during IGT.

Feedback given includes green deck illumination during wins and red deck illumination during loses. Feedback bar tracks fluctuations in total 'bank' balance. Taken from PEBL v0.13 program

Data processing

CCPT summary statistics

Participants completed a standard version of the CCPT administered through the Psychology Experiment Building Language (PEBL v0.13) program (Mueller & Piper, 2014). The number of omission errors and commission errors were recorded in terms of the total per cent of errors in the summary statistics in PEBL. One participant had an extremely high omission error rate having confused Go target and No-Go target instructions and was excluded from further consideration.

Gaussian and ex-Gaussian parameter estimation

Gaussian and ex-Gaussian RT parameters were derived for the following different contextual conditions: in each category of ISI (1000 ms, 2000 ms, and 4000 ms) for test momentum analysis; in each block of 60 trials on the CPT (Blocks 1-6) for time on task analysis; and based on the overall RT throughout the test for examination on speed/accuracy trade-offs. In addition to RTm and RTSD, the coefficient of variation (CoV: RTm divided by RTSD) was also computed as a normalised measure of within-subject variability, thus removing the effect of response speed on the estimate of variability (Antonini, Narad, Langberg, & Epstein, 2013).

The ex-Gaussian RT distribution parameters, μ (*mu*), σ (*sigma*), and τ (t*au*), were calculated using the *egfit* function from the DISTRIB toolbox (Lacouture & Cousineau, 2008) in MATLAB R2012b (Mathworks, Natick MA, 2012) . This function computes an iterative search process to fit the ex-Gaussian probability density function to the frequency distribution, and generates the three parameters from which the observed RTs are most likely to be sampled. The μ parameter represents the mean of the normally distributed component of the frequency distribution and σ the standard deviation, and, τ represents both the mean and standard deviation of the tail-end exponential component (Lacouture & Cousineau, 2008).

Akaike's information criterion (AIC) was used to examine model goodness of fit (Tabachnick & Fiddell, 2013). On a number of cases under the different ISI conditions the ex-Gaussian model did not fit the frequency distribution (*i.e. sigma* or *tau* values were close to zero), in the 1000 ms condition this portion accounted for 1% of cases and in the 2000 ms condition similarly the rate was 1.6%. Further, across the different test blocks the rates where the ex-Gaussian model was a poor fit were as follows: Block 1 (6.3%), Block 2 (4.8%), Block 3 (5.3%), Block 4 (10%), Block 5 (7.4%), and Block 6 (5.3%). No participant demonstrated a consistent pattern of inter-ISI or inter-block poor model fit indicating that lack of fit was momentary and most-likely corresponded to the availability of data to sample from after taking into account withheld responses for any given block (*i.e.* correct No-Go responses). In all of these cases the estimated *mu*, *sigma*, and *tau*, parameters were not included in the analysis rather were replaced with the group averages. In all cases RTs < 100 ms were censored from the remainder of analyses at the beginning of processing owing to the likelihood of anticipated guesses, or extremely late responses to the previous trial (Ulrich & Miller, 1994).

Iowa Gambling Task

Participants completed the IGT using PEBL v.013. Before computing a standard IGT analysis cases were inspected for validity. As the original computerised version of the IGT contains a maximum of 60 possible selections from each deck (Bechara *et al.,* 2000) participants' selections from one deck would be capped to prevent participant maxing out specific decks. Therefore in instances in which a participant maximised a deck by making over 60 selections from one deck were eliminated from the analysis as performance on these trials indicates a different set of decision rules compared to normal selections (see Olson *et al.,* 2016). Sixteen participants (8.4%) in total 'maxed out' a deck in this manner. Deck maximisation occurred on decks A (n = 1), B (n =3), C (n = 9), and D (n = 3). Furthermore, IGT data from three participants were excluded due to technical errors administering the task. Re-testing of these participants would not be appropriate as these individuals would no longer be naïve to the reward and

loss contingencies of each deck. In total the final number of cases available for analysis on the IGT was 170.

We applied a standard IGT analysis examining participants' preference for decks as the task progressed. The total score on the task was measured by the following equation (Bechara *et al.,* 1994):

$$IGT\ score = [\ (C + D) - (A + B)]$$

Where the letters A, B, C, and D indicate the number of selections from each deck.

Positive IGT scores indicate an overall preference for advantageous decks, whereas negative scores indicate an overall preference for disadvantageous decks. Scores on the IGT were computed in five blocks of 20 trials each in order to gauge how participants' performance changed as they learned to discriminate 'good' decks from 'bad' decks.

Data analysis

Mixed-between-within groups ANOVAs were conducted to investigate behavioural data derived from the CCPT. Sleep quality ('Normal Sleeper' and 'Disturbed Sleeper'), social jetlag ('*SJL-LOW*' , '*SJL-INTERMEDIATE*', and '*SJL-HIGH*' groups), and self-reported chonotype ('Earlies', 'Intermediates', and 'Lates'), were inserted in separate models as independent fixed factors and the three test ISI conditions or six test blocks from the CCPT were inserted as repeated measures. Random effects were subsequently added to each of the models adjusting for average sleep duration, SSS score, and 'internal time', as covariates (ANCOVA) to determine the robustness of effects seen in the initial model. Internal time was used to estimate the relative point of an individual's circadian phase when testing occurred and was computed by finding the difference between MSF_{sc} and the time-of-day at which

neuropsychological testing commenced. IGT data was analysed using the conventional mixed ANOVA procedure in order to determine deck preference over time. The aforementioned group variables were inserted as fixed factors in separate models and the five different test blocks comprised of 20 trials were inserted as the repeated measures variable. Subsequent analysis involved breaking down participant selections from individual decks and tracking changes in deck preference across the test trials.

In all cases where main effects were found pairwise comparisons of estimated marginal means were examined using Tukey HSD or Bonferroni *post-hoc* tests for between group comparisons or within subjects comparisons respectively. Sphericity was tested using Mauchly's test of sphericity and where the assumption was violated a Greenhouse-Geisser correction was used for within-subjects effects and interactions. In cases where the 2-dimension interaction term (*GROUP × REPEATED MEAUSRE*) was significant the interaction effect was decomposed using the split method and simple main effects reported. A combination of Pearson or Spearman correlations were performed to explore associations between the three ex-Gaussian parameters (*mu, sigma,* and *tau*) and the two conventional RT parameters (mean and SD) as well omission error rate and commission error rate. Exploratory stepwise regression analyses using a forward selection method were performed for ex-Gaussian parameters to determine the role of reaction speed and variability had on accuracy trade-offs for omission and commission errors.

Protection against inferential errors

Due to the number of separate ANOVAs conducted here we highlight a number of considerations taken in order to decrease the possibility of Type I error (*i.e.* inflated risk of incorrectly rejecting the null hypothesis). On the CCPT analyses there were in total 3 different independent factors and a total of 8 outcome measures assessed making a *Bonferroni* correction for familywise error too unwieldy by creating too stringent a critical α and thereby resulting in the reverse problem of inflated Type II

error risk. To address this problem we decided *a priori* to first examine primary outcome measures derived from the CCPT (omission errors, commission errors, RTm and RTSD) which were corrected using a *Bonferroni* criterion resulting in a critical familywise α for all inferential tests of main and interaction effects of $\alpha_{FW} = .05/4 = .0125$.

Secondary measures such as the CoV RT and ex-Gaussian RTs which were derived from primary measures were not subjected to this correction. The rationale for this being that as the mean and the standard deviations directly determine the coefficient of variation value or are in and of themselves directly determined by the values of the three ex-Gaussian parameters an effect which survives initial familywise correction should be robust against subsequent analysis (as noted by Leth-Steensen *et al.,* 2000). Moreover, we forewent testing the three ex-Gaussian parameters using the less conservative MANOVA method given the amount of dependent variables used. Our interest was not to see if there was an overall effect in the canonically derived variable of *mu, sigma,* and *tau* combined (which would in effect be captured using univariate tests of Gaussian parameters alone) but rather we wanted to specifically decompose the effects of IIV in RT for which separate models are more appropriate (see Leth-Steensen *et al.,* 2000).

Finally concerning the IGT analysis we did not apply a correction for familywise error as only one outcome measure, deck preference score, was addressed. In instances in which participants' selections are interrogated on a deck-by-deck basis a correction is not warranted as the overall scores are ultimately derived from selections made from individual decks.

3.3 Results

Demographic distributions and relatedness of sleep and circadian variables

An inspection of the distribution of chronotypes among the sample revealed that MSF_{sc} had a characteristically normal distribution with a mean of phase of entrainment of 5:38 AM (*SD* = 1.23 h) (Figure 3.4A). SJL in our sample ranged between zero and 6:23 h, with a typical positive skew as previously noted (Figure 3.4B). Exploratory partial correlations which controlled for age and sex, revealed significant moderate magnitude positive correlations between MSF_{sc} and SJL, $r = .487$, $p < .001$ (Figure 3.4C) and significant small magnitude positive correlations between MSF_{sc} and sleep disturbances as measured by PSQI score, $r = .229$, $p = .002$ (Figure 3.4D). Despite both sharing correlations with mid-sleep however SJL and PSQI score seemed to be unassociated, $r_{rho} = .079$, $p = .288$ (Figure 3.4E). An examination PSQI score by univariate ANOVA showed a significant main effect of self-reported chronotype group, $F(2, 183) = 5.577$, $p = .004$, $\eta_p^2 = .05$, with Tukey HSD *post-hoc* comparisons revealing significant differences in sleep disturbance measures between the early chronotypes and late chronotypes, $p = .005$ (Figure 3.4F).

Definition of sample groups

Participant's questionnaire responses were inspected and nominal variables created for mixed factorial analysis. Based on participant's self-reported chronotype on the MCTQ the sample was divided into three groups, 'early-types' (scoring between 0-1), 'intermediate-types' (scoring between 2-4), and 'late-types' (scoring between 5-6), which were utilised in the univariate ANOVA in the previous section. Based on the distribution of SJL accrued by the sample, three equally sized groups were partitioned referred to as SLJ-LOW (0 h – 1:25 h), SJL-INTERMEDIATE (1:25 h – 2:15 h), and SJL-HIGH (> 2:15 h) by means of a tertile split of the cohort. Finally, a PSQI score > 5 was used to distinguish normal sleepers ($n = 69$) from those that experienced frequent sleep disturbances ($n = 115$).

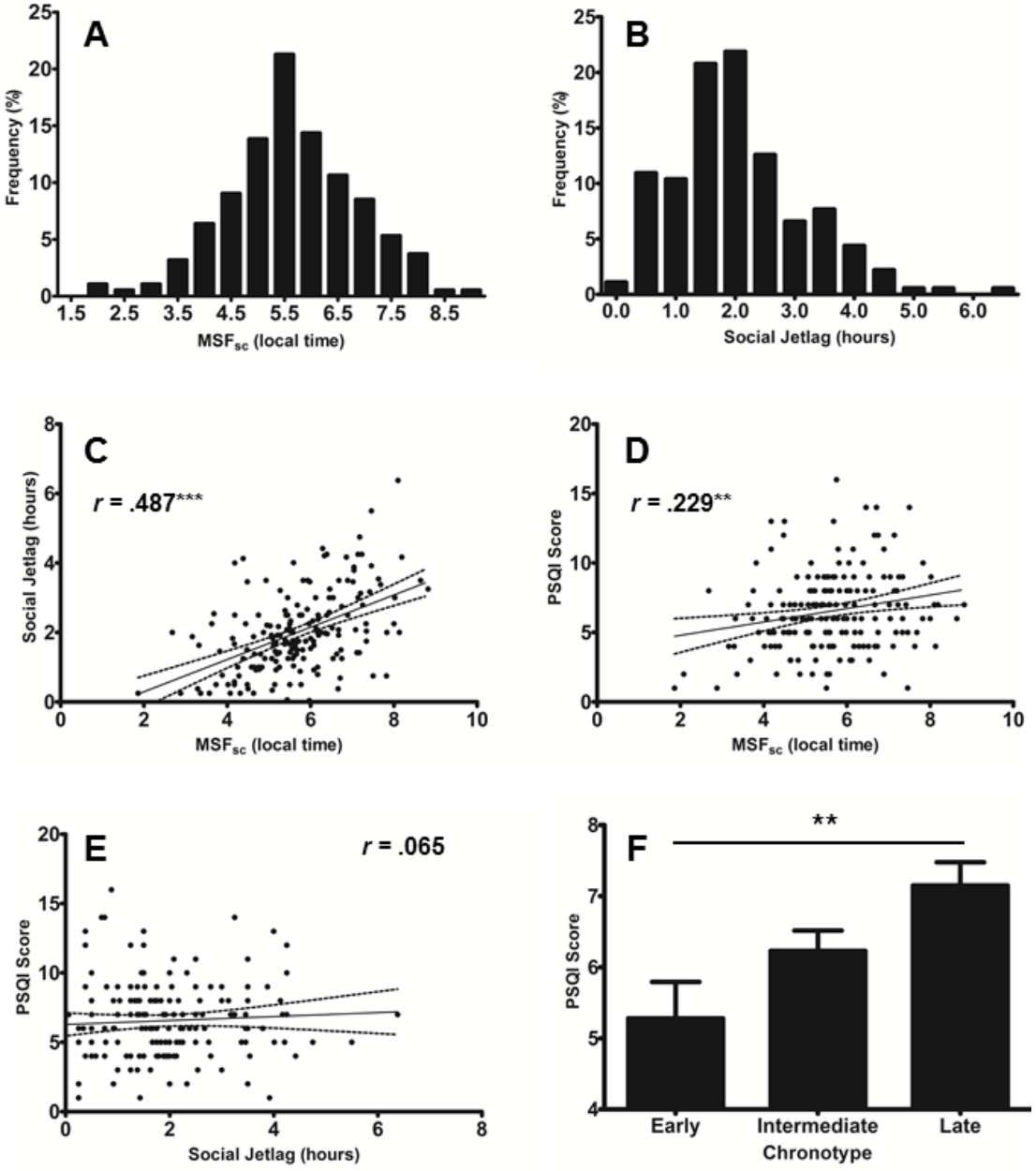


Figure 3.4 Sample characteristics of questionnaire measures assessed

*(A) Distribution of mid-sleep on free days (MSF_{sc}) (B) Distribution of absolute SJL in accrued by sample in hours (C) Significant correlation between MSF_{sc} and SJL (D) Significant correlation between MSF_{sc} and total PSQI score (E) Non-significant correlation between SJL and total PSQI score (F) Between group comparisons of sleep quality among self-reported chronotypes. * p <.05; ** p < .01; *** p < .001. Error bars denote SEM.*

Summary measures of response accuracy and reaction time on CCPT

We did not detect any gross differences between groups in any of the ANOVAs conducted exploring omission error or commission error rates on the CCPT (Table 3.2). The results suggest that neither chronotype or sleep and circadian rhythm disruption produced any deficits in performance accuracy. There was a substantial main effect of the ISI condition on both omission errors and commission errors revealing that target accuracy (*i.e.* fewer omission errors) improved as the ISI increased, $F(1.9, 360.7) = 27.945$, $p < .001$, $\eta_p^2 = .13$, while conversely, faster ISIs were associated with better correct rejection of non-targets (*i.e.* fewer commission errors), $F(2, 374) = 13.851$, $p < .001$, $\eta_p^2 = .069$. The ISI × GROUP interaction term was not statistically significant among any of the ANOVA models.

Concerning the reaction time of participants responses on the CCPT, we detected a significant main effect for SJL group, $F(2, 185) = 6.75$, $p = .001$, $\eta_p^2 = .068$, such that the greater the SJL accrued by the sample, the faster the participants' RTm (Table 3.2., Figure 3.5A.). Tukey post-hoc tests revealed significant differences between SJL-LOW and SJL-INTERMEDIATE groups ($p = .005$) and also between SJL-LOW and SJL-HIGH groups ($p = .005$), but not between SJL-INTERMEDIATE and SJL-HIGH groups ($p = .997$). The effect on RTm appeared to be specific to SJL as ANOVA models utilising chronotype as the between subjects factor did not show any differences between self-reported early-types, intermediate-types, and late-types, $F(2, 185) = .379$, $p = .685$, , $\eta_p^2 = .004$ (Table 3.2., Figure 3.6A), nor were any differences between normal sleepers and disturbed sleepers detected, $F(1, 182) = .005$, $p = .943$, , $\eta_p^2 < .001$ (see Table 3.2.). Further, after controlling for participants' self-reported wakefulness rating at the time of testing, average sleep duration, and internal time of day (time of testing relative to mid-sleep on free-days; utilised as a phase marker of subjective circadian phase), the effect of SJL group on CCPT RTm persisted, $F(2, 182) = 5.17$, $p = .007$, $\eta_p^2 = .054$.

There was a large main effect of the ISI condition on RTm, $F(1.71, 318.74) = 371.63$, $p < .001$, $\eta_p^2 = .665$, indicating that the speed of individuals' response was primed by the momentum of stimuli appearing on the screen (*i.e.* the smaller the ISI, the faster

the RT). There were no significant interaction effects between ISI and SJL detected (Table 3.2).

An initial analysis of reaction time variability using the summary measure of RTSD found that, similar to RT, there was a main effect of SJL group, $F(2, 185) = 7.03$, $p = .003$, $\eta_p^2 = .061$, with the SJL-LOW group showing greater RTSD than the SJL-INTERMEDIATE group ($p = .048$) and the SJL-HIGH group ($p = .003$) (Figure 3.5B.). There were not any significant between group differences in RTSD as a function of chronotype or sleep quality (Table 3.2., Figure 3.6B). As with RT there was a significant main effect of ISI on the variability of participants response time (RTSD), $F(1.46, 273.28) = 7.4$, $p = .002$, $\eta_p^2 = .038$.

Because RTSD is closely dependent on RT however we repeated these analyses using the coefficient of variation (CoV) of RT as a dependent variable in order to separate response variability from RT. Using this approach we did not detect any significant main effect of SJL on response variability between groups, $F(2, 185) = 2.971$, $p = .054$, $\eta_p^2 = .031$, and the previously noted main effect of ISI disappeared also, $F(1.5, 287.17) = 1.022$, $p = .361$, $\eta_p^2 = .005$, (Figure 3.5C.). There was not any significant SJL × ISI interaction effect employing either RTSD or CoV as dependent variable. For comparative purposes these analyses were performed using self-reported chronotype as the between subjects factor and in neither of the RTSD or CoV models were there any main significant effects of chronotype found (Figure 3.6 B & C).

Ex-Gaussian measures of reaction time and inter-individual variability

As reaction time is typically positively skewed its frequency distribution it is better approximated using a combination of Gaussian and exponential functions. Therefore we examined the ex-Gaussian parameter estimates of RT to further interrogate the effects seen from utilising the summary measures alone. Among the ex-Gaussian parameters of RT there were significant main effects of SJL group seen for *mu*, $F(2, 185) = 3.611$, $p = .029$, $\eta_p^2 = .038$, and for *tau*, $F(2, 185) = 5.727$, $p = .004$, $\eta_p^2 = .058$, but not for *sigma*, $F(2, 185) = 2.040$, $p = .133$, $\eta_p^2 = .022$ (Figures 3.5D, E & F). As demonstrated

previously using traditional Gaussian measure of mean RT, Tukey post-hoc comparisons revealed that significant differences were only present between the SJL-LOW group compared to the SJL-INTERMEDIATE and SJL-HIGH groups, such that both *mu* and *tau* were smaller as the amount of SJL accrued by individuals increased (data and post-hoc differences presented in Figures 3.5D & F).

There was a significant main effect of ISI on each of the ex-Gaussian parameters: *mu*; $F(1.63, 301.23) = 250.04$, $p < .001$, $\eta_p^2 = .575$, *sigma; F*(1.78, 329.24) = 9.25, $p < .001$, $\eta_p^2 = .048$, *tau*; $F(1.8, 332.57) = 7.13$, $p = .001$, $\eta_p^2 = .037$, such that shorter ISIs produced faster RTs and less variability of RT. There were no significant interaction effects between ISI and SJL group detected in any of the models. It appears again that the between group differences are underpinned by SJL specifically as comparative models utilising self-reported chronotype as the between subjects factor failed to detect any significant main effects for differences between early-types, intermediate-types, or late-types for *mu*, $F(2,185) = .067$, $p = .935$, $\eta_p^2 = .001$, *sigma*, $F(2, 185) = .014$, $p = .986$, $\eta_p^2 < .001$, or *tau*, $F(2, 185) = .501$, $p = .607$, $\eta_p^2 = .005$ (Figures 3.6D, E, & F). The pattern of a significant main effect for the ISI condition persisted ($p_{ALL} < .05$) and no significant ISI × CT interaction effects were detected.

Gaussian and ex-Gaussian parameters as a function of block

To explore the potential mediating effect of time on task on subject's performance on the CCPT, mixed between-within-groups-ANOVAs were conducted with SJL group inserted as the between groups factor and CCPT test block (360 trials divided into 6 blocks of 60 trials each) inserted as the within groups factor. Inspection of Gaussian parameters first revealed significant main effects for SJL on mean RT, $F(2, 185) = 6.44$, $p = .002$, $\eta_p^2 = .065$, and on RTSD, $F(2, 185) = 6.92$, $p = .001$, $\eta_p^2 = .070$. Tukey *post-hoc* tests indicated that the SJL-LOW group was differentiated from the two other SJL groups by having a slower mean RT and greater variability in RT ($p_{ALL} < .05$). The main effect for block revealed that participants' mean RT did not change as time-on-task progressed, $F(3.71, 686.8) = 2.214$, $p = .051$, $\eta_p^2 = .012$, however there was a

Table 3.2. Mixed factorial ANOVAs examining CCPT outcome measures as a function of self-reported chronotype (CT), social jetlag (SJL), and sleep quality (PSQI score).

	Target Accuracy (% correct hits)		Non-target Accuracy (% correct rejections)		RTm (*ms*)		RT SD (*ms*)	
	F	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
CT	$F(2, 185) = .986$	.011	$F(2, 185) = .633$	.006	$F(2, 185) = .379$	.004	$F(2, 185) = .671$	.004
SJL	$F(2, 185) = .306$	.003	$F(2, 185) = .113$	.023	**$F(2, 185) = 6.75$****	**.068**	**$F(2, 185) = 6.04$****	**.061**
PSQI	$F(1, 182) = .837$	.005	$F(1, 182) = .031$	.001	$F(1, 182) = .005$	.001	$F(1, 182) = 2.619$	.014
ISI	**$F(2, 374) = 27.945$*****	**.130**	**$F(2, 374) = 13.85$*****	**.069**	**$F(2, 374) = 367.64$*****	**.665**	**$F(2, 374) = 7.395$****	**.038**
CT × ISI	$F(4, 370) = .50$	.005	$F(4, 370) = .621$	.007	$F(4, 370) = .311$	.003	$F(4, 370) = .332$	.004
SJL × ISI	$F(4, 370) = .869$	.009	$F(4, 370) = .717$	.008	$F(4, 370) = .399$	.004	$F(4, 370) = 1.22$	.008
PSQI × ISI	$F(2, 364) = 1.72$	.009	$F(2, 364) = .047$	.001	$F(2, 364) = 1.393$	.008	$F(2, 364) = 3.55$*	.019

*Table summarises the results of twelve separate mixed-between-within group ANOVAs utilising self-reported chronotype (CT), social jetlag (SJL), and sleep quality (PSQI score) as independent measures, and CCPT measures of accuracy and RT inserted as outcome measures. Main effects of group, within group effects of interstimulus interval (ISI), and interaction terms reported. *p < .05; **p < .01; *** p < .001. Bold denotes significant effects after Bonferroni correction*

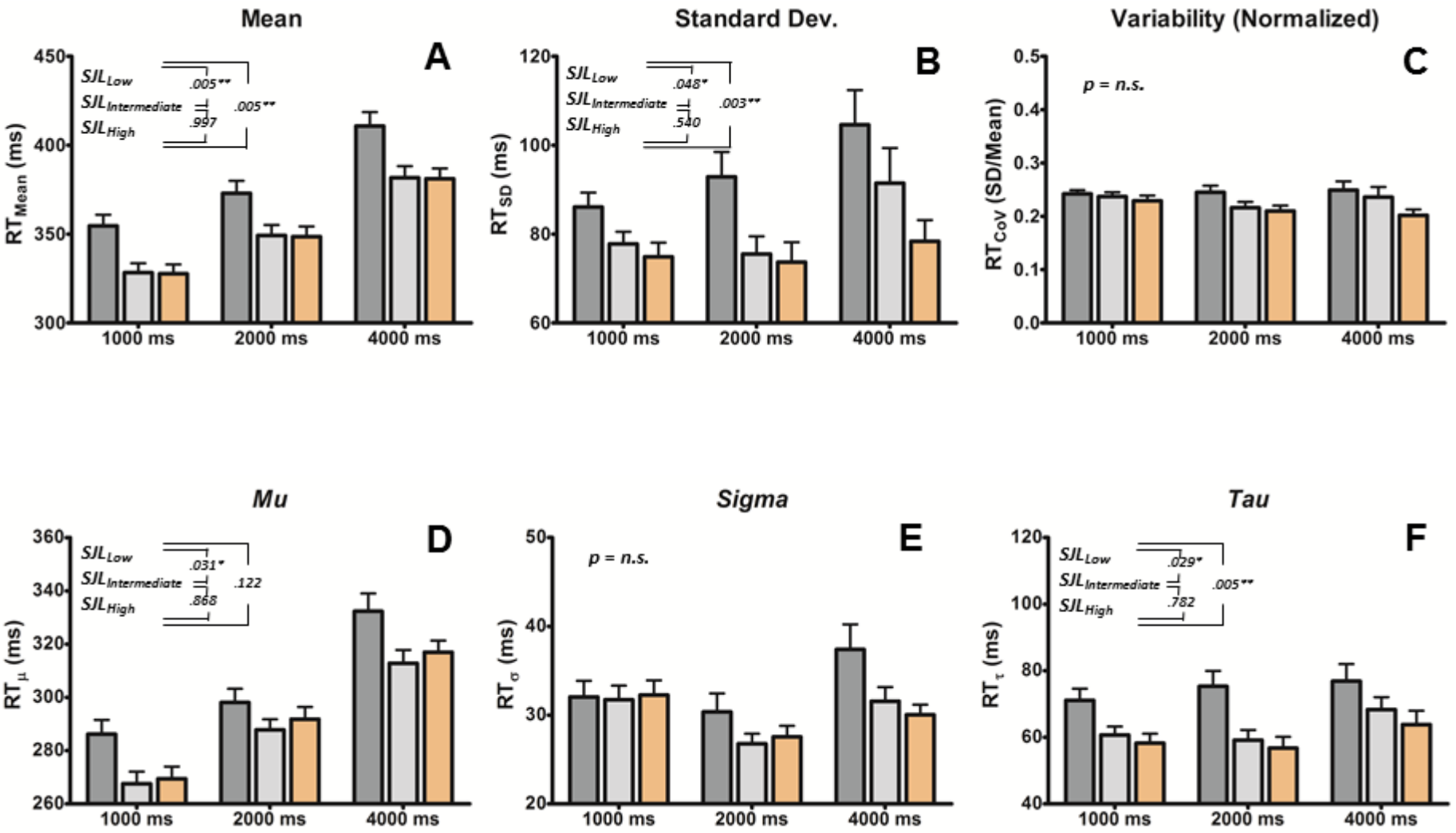


Figure 3.5. Gaussian and ex-Gaussian RT measures as a function of social jetlag.

*(A) Between group differences on mean RT (B) Between group differences on standard deviation of RT (C) Non-significant model of standardised variability of RT (D) Between group differences for normally distributed component of ex-Gaussian frequency distribution Mu (E) Non-significant model for Sigma (F) Between group differences for Tau RT. Dark grey bars denote low SJL group, light grey bars denote intermediate SJL group, and Orange bars denote high SJL group. *p < .05; **p < .01; ***p < .001*

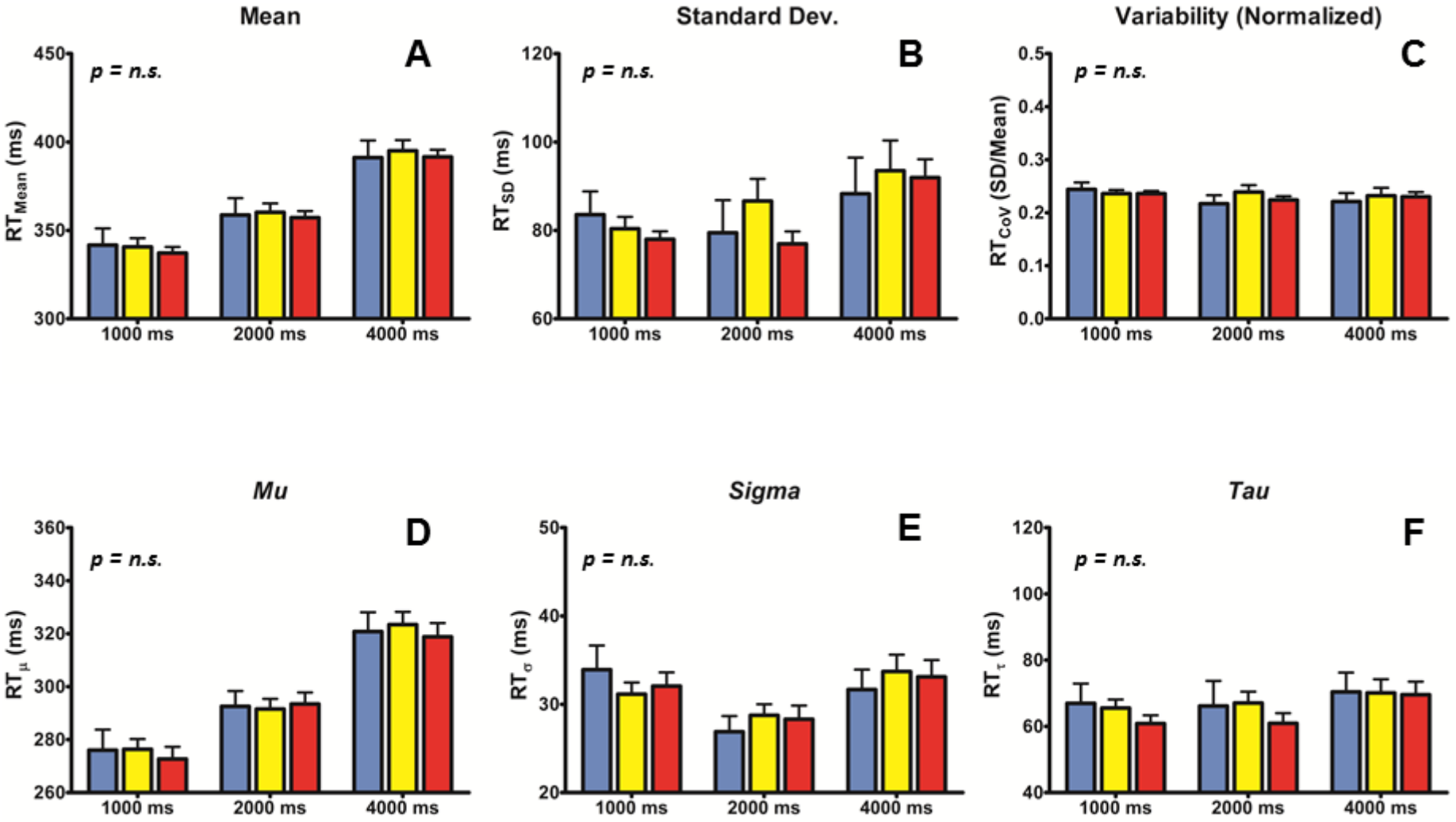


Figure 3.6. Gaussian and ex-Gaussian RT measures as a function of self-reported chronotype

Non-significant ANOVA models showing (A) mean RT (B) standard deviation of RT (C) standardised variability(D) Mu (E) Sigma, and (F) Tau. Blue bars denote early CTs, yellow bars denote intermediate CTs, and red bars denote late CTs. n.s. indicates non-significant differences for main group effect

significant main effect of block found for RTSD, $F(2.86, 528.2) = 3.735$, $p = .013$, $\eta_p^2 = .02$, with Bonferroni *post-hoc* tests revealing the only significant differences between Block 1 and Block 2 ($p = .013$).

When RTSD was considered independently of mean RT using the coefficient of variation of RT as an outcome measure in the ANOVA model there was a significant main effect for SJL detected, $F(2, 185) = 3.75$, $p = .025$, $\eta_p^2 = .039$, with Tukey post-hoc tests showing the only significant differences between the SJL-LOW group and the SJL-HIGH group ($p = .018$). A significant main effect of block was again noted, $F(2.88, 532.14) = 5.73$, $p = .001$, $\eta_p^2 = .03$, with Bonferroni *post-hoc* tests only showing differences between Block 1 and Block 2 ($p = .001$), and between Block 1 and Block 3 ($p = .036$) indicating that the change in response variability as the task went on did not persist to the latter half of the test. In each of the models for meat RT, RTSD, and CoV there were not any significant SJL × BLOCK interactions detected.

Concerning the ex-Gaussian parameter estimates of RT there were significant main effects in group comparisons for *mu*, $F(2, 185) = 3.41$, $p = .035$, $\eta_p^2 = .036$, and *tau*, $F(2, 185) = 9.86$, $p < .001$, $\eta_p^2 = .096$. Tukey post-hoc tests showed that the SJL-LOW group performed significantly slower than the SJL-INTERMEDIATE group on the normally distributed *mu* component of RT ($p = .035$), and significantly slower than the SJL-INTERMEDIATE group ($p = .004$) and the SJL-HIGH group ($p < .001$) on the exponential *tau* component of RT. The main effect for block was significant for *mu*, $F(4.11, 759.57) = 3.54$, $p = .007$, $\eta_p^2 = .019$, but not for *tau*, $F(4.59, 848.74) = .257$, $p = .925$, $\eta_p^2 = .001$. The SJL × BLOCK interaction effect was not significant. There was not a significant main effect for group on the *sigma* component of RT, $F(2, 185) = .827$, $p = .439$, $\eta_p^2 = .009$. There was a significant main effect of Block, $F(4.33, 800.55) = 6.35$, $p < .001$, $\eta_p^2 = .033$ such that the variability of the normally distributed component of RT increased as time on task increased. The SJL × BLOCK interaction effect was not significant. Gaussia and ex-Gaussian parameters expressed as a function of time-on-task appear in Figure 3.7 A – F.

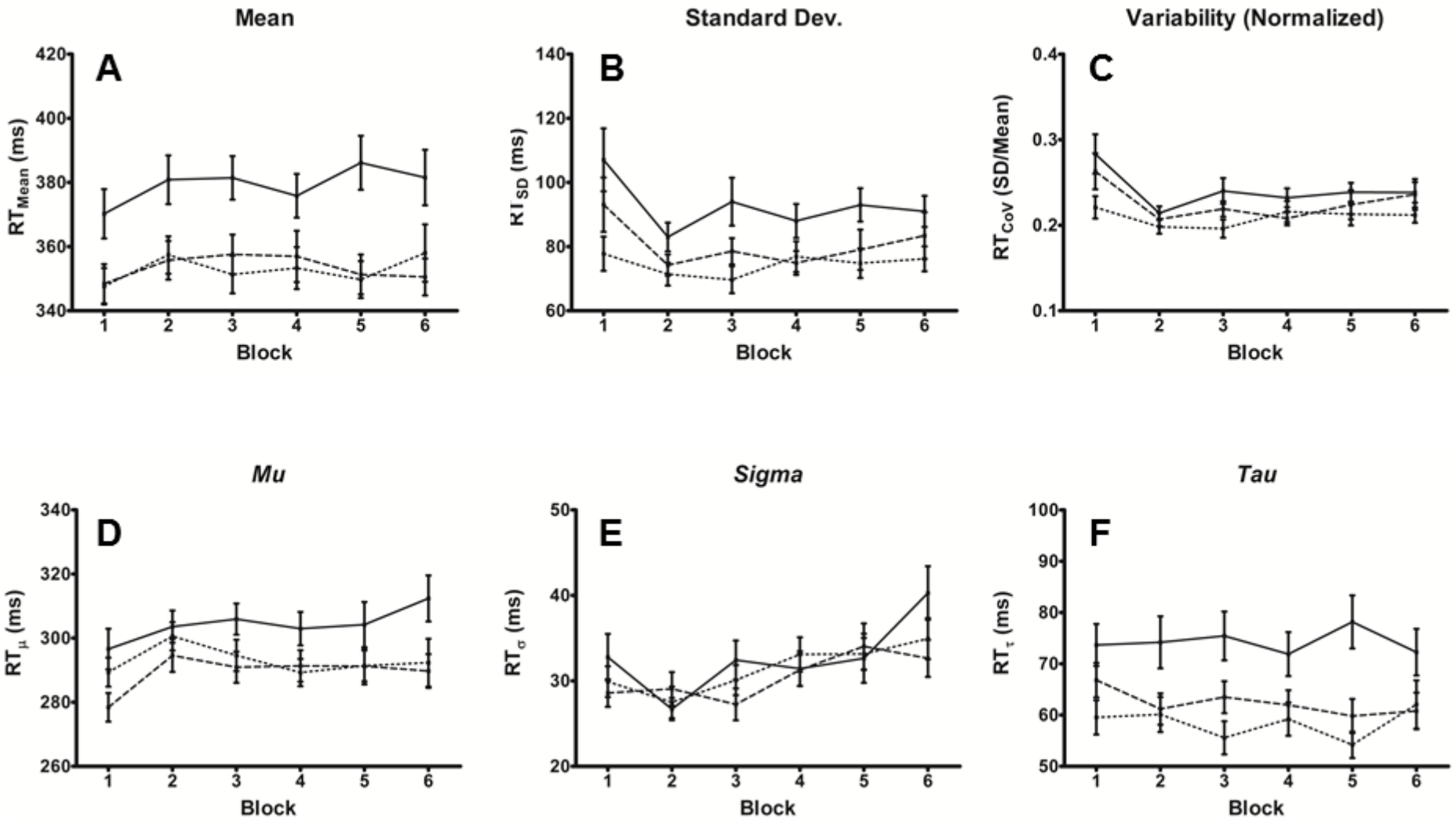


Figure 3.7.Time-on-Task changes in reaction time on CCPT

Figures above show changes in (A) mean RT (B) standard deviation in RT (C) the coefficient of variation of RT (D) Mu (E) Sigma, and (F) Tau as a function of CCPT test block. Each block represents 60 trials of the CCPT during which time three 20 stimuli sub-blocks are presented at 1000 ms, 2000 ms, and 4000 ms ISI. Black line represents low SJL group, the partially broken line represents the intermediate SJL group, and the dotted line represents the high SJL group

Correlations between reaction time, omission errors, and commission errors

In order to ascertain the relationships between reaction time and IIV of reaction time we conducted a series of correlations between RT, RTSD, RT CoV, *mu, sigma,* and *tau,* and measures of performance accuracy in response to targets and non-targets. Correlation matrix of variables explored is presented in Table 3.3. Notably, we found that among ex-Gaussian parameters assessed that *mu* values were negatively correlated with omission errors, while both *sigma* and *tau* values were both positively correlated with omission errors Furthermore, we detected a strong negative correlation between *mu* and commission errors and a moderate negative correlation between *tau* and commission errors.

Exploring how ex-Gaussian measures moderate errors of omission and errors of commission on the CCPT

Further to the associations between ex-Gaussian reaction time parameters and both errors of omission and commission revealed by correlational analyses we conducted exploratory regression analyses to assess the degree to which response accuracy was predicted by reaction time and IIV of reaction time. Two backward enter linear regressions were conducted using the rate of omission errors and the rate of commission errors as dependent variables. The predictors were ex-Gaussian variables *mu, sigma,* and *tau* which were entered in a stepwise manner into the regression models.

The final model for predicting errors of omission comprised of all three predictors was statistically significant, $F(3, 184) = 16.011$, $p < .001$, accounting for approximately 19.4% of the variance in omission errors ($R^2 = .207$; adjusted $R^2 = .194$). The raw and standardized regression coefficients of the predictors together with their correlations with each other and their squared semi-partial correlations are shown in Table 3.4. *Mu* was entered first into the regression model, followed by *sigma* and finally *tau*. The variable that received the strongest weight in the final model was *mu* value with 14.5% of the variance in omission error rate accounted

uniquely by this variable alone followed by *tau* score which predicted 5.1% of the variance.

When non-target accuracy was examined the final model was comprised of all predictors and was statistically significant $F(3, 184) = 47.048$, $p < .001$, and accounted for approximately 42.5% of the variance in commission error rate ($R^2 = .434$; adjusted $R^2 = .425$). The raw and standardized regression coefficients of the predictors together with their correlations with each other and their squared semi-partial correlations are shown in Table 3.5. As shown *mu* was the most meaningful predictor of commission error frequency predicting 39.5% of the variance in errors of commission committed by individuals on the CCPT.

Table 3.3. Correlations between summary performance measures, Gaussian and ex-Gaussian RT parameters

	Omission Errors	Commission Errors	RTm	RTSD	RT CoV	RT μ (*Mu*)	RT σ (*Sigma*)	RT τ (*Tau*)
Omission Errors	-							
Commission Errors	.356***	-						
RTm	-.064	.-556***	-					
RTSD	.313***	-.093	.539***	-				
RT CoV	.392**	.127	.198**	.926***	-			
RT μ (*Mu*)	-.244**	-.590***	.839***	.090	-.239**	-		
RT σ (*Sigma*)	.144*	-.075	.485***	.278***	.121	.506***	-	
RT τ (*Tau*)	.277**	-.191**	.661***	.858***	.691***	.158*	.205**	-

*Correlation matrix showing relatedness of primary accuracy outcomes derived from CCPT: Omission errors and commission errors (measured as per cent) and Gaussian and ex-Gaussian reaction time variables. RTm = mean reaction time, RTSD = standard deviation of reaction time, RT CoV = coefficient of variation of reaction time, Mu and Sigma represent the mean and standard deviations of the normally distributed portion of the reaction time curve respectively and Tau represents and the mean and standard deviation of the exponential component of the curve. *p < .05; **p < .01; ***p < .001*

Table 3.4. Regression model predicting CCPT omission errors using ex-Gaussian parameters

Final Model	B	SE_B	β	sr^2
Constant	.022	.005		
μ (*Mu*)	-	-	-.443	.145
σ (*Sigma*)	-	-	.321	.007
τ (*Tau*)	-	-	.231	.051

*R^2 = .207; adjusted R^2 = .194, p < .001. Predictor variables inserted: mu, sigma, and tau measured in milliseconds. B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in the proportion of omission errors made accounted for by variable. * p < .05 *** p <.001*

Table 3.5. Regression model predicting CCPT commission errors using ex-Gaussian parameters

Final Model	B	SE_B	β	sr^2
Constant	1.413	.087		
μ (*Mu*)	-.004	.000	-.731	.395
σ (*Sigma*)	.006	.001	.324	.008
τ (*Tau*)	-001	.000	-.142	.002

*R^2 = .434; adjusted R^2 = .425, p < .001. Predictor variables inserted: mu, sigma, and tau measures in milliseconds. B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in the proportion of commission errors made accounted for by variable. * p < .05 *** p <.001*

Standard IGT analysis

A mixed ANOVA showed that net IGT score increased across test blocks reflecting that individuals learned to discriminate advantageous decks from disadvantageous ones. As Mauchly's *W* was significant, χ^2 (9) = 26.763, p =.002, a Greenhouse-Geisser correction was used. Results indicated that there was a significant main effect for block, $F(3.69, 620.4) = 31.702$, $p < .001$, $\eta_p^2 = .159$ (Figure 3.8), with Bonferroni *post-hoc* comparisons showing that all net gain scores on all subsequent blocks significantly differed from the first ($p_{ALL} < .001$). We detected a marginally significant main group effect of sleep quality, $F(1, 168) = 3.886$, $p = .50$, $\eta_p^2 = .023$, which indicated that disturbed sleepers had lower net IGT scores than normal sleepers. There was not a significant interaction effect between block and sleep quality detected however, $F(3.69, 620.4) = 1.45$, $p = .220$, $\eta_p^2 = .009$.

Further, we wished to examine if the apparent differences in net IGT score were more pronounced considering only the late stages of the IGT test. The net IGT score was calculated for the final 60 trials representing a period during which the individuals were adequately exposed to the reward contingencies of the test, separating the and the earlier 40 trials during which responding is ambiguous. Independent samples t-test with a correction for unequal variances revealed that disturbed sleepers (64.7%) had significantly lower net IGT scores over later test trials compared to normal sleepers (35.3%), Welches' $t(94.42) = 2.05$, $p = .043$, d =.347. Neither the main effect of group nor any of the group × block interactions were significant in any of the ANOVA models for SJL or self-reported chronotype.

Comparisons of deck selections

Because analysis of net IGT scores indicated that there may exist differences between deck selection strategies as a function of sleep quality, we performed a closer inspection of deck choices made throughout the task. Separate mixed ANOVAs were performed assessing the main within group effects for block and the main group effect for sleep quality. As expected there were significant main effects for test block

on deck choices on deck A, $F(3.81, 640.65) = 37.947$, $p < .001$, $\eta_p^2 = .184$, deck B, $F(3.6, 606.07) = 7.197$, $p < .001$, $\eta_p^2 = .041$, deck C, $F(3.33, 559.66) = 17.855$, $p < .001$, $\eta_p^2 = .096$, and deck D, $F(3.79, 637.44) = 9.926$, $p < .001$, $\eta_p^2 = .056$, such that choices from the disadvantageous decks A and B significantly decreased as the task progressed while selections from advantageous decks significantly increased as the task progressed. We detected a significant main group effect of sleep quality on selections made on deck B, $F(1, 168) = 4.238$, $p < .041$, $\eta_p^2 = .025$, with no differences detected for other decks (Figure 3.9 A-D). There were no interaction effects detected in any of the models.

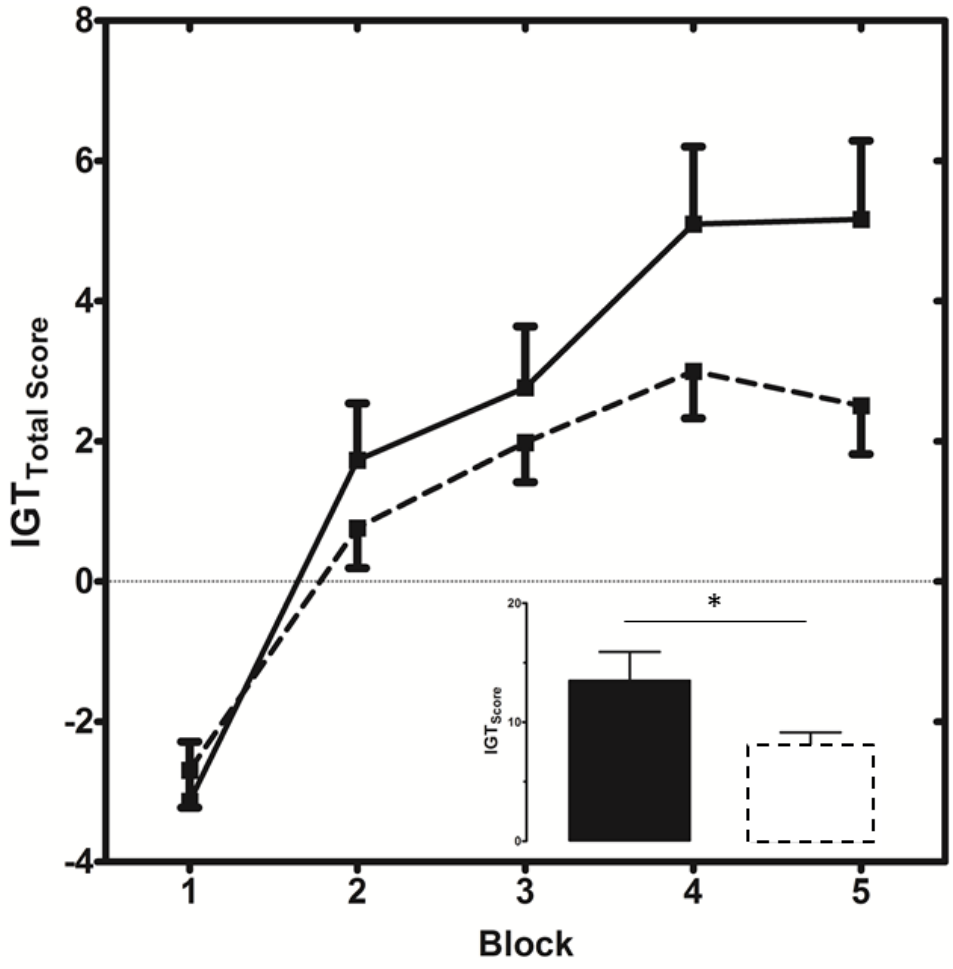


Figure 3.8 Iowa Gambling Task total score as a function of block

*Graph shows net IGT score increasing as a function of test block indicating that participants learned to discriminate and select advantageous choices over disadvantageous ones as the test progressed. Disturbed sleepers (broken line) show significantly lower scores than normal sleepers (full line) on the cumulative net score on the final 60 trials of task. *p < .05*

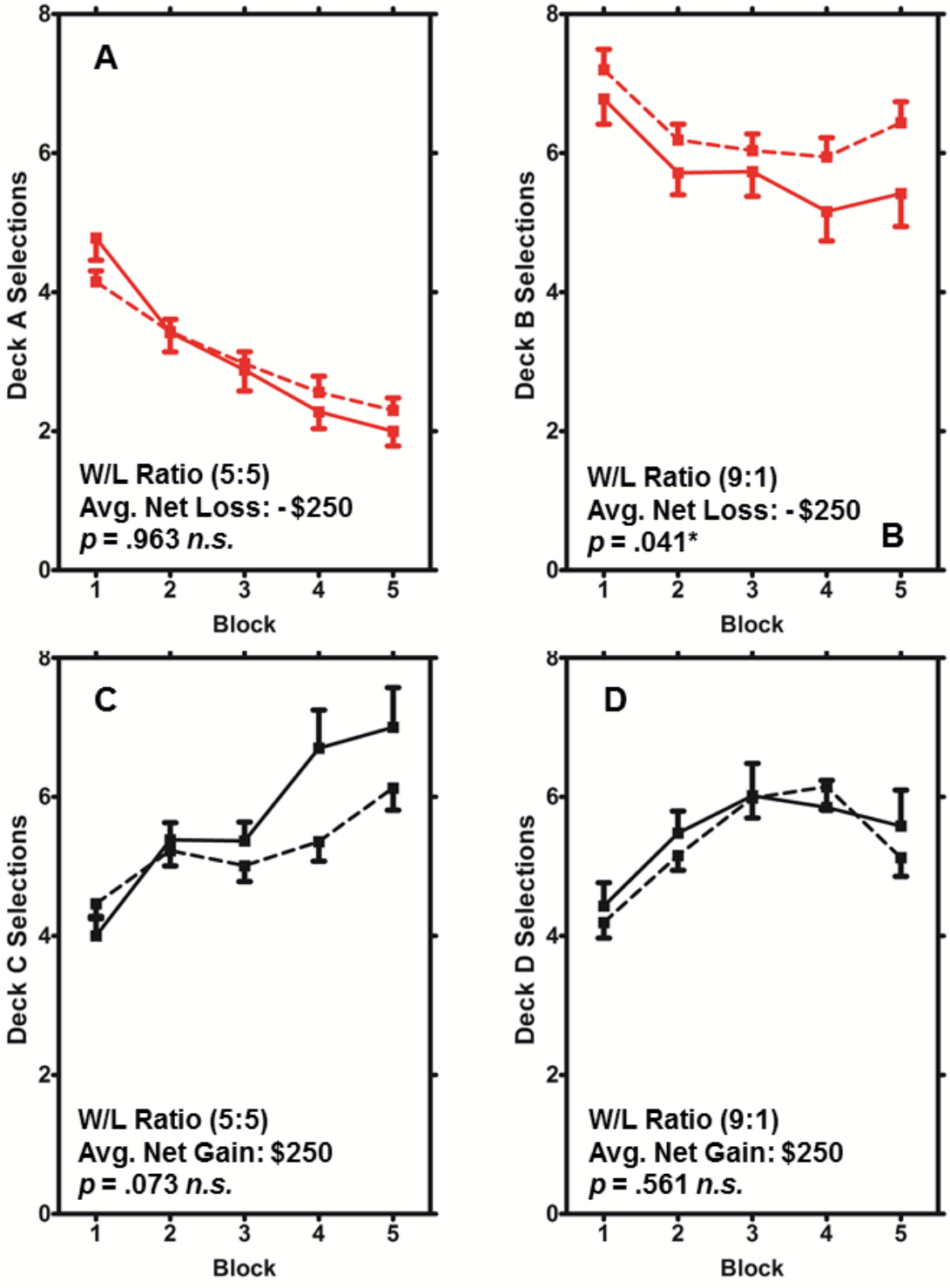


Figure 3.9. IGT performance separated by deck

*Panels show number of selections made by participants from each IGT deck. (A) = deck A, (B) = deck B, (C) = deck C, and (D) = deck D. Full line denotes performance over time for normal sleepers, broken line denotes disturbed sleepers. Red indicates disadvantageous decks, black indicates advantageous decks. Note significant differences in deck selection between groups on deck B, the high win frequency, low net gain deck. * p < .05.*

3.4 Discussion

The current study set out to examine the extent to which parameters measuring habitual sleep and circadian rhythm disruption were associated with putatively dissociable indicators of impulsivity and inattention in a sample of healthy young adults in order to better understand the pathophysiology of adult ADHD. Our most notable finding was that recurring workday-free day circadian misalignment typified by social jetlag was associated with significantly faster and less variable responses on a response inhibition task conventionally used to assess behavioural responding in ADHD.

Generally speaking, on such measures fast reaction times are associated with increased errors of commission, reflecting an overall more impulsive response style, whereas greater variability is associated with a greater amount of omission errors reflecting inattentive response (Epstein *et al.,* 2003). Decomposition of individual reaction times to reflect estimates of ex-Gaussian distribution which was found to be a superior predictor of error variability in part confirmed these assumptions. Consistent with others (Hwang-Gu *et al.,* 2013) we found that the *mu* parameter which represents the normally distributed component of the frequency distribution was the greatest predictor of commission errors whereas a greater value for *tau* which indicates reaction times that are excessively longer than normal, predicted omission errors. Group-wise approaches focusing on ex-Gaussian reaction time parameters showed that individuals that experienced greater social jetlag had a smaller *mu* and also a smaller *tau* than their low social jetlag counterparts suggesting that they simultaneously responded more impulsively but also displayed less inter-individual variability which is thought to reflect a more robust level of sustained attention. Studies with ADHD individuals show that, similar to more severely socially jetlagged individuals in the current study, a significantly smaller *mu* parameter is frequently noted compared to normal controls (Hervey *et al.,* 2006; Hwang-Gu *et al.,* 2013; Williams *et al.,* 2007; Vaurio *et al.,* 2009). The most replicated finding from the studies which examine IIV differences in ADHD however is that of an elongated *tau* which is representative of sustained attention deficits (Tarantino *et*

al., 2013; Gmehlin *et al.,* 2014; Leth-Steensen *et al.,* 2000; Hervey *et al.,* 2006). Applying this theory to the current data at first glance it would appear that low social jetlag individuals are more susceptible to lapses in attention on the CCPT, which is inconsistent with previous reports indicating that greater weekend-weekday misalignment is associated with greater errors of omission on similar behavioural tasks (Kim *et al.*, 2011). A number of factors differentiate the data found in the current cohort from previously reported findings in clinical populations however. Contrary to previous findings, both *mu* and *tau* parameters are positively correlated with one another in the current study indicating that generally slower reaction times are associated rare/infrequent excessively long reaction times. Furthermore, our regression model shows that infrequent long responses are protective against commission errors. One possible interpretation of the data found in the present study therefore is that greater variability of infrequent slow reaction times indexed by greater values of *tau* may be reflective of a slower, more cautious response style in which participants maintain and effort to minimise errors of commission. Such an interpretation would appear consistent with studies which show that less volatile shifts in sleep timing is negatively correlated with self-reported risk-taking behaviour (O'Brien & Mindell, 2005; Pasch *et al.,* 2010).

As previous studies have shown that task performance is moderated by energetic factors of the task (Hervey *et al.,* 2006) and also that vigilance decreases as the time-on-task increases (Tarantino *et al.,* 2013) we examined if the momentum of the delivery of test stimuli or the test block produced any different directional effects on reaction time parameters. Consistent with previous reports which show the reaction time of participants is primed by the momentum of the task we found that reaction times of both normal and exponential parameters increased as the ISI of test stimuli became greater (Hwang-Gu *et al.,* 2013; Hervey *et al.,* 2006). When performance was assessed as a function of block we found among all groups that the reaction time variability of fast reactions (*sigma*) increased as the time-on-task increased indicating a waning of sustained attention over time, however this trend was not observed for the *tau* parameter.

Unlike, previously reported findings from ADHD samples we did not detect that between group differences in Gaussian or ex-Gaussian measures of reaction time were moderated to any significant degree by ISI or block. Previous studies have shown that as time-on-task increases, individuals with ADHD display a disproportionately increased rate of omission errors, mean reaction time, reaction time variability and *tau* parameter, indicating an increased burden on attentional resources over time (Hwang-Gu *et al.,* 2013; Tarantino *et al.,* 2013). Additionally, individuals with ADHD are shown to display more profound response slowing as the speed of the test slows (Hervey *et al.,* 2006). Instead our findings show that between group differences on reaction time remained stable throughout the test and were not modified by the contextual features of the CCPT, further speaking to the suggestion that responses are slower in individuals with low levels of social jetlag because of a speed/accuracy trade-off rather than attentional deficits and this further points to the specificity of the behavioural domain affected by circadian perturbation.

Importantly, the effects that we observe on the CCPT seem to be specific to social jetlag as comparisons using self-reported chronotype and sleep quality groups do not find similar effects. We also note that these differences in performance are present after controlling for subjective sleepiness rating as well as the point in individual circadian phase when behaviours were assessed. As social jetlag represents a state of chronic circadian misalignment through the interaction of an individual's biological phase of entrainment and the social schedules which might conflict with an individual's chronotype our findings have implications for the apparent later chronotype/circadian typology frequently noted in studies examining impulsive traits (Muro *et al.,* 2013; Prat & Adan, 2012) as well as in clinically confirmed cases of ADHD (Van Veen *et al.,* 2010; Van der Heijden *et al.,* 2005b; Bijlenga *et al.,* 2013a). Our findings suggest that studies which do find markers of increased impulsivity among evening-types and/or later chronotypes such as the findings reported by Kang *et al.* (2015) may be mediated through a greater degree circadian misalignment to which evening/late types are typically more exposed.

From a neurobiological perspective, inhibitory and attentional deficits found in ADHD are thought to emerge as a result of hypofunctioning mesocortical and mesolimbic dopaminergic neural transmission (Sagvolden *et al.,* 2005). On response inhibition tasks similar to the one utilised in this study, imaging data have shown that start-stop reaction time is negatively correlated with cortical dopamine release in frontal regions (Albrecht *et al.,* 2014). Furthermore, fMRI studies have indicated that response inhibition, reaction time latency, and intra-individual variability, are behavioural components that are associated with conflict processing networks of the brain eliciting increased activation of frontal structures such as the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) which contain dense dopaminergic projections (Aarts, Roelofs, & van Turennout, 2009; Ridderinkhof *et al.,* 2004; de Wit *et al.,* 2006; van Belle *et al.,* 2015). Attenuated activation of such regions has been noted in ADHD also during on task performance (Durston *et al.,* 2003; Rubia *et al.,* 1999; Hauser *et al.,* 2014).

One theoretical reason for the response pattern seen in our findings links the circadian system to dysregulation among dopaminergic cortical pathways. A small number of recent imaging studies exist in the literature examining cases of circadian disturbance and its effects on brain activation. Hasler *et al.* (2012) showed in a sample of adolescents that greater weekend-weekday advances in midsleep decreased activation of the mPFC and ventral striatum in response to reward which the authors suggest may indicate reduced regulatory response and reward sensitivity. Further, Coutinho *et al.* (2015) studied a group of individuals experiencing short-term jetlag having undergone recent trans-meridian flight and found differential activation of the default mode network (DMN) in those that were jetlagged compared to controls. The DMN is a distributed brain system comprised of medial and parietal regions as well the previously implicated mPFC region, the deactivation of the which is associated with goal directed behaviour, target detection, and attention in which phasic dopamine release has a crucial modulatory role (Liddle *et al.* 2011; Caron & Wightman, 2009).

In light of the current findings it seems plausible to suggest that recurring circadian rhythm disruption may promote a condition which involves non-optimal regulation of frontal cortex processes. It is presently understood that the dopaminergic system is under profound circadian control (Mukherjee *et al.,* 2010) and it might be speculated that a greater amount of social jetlag may have a maladaptive effect on such networks presumably acting as a risk factor for hypodopaminergic activity as is similarly found in ADHD. This is further spoken to by findings indicating that treatment of individuals with ADHD with indirect dopamine agonist methylphenidate is shown to moderate reaction time and IIV by bringing a shortened *mu* and elongated *tau* into a normal range (Epstein *et al.,* 2006) strongly suggesting a role for hypofunctioning of these pathways with the response patterns seen among high social jetlag individuals in the present data. Further experimental work involving behavioural and imaging techniques as well as studies which replicate the present findings are required to understand the precise nature of the relationships involved. Particularly, it remains unascertained whether circadian misalignment interacts with ADHD diagnosis exacerbating impulsive or inattentive responding on measures such as the CCPT representing a novel target for future investigation.

Regarding IGT performance we found that decision making among our sample differed as a function of sleep quality but not chronotype or social jetlag. These findings are consistent with reports which show that sleep loss and disruption adversely affect performance on the task suggesting that poor sleep quality might lead to deficits in processing affective information (Killgore, *et al.,* 2006, 2007, 2012). One behavioural component related to better performance on the IGT involves the ability of the participant to delay gratification. Impaired IGT performance occurs when individuals are unable to forego larger short-term gains in favour of better long-term outcomes. These data can be better understood by applying cognitive models such as the Expectancy Valence Model (EVM; Busemeyer & Stout, 2002) which interrogate participants' selections by parsing separate components of task performance which are thought to be better indicators of task performance than summary measures alone. Applying the EVM to IGT performance has previously

shown that recent sleep debt and greater daytime sleepiness are factors associated with an overemphasis on short-term outcomes over temporally distant ones (Olson *et al.,* 2016). One explanation for our findings therefore might be that disturbed sleepers pay more attention to recent proximal outcomes rather than distal ones perhaps due to a general deficit in attention span or relying on different strategies for accumulating rewards related to specific executive function differences such as differential planning/reasoning characteristics. Other interpretations of the IGT suggest that individuals are influenced by other factors outside of the conventional goal of maximising long-term outcomes (Horstmann *et al.,* 2012). Particularly revealing in this regard are studies which indicate that disadvantageous decks with higher payout frequencies are often favoured throughout the task, indicating that individual sensitivity to reward informs selection strategy. The current results demonstrate that although both groups indicate a preference for advantageous decks over time, group-wise comparisons show that disturbed sleepers chose more from the high reward frequency deck B perhaps reflecting that such individuals are differentially affected by rewarding stimuli. Such an interpretation is supported within the broader literature showing that sleep loss results in riskier decisions biased towards optimising gains on behavioural gambling tasks (McKenna *et al.,* 2007) and numerous imaging studies which show sleep restriction and poorer sleep quality to be implicated with differential reactivity of subcortical and prefrontal brain structures involved in the anticipation and accumulation of rewards such as the striatum and mPFC (Gujar *et al.,* 2011; Mullin *et al.,* 2013; Venkatraman, 2007, 2011; Holm *et al.,* 2009). Furthermore, PET studies have linked increases in dopaminergic neurotransmission within mesolimbic reward networks following sleep loss including in aforementioned brain regions (Volkow *et al.,* 2008, 2009). It may be the case that our observations therefore are motivated by differences in reward sensitivity within individuals caused by poor sleep quality thus linking sleep disturbance to behavioural and function differences canonically associated with ADHD. The degree to which differences in IGT performance in the current sample are informed specifically by steeper/shorter delay gradient versus a hypersensitivity to reward, though both very similar factors, is best assessed by alternative

experimental models. Future studies would benefit from assessing delay and probability discounting as well as paradigms which focus on extinction latency and reversal learning.

In interpreting the findings of the current study we highlight a number of limitations. The data described in our sample are cross-sectional and quasi-experimental in design with groups derived from convenience sampling methods. Though the cause/effect relationships were assumed to be unidirectional the associations described may be also be bidirectional in nature (for example rather than poor sleep quality impacting reward systems, increased pursuit of late-night rewarding stimuli through social activities and/or television/computer screen exposure may reduce the quality of sleep ones' sleep). Longitudinal data are needed to conclusively investigate if the behavioural outcomes described are indeed as a result of sleep and circadian rhythm disturbances. Furthermore, the results described are from a normative sample and it remains uninvestigated whether similar findings hold true for cases of clinically confirmed ADHD.

In conclusion, the findings described in this chapter suggest a role for sleep and circadian rhythm disturbances impacting neurobehavioural domains which purportedly underlie ADHD symptomatology. In a normative sample we found that indicators of diminished inhibitory control and risky decision making were respectively associated with social jetlag and poorer sleep quality. Importantly, these relationships appear to be independent as social jetlag and sleep quality were uncorrelated and the outcome measures assessed index two purportedly separable behavioural components, namely inhibitory dysfunction and delay aversion which have distinct pathophysiological backgrounds. Moreover, self-reported chronotype was not found to be a predictor of performance on either of the tests used. These findings have implications for the interpretation of previous studies which have linked individual differences in circadian clock functioning (*i.e.* chronotypes, circadian typologies) with traits such as sensation seeking and impulsiveness. By partially recapitulating ADHD-like behaviours, which might be considered intermediate phenotypes of symptom liability and/or constitute relevant

epiphenomena of the disorder, in a sample individuals experiencing sleep and circadian rhythm disturbances our findings contribute to the literature which links sleep impairments and circadian clock dysfunction with ADHD.

Chapter 4

Assessing differences in event-related potentials during Continuous Performance Tasks in individuals experiencing high and low levels of social jetlag

The author would like to thank Lilian Haarde, Carsten Klein, and Chris Hören for their assistance with data acquisition for this experiment and thank Dr. Markus Hofmann and Prof. Ralph Radach for their interest in my work and the opportunity to collaborate with the General and Biological Psychology Department at the University of Wuppertal

Abstract

Brain imaging studies conducted in both childhood and adult cases of ADHD have revealed similar patterns of hypoactivation of cortical regions during tasks involving sustained attention and response inhibition. Recently, a number of studies have described functional activation deficits in structures similarly recruited during such tasks between early and late chronotypes, with circadian misalignment often suspected as a contributing factor. Among the most consistent findings from the EEG literature examining continuous performance tasks in adult ADHD is an attenuated P300 amplitude which is thought to reflect deficits in attentional processing. Recalling that we observed performance differences in higher social jetlag groups on the CCPT in Chapter 3, the current study aimed to examine potential neural features of differential performance in individuals experiencing frequent circadian misalignment through social jetlag and those that did not in an attempt to better understand how social jetlag might be related to ADHD symptoms in adults. In this study a purposeful sample of high (n =8) and low social jetlag (n = 8) individuals were identified using the Munich Chronotype Questionnaire applied amongst a student population. Group-wise differences in behavioural performance and event-related potentials were compared on two continuous performance tasks; the CPT-AX and CCPT. Preliminary results show on the CPT-AX a significantly shorter P3 peak latency in the High-SJL group compared to the Low-SJL during which might signify different response selection strategies between the two groups. Furthermore, on the CCPT we found that P3 amplitudes increased as the momentum of the task slowed (*i.e.* ISIs became shorter) in the Low-SJL group, however this effect was diminished in the High-SJL possibly indicating differential recruitment of attentional resources as task demands increase. The differences revealed at this preliminary phase of investigation deserve replication in larger cohorts and a thorough evaluation of other ERP effects that may be present. Further study may illuminate to what degree circadian rhythm disturbances and the modern habitual misalignments of sleep are implicated in neuropsychiatric disorders such as ADHD.

4.1 Introduction

Given the preponderance of previously highlighted evidence which points to an association between a later diurnal preference and traits such as impulsivity, risky decision making, and neurocognitive dysfunction (Tonetti et al., 2010; Caci *et al.,* 2004; Prat & Adan, 2013; Muro *et al.,* 2012; Ponzi, *et al.,* 2014), as well as performance deficits on tasks designed to model such behaviours (*e.g.* Kang *et al.,* 2015; Schmidt *et al.,* 2015), interesting questions arise concerning differences in the patterns of brain functioning among individual chronotypes.

Previously, functional imaging studies have been used to examine differences between circadian typologies and have shown pronounced differences between morning and evening types during task performance. On a reward processing task evening types were shown to have an altered neural response to reward relative to those classified as morning types (Hasler *et al.,* 2013). Specifically, attenuated reactivity of the mPFC during the anticipation phase of reward and increased ventral striatum reactivity during wins was demonstrated in evening types indicating a role for differential frontal structure activation underpinning reward circuit functioning. Chronotype specific patterns in brain activation have also been noted during performance on semantic priming tasks where late types show faster reaction times versus early types who in turn show reduced recruitment of brain regions relevant to semantic priming (Rosenberg *et al.,* 2015). In another study conducted by the same group a DTI protocol examining measures of white matter integrity found structural differences among chronotypes such that late types showed significantly reduced indicators of fibre density and myelination in the ACC and corpus callosum relative to early and intermediate types (Rosenberg *et al.,* 2014). The authors note such findings are similar to structural abnormalities associated with mood disorders (Brambilla *et al.,* 2003; Barnea-Goraly *et al.,* 2009) suggesting a possible intermediate marker of condition liability uncovered by these findings.

In several of the aforementioned reports the authors frequently acknowledge that where functional abnormalities are present among late chronotypes, maladaptive lifestyle choices such as increased alcohol and cigarette intake may be co-

precipitating factors for such outcomes (Hasler *et al.,* 2013; Rosenberg *et al.,* 2014). Interestingly, these aforementioned studies also highlight that a functional jetlag via misalignment occurring through interaction with pressure entraining to the social clock might underlie such differential patterns of brain activity. Given that the 'social jetlag' parameter computed by the MCTQ measure of chronotype predicts lifestyle factors such as cigarette and alcohol intake over chronotype alone and functions also as a suitable proxy for measuring circadian misalignment accrued during the typical week, it is surprising that studies have not yet explicitly addressed the potential effects of this factor in predicting neuropsychological performance. Support for such an association in gleaned from previous reports which suggested that actigraphy determined weekend-weekday advances in sleep timing in adolescents are related to differential activation of the mPFC and striatum in response to reward (Hasler *et al.,* 2012) resembling the effects seen in late chronotypes. Furthermore, an earlier study examining the effects of repeated exposure to jetlag in a sample of female flight attendants describes evidence of temporal lobe atrophy (Cho *et al.,* 2001) perhaps indicating that social jetlag might produce similar effects and might be a relevant factor where structural differences in the cortex are described between chronotypes.

A prevailing trend of the findings of this research piece up to this point has been the implication that social jetlag is a closer predictor of ADHD related symptoms than chronotype itself. Given that a reasonable amount of evidence exists to suggest that social jetlag might mediate neurophysiological indicators of performance we conducted an exploratory study to probe for the effects of SJL dose upon neurophysiological parameters during task performance associated with ADHD. The reason for this was twofold: (i) because several of the imaging studies previously highlighted here emphasise differential reactivity of several overlapping brain regions as are implicated in ADHD such as the mPFC and ACC (Durston *et al.,* 2003; Rubia *et al.,* 1999; Hauser *et al.,* 2014) that are also involved in motivational responding and response inhibition and (ii) the behavioural findings which we report in Chapter 3 indicate similar features on CCPT performance that is influenced by SJL as are reported among individuals with ADHD (Hervey *et al.,* 2006; Hwang-Gu *et al.,* 2013). Driven by our previous findings which used the continuous

performance task we attempted to replicate behavioural findings utilising two variants of the continuous performance task, the CPT-AX and the previously used CCPT, during which concurrent event-related brain potentials (ERPs) were assessed through electroencephalography (EEG) recording. The advantage of using an ERP based approach during behavioural tasks such as these allows for a higher temporal resolution and functional exploration of the neuroelectric underpinnings of cognitive processes involved in attention to stimuli and response inhibition (Banaschewski & Brandeis, 2007; Patel & Azzam, 2005).

Two ERP wave features related to impulsivity and attention respectively are the N200 and P300 components. The N200 (or N2) component refers to a negatively trending deflection occurring approximately 200 ms after target presentation which often results from a deviation in the form of the target stimulus from the prevailing stimulus and is an ERP component which has been linked to the cognitive process of stimulus identification and distinction (Hoffman, 1990; Patel & Azzam, 2005). On response inhibition tasks the N2 is known to show different elicitation strengths in healthy individuals in relation to response targets with larger amplitude potentials generated in response to No-Go stimuli than for Go-targets (Eimer, 1993; Jodo & Kayama, 1992). Among individuals with ADHD an attenuated frontal No-Go N2 has been noted (Pliszka, Liotti, & Woldorff, 2000) suggesting that this component might be associated with impulsive symptoms and inhibitory deficits though these findings have not been universally reported in other ADHD cohorts (Fallgatter *et al.*, 2004; Overtoom *et al.*, 1998). The P300 (or classic P3, P3b) component refers to a positive going ERP localised maximally at the parietal region of the scalp (typically at position Pz) occurring between 300 – 700 ms after stimulus presentation and is implicated in executive functions such as attentional resource allocation and event categorisation (Donchin & Coles, 1988; Polich, 2007). An earlier variant of the P3 wave known as the P3a has also been noted peaking 60-80 ms before the previously described classic component and is associated with the detection of novel or salient stimuli (Polich, 2003). Here we focus on the classic P3 component (referred to simply as 'P3' in the remainder of this chapter) as it is more widely studied in the literature on ADHD. Among the most frequently reported ADHD related ERP findings is that

of a decrease in the P3 amplitude and delayed peak latency (reviewed in Barry *et al.*, 2003). Numerous adult findings using visual Go/No-Go tasks similar to the ones employed in earlier chapters show attenuated P3 amplitude in individuals with ADHD compared to controls (Rodriguez & Baylis, 2007; Dhar *et al.*, 2008; Wiersema *et al.*, 2006). Importantly, the magnitude of the P3 amplitude in these studies is thought to reflect the allocation of consciously controlled attentional resources to stimuli that are important in the task and the latency purportedly corresponds with the processing speed of evaluation of the stimulus (Dhar *et al.*, 2008; Szuromi *et al.*, 2011). The interpretation here is that in the context of ADHD there is marked dysfunction among the cortical generators of these potentials.

Another interesting characteristic of the P3 wave concerns the topography of the ERP which occurs more centrally over the scalp during No-Go stimuli presentations compared to trials where Go stimuli are presented (Bokura, Yamaguchi, & Kobayashi, 2001; Fallgatter *et al.*, 2004). Differences in this so called 'No-Go anteriorisation' (NGA) in response to trials during which individuals must execute or suppress prepared motor responses has been consistently demonstrated and is suggested to be an important neurophysiological correlate of cognitive response control (Fallgatter, Brandeis, & Strik, 1997; Fallgatter, Bartsch, Herrmann, 2002; Fallgatter & Strik, 1999). In a previous study which compared ADHD boys and control cases Fallgatter *et al.* (2004) reported a higher voltage peak for Go trials compared to No-Go trials at position Pz in both groups however when NGA indicators were assessed control cases showed the typical anteriority effect indexed by a greater No-Go ERP amplitudes recorded at Cz which was attenuated in ADHD patients. Further study has implicated NGA as a candidate endophenotypic marker for dysfunction of inhibitory processes in ADHD (Baehne *et al.*, 2009).

As well as the position of the recording electrode the amplitude of the P3 component differs according to contextual features of the task such as the stimulus probability and the interstimulus interval (Nakajima & Imamura, 2000). A frequently described moderating effect of the interstimulus interval (ISI) involves longer ISIs producing greater amplitudes than shorter ones in normal individuals (Key, Dove, &

Maguire, 2005; Polich, 2007; Polich, 1990). This effect is also known to be present only for relatively fast ISIs but absent for longer intervals in the region of 6-8 s where amplitudes remain fairly constant suggesting that within a relatively rapid timeframe the P3 amplitude might represent increased demand on system resources (Gonsalvez & Polich, 2002). This has been interpreted within the framework of indexing trace decay rates associated with working memory (Gonsalvez & Polich, 2002) or in the context of stimulus detection and response inhibition, might represent an increased burden on attention as ISI either increases or decreases, potentially leading to less task engagement (*i.e.* off-task behaviour or distraction).

The purpose of this study was to explore whether differences in evoked ERPs were detectable between samples of individuals showing low and high levels of social jetlag in an effort to recapitulate related patterns of ADHD brain activity. EEG data were obtained during completion of two tasks: the CPT-AX, during which participants were required to respond by button press to a rare 'Go' stimulus occurring in the context of a prevailing 'No-Go' stimulus, and secondly, a version of the previously utilised CCPT during which participants were required to withhold their response when presented with a 'No-Go' stimulus occurring in the context of a prevailing 'Go' condition. We combined hypothesis driven approaches inspired by previously cited reports of classic ERP studies in ADHD (Overtoom *et al.,* 1998; Fallgater *et al.,* 2004) with a data driven approach focused on examining neural correlates of the faster RTs on the CCPT trials shown in the high SJL groups detected in Chapter 3. We intended to conduct an analysis of data focusing on the N2 ERP component and the NGA related topography of the P3 component however due to a low final *n* in either group and a limited number of artefact free segments appearing at frontocentral regions the preliminary findings reported here focus only on the amplitude and latency of the P3 component at the parietal position (Pz).

4.2 Materials and methods

Participants

Individuals selected for inclusion in this study were recruited from an initial sample of 84 young adults (75% female) with a mean age of 24.12 years (*SD* = 6.17) that were enrolled on the undergraduate psychology programme at Wuppertal University (Bergische Universität Wuppertal, North Rhine-Westphalia, Germany). Participants completed an online version of the MCTQ to examine SJL scores (mean = 1.38 h, *SD* = .74, range .04 – 3.62 h) from which a purposeful sample of low-SJL (SJL < 1 h) and high-SJL (SJL > 2 h) individuals were selected for electroencephalography. In total eighteen individuals were assessed with *n* = 9 in each group and had a mean age of 25.56 (*SD* = 5.76). Originally we had envisaged to recruit larger size sample for each group however due to coincidence during the summer exam semester only preliminary data are described in this study. The low-SJL group (M: 2, F: 7) were reported to have accumulated a mean .64 h (*SD* = .25) of SJL in a typical week and the high-SJL group (M: 3, F: 6) had a mean SJL of 2.73 h (*SD* = .52). Each cohort was free of self-reported psychiatric/neurological illness. Participants were awarded course credit hours *("versuchspersonenstunden")* in exchange for their participation as full time German psychology courses require students to experience a minimum number of research hours during course completion. Ethical approval for this study was granted by the Biomedical and Life Sciences Committee at Maynooth University and approved by the Department of General and Biological Psychology's internal review board at Wuppertal University and written consent was obtained (Appendix H).

Neuropsychological tasks

Participants' performances were investigated in an electrically shielded room which was kept dimly lit during data acquisition. Participants were seated on a comfortable chair in front of a 1020 x 768 resolution 48 cm computer monitor at a viewing distance of approximately 70 cm. Both tests were programed and performed in PsychoPy (v 1.82) (Pierce, 2009). During stimulus presentation characters presented on screen appeared in white against a black background and appeared within an

inner fixation area demarcated by two white bars which were continuously presented in the centre of the screen. To familiarise themselves with the test participants performed a single block of five practice trials before beginning the experiment. Stimulus and response triggers were sent using PsychoPy. Speed and accuracy were both encouraged. The CPT-AX was performed first followed by the CCPT as it was the shorter of the two tasks and allowed for a short rest period between tasks in order to prevent participant fatigue.

Continuous Performance Task AX version (CPT-AX)

We adapted an AX version of the CPT as reported in Overtoom *et al.* (1998). The test consisted of the letters 'A', 'B', 'C', 'D', 'E', 'F', 'G', 'H', 'J', 'L', and 'X'. The test lasted for a total of 400 trials where letters were presented in a pseudorandom order successively after each trial for a total on screen time of 150 ms and an inter-stimulus interval of 1250 ms. Thus the test took 8.33 min to complete. The target letter 'X' appearing after 'A' (Go Target) and the 'A' appearing without 'X' (No-Go Lure) each appeared 10% of the time. During presentation of the target stimulus individuals were required to press the SPACEBAR button on the keyboard. The letters A and H appeared with a probability of 20% and the letters B', 'C', 'D', 'E', 'F', 'G', 'J', and 'L' appeared with a frequency of 5%.

Conners' Continuous Performance Task (CCPT)

We adapted a version of the previously described Conner's Continuous Performance Test (CCPT; Conners *et al.,* 2003). The test consisted of 360 trials during which individuals were required to respond to letters appearing on the screen as quickly and as accurately as possible by pressing the SPACEBAR key. The No-Go target was replaced in this iteration of the test with the letter 'O' to avoid confounding Go associations with the letter 'X' learned in the previous CPT-AX task. During the No-Go trial individuals had to withhold their responses. The inter-stimulus interval (ISI) between trials varied between blocks of 1000 ms, 2000 ms, and 4000 ms. Each ISI condition block was presented consecutively for 20 trials and blocks were randomised for each participant before completing the procedure. The No-Go target

'O' occurred with a frequency of 10% and the task duration lasted approximately 14 mins.

Electrophysiological recording

EEG data were obtained using a BrainAmp Standard 64-channel system (Brain Products GmbH, Gilching, Germany) with Acticap active electrodes (Brain Products GmbH) placed over the scalp according to the International 10-20 positioning system (Jasper, 1958). Scalp electrodes were held in place using an electrocap and adhesive rings with SuperVisc Electrolyte-Gel (Easycap GmbH, Herrsching, Germany) applied to electrode site to aid electric conductivity. Active electrodes consisted of three midline leads (Fz, Cz, Pz) from which we intended to investigate the anteriority of ERPs in this phase of analysis as well as electrodes placed at FP1, FP2, AFz, Af3, Af4, Af7, Af8, F1, F2, F3, F4, F5, F6, F7, F8, Fc1, Fc2, Fc3, Fc4, Fc5, Fc6, Fc7, Fc8, C1, C2, C3, C4, C5, C6, T7, T8, Cp1, Cp2, Cp3, Cp4, Cp5, Cp6, Tp7, Tp8, Tp9, P1, P2, P3, P4, P5, P6, P7, P8, Po3, Po4, Po7, Po9, Po10, Oz, O1, and O2 from which data were recorded for a comprehensive analysis once sample size permits. A single right mastoid placed electrode at the M2 position was used as the recording reference. The ground electrode was placed over the inion of the occipital midline. Electrooculogram (EOG) data were acquired to record eye-movements using a single vertical EOG active electrode placed above the right eye. Electrode impedances were constantly kept below 5 kΩ during EEG recording. All signals were sampled continuously with a sampling rate of 250 Hz. Data were band-pass filtered offline between 0.1 and 30 Hz with a 24 dB slope and contained a notch-filter at 50 Hz in order to obtain a satisfactory signal to noise ratio for each participant.

Treatment of data

Raw data were inspected and all offline treatment steps were performed using Brain Vision Analyzer 2.0 software (Brain Products GmbH). Firstly, data were re-referenced to the average reference and a semi-automatic artefact rejection procedure was implemented which excluded all segments with amplitudes greater than 98 μV occurring during the first 500 ms after stimulus onset (Fallgater *et al.,* 2004).

Movement artefacts and artefacts emerging as a result of electrode impedance drift were further rejected via visual inspection of the data. We used the Independent Component Analysis (ICA; Onton *et al.,* 2006) function in the software to identify and correct data for blink artefacts. In some participants particularly noisy fontal channels (FP1/2) which persisted as this stage were excluded from further analysis. ERP segments were stimulus locked and consisted of a time window of 900 ms in duration which contained a 100 ms pre-stimulus interval used for baseline correction. A minimum of 20 artefact free segments were required for inclusion in the analysis. At this stage of analysis two participants were excluded (n = 1 from each SJL group) for having too few data. Subject grand averages were computed for each condition on the CPT-AX ('Go' versus 'No-Go') and each condition and each ISI (1000 ms, 2000 ms, and 4000 ms) on the CCPT. Peak detection of P300 components was scored using the largest positive peak between 300 and 700 ms (Overtoom *et al.,* 1998). For peaks within this window within subject grand averages for amplitudes (μV) and latencies (ms) were calculated and exported for analysis.

Data analysis

Behavioural indicators of performance such as the gross number of omission errors and commission errors on the CPT-AX and the gross number of omission errors and commission errors, mean reaction time and reaction time variability (RT) on the CCPT were compared via independent samples t-tests. Electrophysiological parameters investigated were peak amplitude and latency of the P300 component and were assessed using mixed ANOVAs. We originally intended to investigate differences in No-Go related 'anteriorisation' of P300 activity during the CPT-AX task and therefore wished to conduct mixed ANOVAs for amplitude and latency using a 2x2x3 design with SJL group as the between subjects factor ('low-SJL' vs 'high-SJL'), and condition ('Go trial' versus 'No-Go trial'), and midline electrode position ('Fz' versus 'Cz' versus 'Pz') inserted as within groups factors. Due to difficulties obtaining a satisfactory signal from frontal and central leads we limited our analysis to the group × condition comparisons however. On the CCPT we investigated the moderating role of task momentum on neuroelectric activity as this

factor showed a main effect for response speed among individuals in the results reported in Section 3.3. We conducted two mixed 2x2x3 ANOVAs examining P300 activity at position Pz in which group was inserted as the between subjects factor, with condition and ISI (1000 ms, 2000 ms, and 4000 ms) inserted as within subject factors. Tests for the assumption of sphericity for within group effects and interaction effects were non-significant and therefore no correction Greenhouse-Geisser correction was applied. We considered results indicating $p < .05$ as statistically significant.

4.3 Results

Task performance

First we conducted an inspection of participant's response patterns and reaction time data on the CPT-AX and CCPT tests. We included the previously described errors of omission and commission, mean reaction time and standard deviation in reaction time as a measure of performance variability. On the CPT-AX there were no errors of omission present in either of the groups signifying that participants did not fail to detect any of the Go targets presented and therefore group comparisons could not be performed. On CPT-AX commission errors we did not find a significant difference between groups, t = -.115, p = .910 (Figure 4.1A), and response speed measures were similar between groups with no differences detected in mean reaction time, t = -.995, p = .337 (Figure 4.1B), or reaction time variability, t = -1.80, p = .094 (Figure 4.1C). Similarly on task performance on the CCPT we did not find any differences in the number of omission errors, t = -.078, p = .939 (Figure 4.2A), or commission errors, t = -.084, p = .934 (Figure 4.2B). An inspection of reaction time data showed no differences in mean reaction time of responses, t = -.566, p = .580 (Figure 4.2C), or response time variability, t = -1.164, p = .093 (Figure 4.2D).

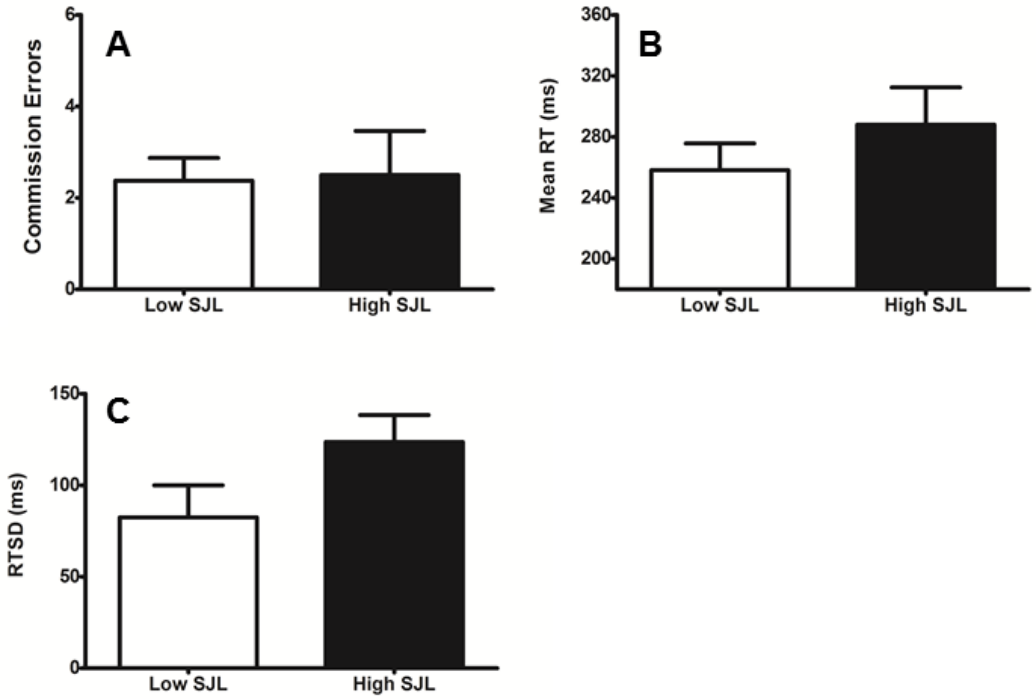


Figure 4.1. CPT-AX behavioural parameters

Figures above show between group comparisons for (A) number of commission errors, (B) mean reaction time of responses, and (C) the variability of reaction time. White bars indicate low-SJL group, black bars the high-SJL group.

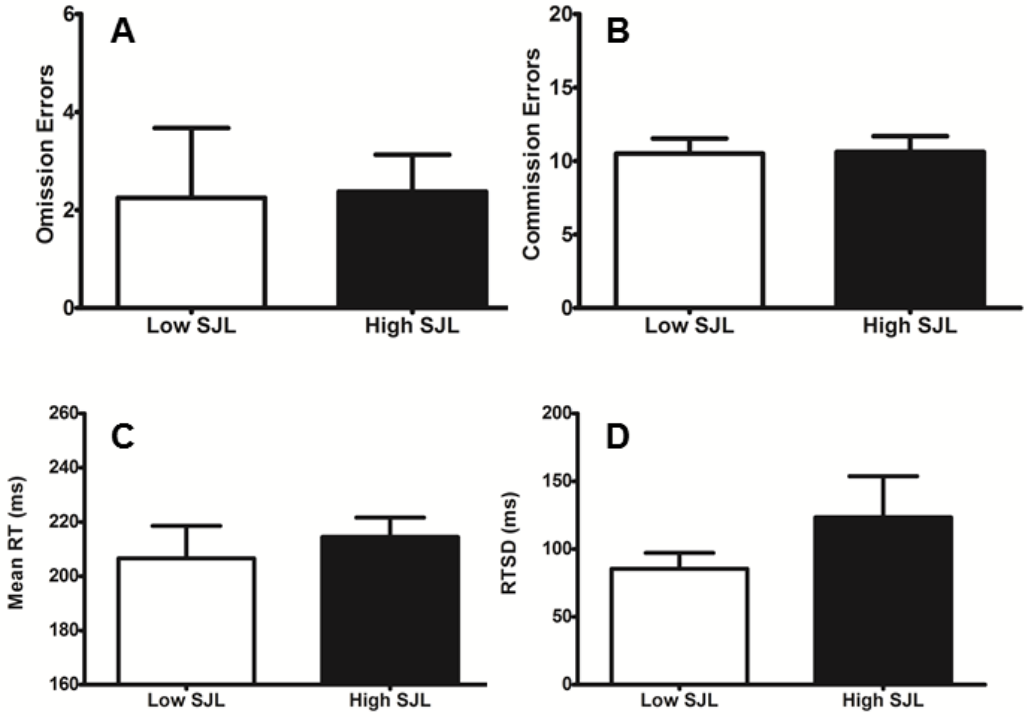


Figure 6.2. CCPT behavioural parameters

Figures above show between group comparisons for (A) number of omission errors, (B) commission errors (C) reaction time and (D) variability of reaction time. White bars indicate low-SJL group, black bars the high-SJL group

Electrophysiological data

We focused our analysis of ERPs generated in response to the CPT-AX and CCPT stimulus presentations around the P3 component appearing at a parietal maximum. To analyse peak amplitudes and latencies of the P3 component at electrode position Pz during CPT-AX performance, a mixed ANOVA consisting of 'condition' (Go target vs No-Go target) as the within subjects factor and 'group' (low SJL vs high SJL) inserted as the between subjects factor. Examination of peak amplitude revealed a statistically significant main effect for condition, $F(1, 14) = 8.976$, $p = .01$, $\eta_p^2 = .391$, with the rarer 'Go' condition eliciting a greater peak potential relative to 'No-Go' condition (Figure 4.3A). There was not a significant main effect for group, $F(1, 14) = 3.4$, $p = .086$, $\eta_p^2 = .840$, or group × condition interaction, $F(1, 14) = .05$, $p = .827$, $\eta_p^2 = .004$ (Figure 4.3A). Examination of component latency revealed a statistically significant main effect for group, $F(1, 14) = 22.89$, $p < .001$, $\eta_p^2 = .621$, such that the latency until P3 peak was significantly shorter in the high-SJL group (Figure 4.3B & Figure 4.4). We also detected a significant interaction effect for group × condition, $F(1, 14) = 5.6$, $p = .033$, $\eta_p^2 = .286$. Examination of the interaction term split by group did not find any significant main effects for condition in the low SJL group [$F(1, 7) = 2.3$, $p = .173$, $\eta_p^2 = .248$, Figure 4.3B)] however a marginal significant effect for condition was present in the high SJL group [$F(1, 7) = 4.87$, $p = .063$, $\eta_p^2 = .410$] with longer latencies during 'Go' trials (mean = 432 ms) compared to 'No-Go' trials (mean = 380 ms).

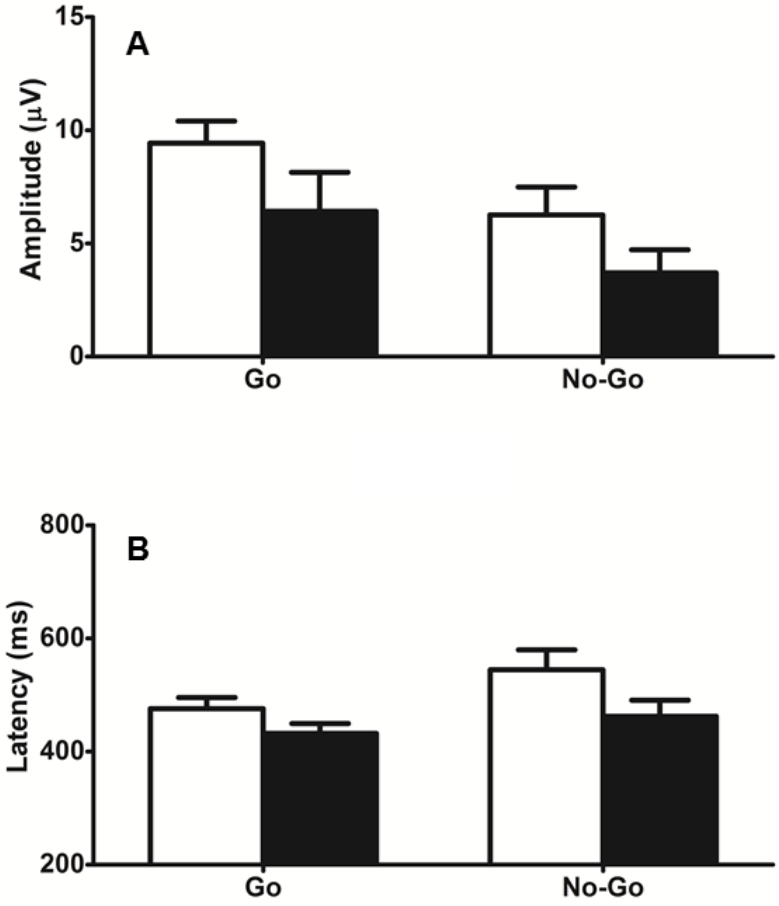


Figure 4.3. Amplitudes and latencies of P3 component during CPT-AX task

Figures above show between and within group comparisons for (A) peak P3 amplitude on 'Go' and 'No-Go' trials in low-SJL (white) and high-SJL groups (black). We note greater evoked amplitude in response to 'Go' stimuli compared to 'No-Go' stimuli but no significant main effects for group or interaction effects between group and condition. (B) shows P3 peak latencies where we did not detect a significant main effect for condition however the high-SJL group showed shorter latencies compared to the low-SJL group ($p < .001$). A significant interaction effect suggested that this effect might be moderated by condition whereby the high-SJL group latencies differed within group as a function of condition (Go trails > No-Go trials, $p = .063$.

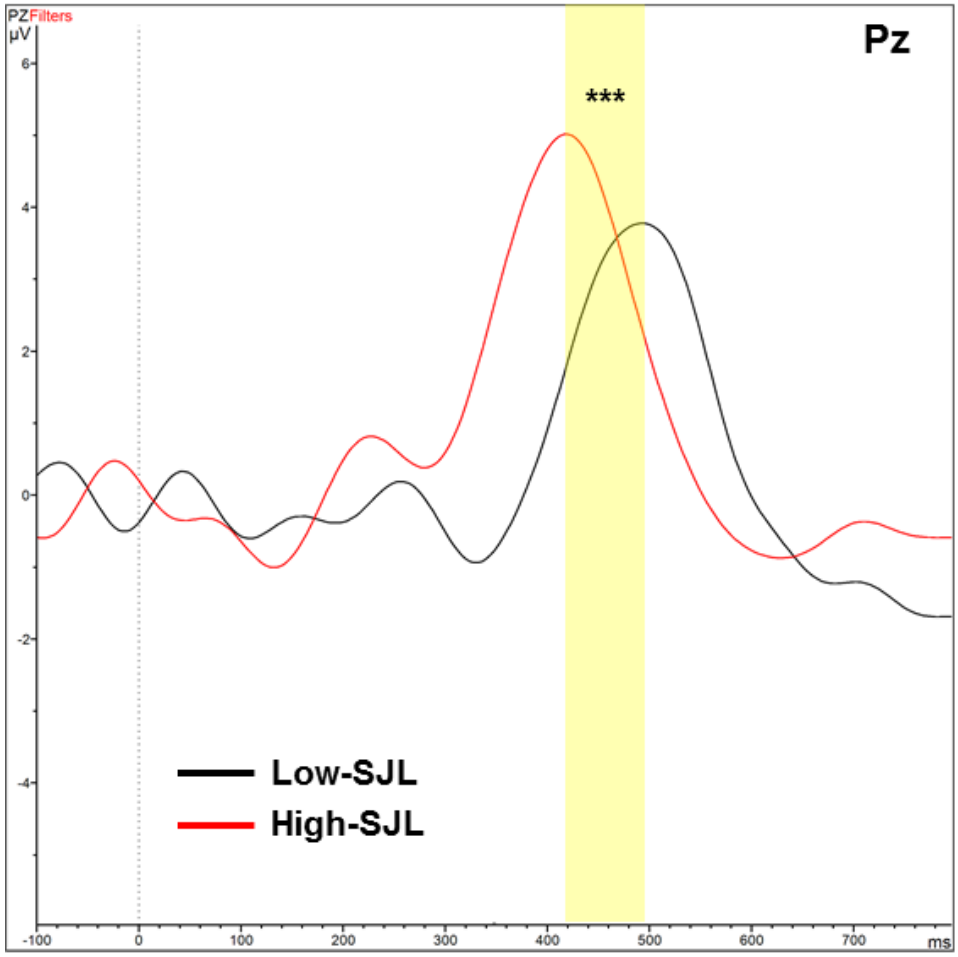


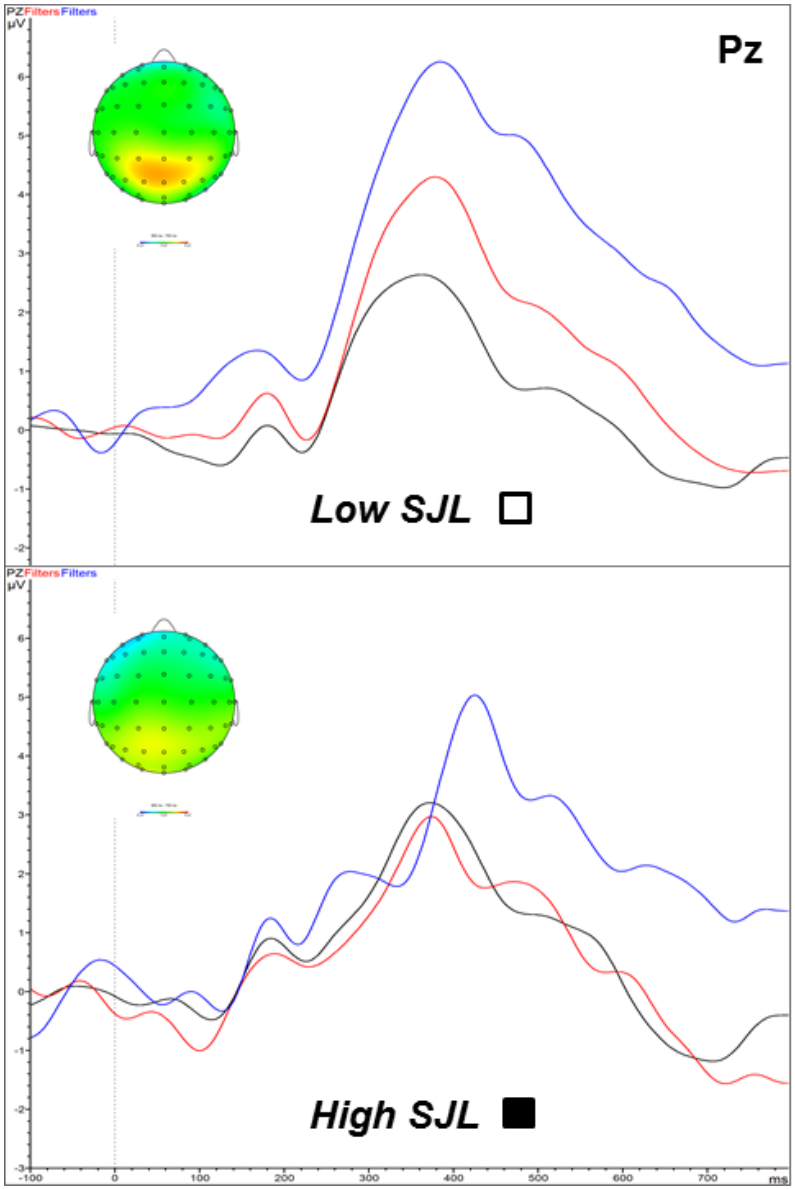
Figure 4.4. Low and high SJL group latencies of P3 ERP on CPT-AX

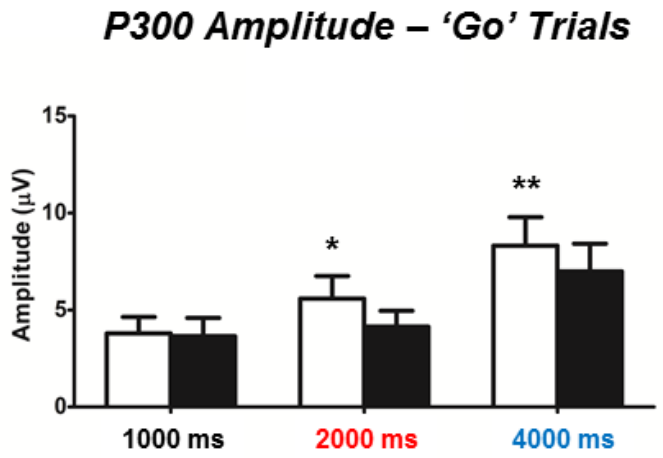
*Figure shows the grand averaged P3 event related potential in response to Go trials on the CPT-AX. ANOVA main effects for group show a statistically significant shorter latency in high-SJL group (red line) compared to low-SJL group (black line).The peak latency of each group intersected by the perimeter of the yellow highlighted bar. For visualisation purposes ERPs appear with a low pass 8 Hz filter (24dB slope). *** p < .001.*

To analyse peak amplitudes and latencies of the P3 component at electrode position Pz during CCPT performance, mixed ANOVAs were conducted with 'condition' (Go target vs No-Go target) and the interstimulus interval ('ISI': 1000 ms, 2000 ms, and 4000 ms) inserted as within subject factors and group inserted as the between subjects factor. For the P3 amplitude this analysis revealed a significant main effect for condition, $F(1, 14) = 19.345$, $p = .001$, $\eta_p^2 = .58$, a significant main effect for ISI, $F(2, 28) = 10.46$, $p < .001$, $\eta_p^2 = .428$, and a significant interaction effect for ISI ×

group, $F(2, 28) = 3.99$, $p = .03$, $\eta_p^2 = .222$. The main effect for condition reported was such that evoked P3 amplitudes were greater during No-Go stimuli presentations than for Go stimuli and regarding the main effect for ISI detected we found that amplitudes became progressively greater during longer ISI trials with the 4000 ms trials eliciting significantly greater potentials compared to 1000 ms ($p = .001$) and 2000 ms conditions ($p = .047$) which were revealed by Bonferroni *post-hoc* comparisons. Decomposition and *post-hoc* analyses of the two-term ISI × group interaction revealed that P3 amplitude was differentiated among the low-SJL group as a function of ISI [4000 ms trials eliciting significantly greater potentials compared to 1000 ms ($p = .009$) and 2000 ms conditions ($p = .005$)] however this was attenuated among the high-SJL group which showed no significant differences between ISIs ($p_{ALL} > .6$). The main effect of group was not significant, $F(1, 14) = .886$, $p = .368$, $\eta_p^2 = .058$, neither were the remaining interaction effects for 'condition × group' [$F(1, 14) = .211$, $p = .653$, $\eta_p^2 = .015$], 'condition × ISI' [$F(2, 28) = 1.76$, $p = .190$, $\eta_p^2 = .112$, or the 3-dimensional 'condition × ISI × group' interaction [$F(2, 28) = 1.39$, $p = .266$, $\eta_p^2 = .090$].

For the latency of the P3 peak we detected a statistically significant main effect for condition, $F(1, 14) = 18.075$, $p = .001$, $\eta_p^2 = .564$, and a statistically significant main effect for ISI, $F(2, 28) = 4.25$, $p = .024$, $\eta_p^2 = .233$. The main effect for condition reported was such that the latencies of the evoked P3 potentials were longer during No-Go stimuli presentation than for Go stimuli and the main effect for ISI showed a trend towards delayed latencies as ISI increased, though Bonferroni *post-hoc* comparisons did not reveal any significant differences ($p_{ALL} > .06$). The main effect of group was not significant, $F(1, 14) = .886$, $p = .884$, $\eta_p^2 = .002$, and neither were the remaining interaction effects for 'condition × group' [$F(1, 14) = .309$, $p = .587$, $\eta_p^2 = .022$], 'ISI × group', [$F(2, 28) = .589$, $p = .562$, $\eta_p^2 = .040$], 'condition × ISI' [$F(2, 28) = .647$, $p = .531$, $\eta_p^2 = .044$, or the 3-dimensional 'condition × ISI × group' interaction [$F(2, 28) = .432$, $p = .522$, $\eta_p^2 = .030$].





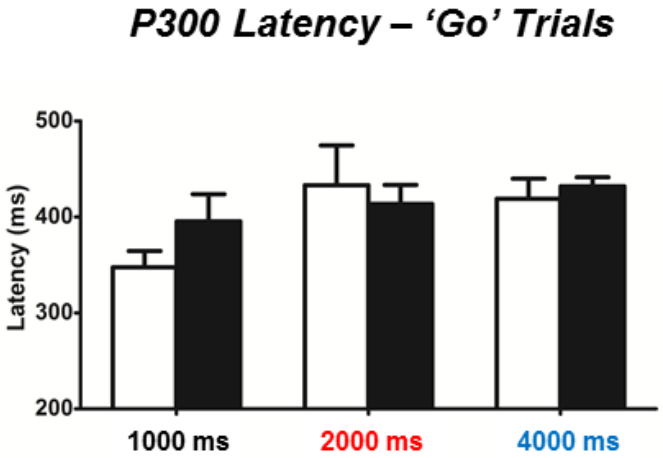


***Figure 4.5**: Description box for this figure appears overleaf*

Figure 4.5. Low and high SJL group comparisons of P3 ERP on CCPT as a function of interstimulus interval

*Figure shows the grand averages for the P3 event related potential in response to Go trials on the CCPT for the low-SJL group (white bars) and the high-SJL group (black bars). Findings show that in the low-SJL group the P3 amplitudes become significantly greater as a function of ISI (upper left panel), however this effect is not noted in the high SJL group (lower left panel). Post-hoc comparisons of the main effect for ISI in the low-SJL group revealed that P3 amplitude is significantly greater during the 2000 ms and 4000 ms condition relative to the 1000 ms condition (indicated by asterisks in the upper right panel) but the increase in the high-SJL as a function of ISI was not significant. There were not any significant differences in the peak latencies of the P3 component between groups. Topographical maps show the mean amplitude among all ISI conditions in each group given between 300 – 700 ms. * p < .05, ** p < .01. For visualisation purposes, ERPs appear with a low pass 8 Hz filter (24dB slope).*

4.4 Discussion

The purpose of this study was to explore behavioural responding on two continuous performance tasks involving response inhibition and sustained attention and the electrophysiological correlates of performance associated with both domains of cognitive performance. The reason for doing so was to identify possible intermediate indexes of brain function previously implicated in ADHD and explore to what degree they might be reproduced in a healthy sample of adults that experienced significant levels of circadian misalignment measured as social jetlag. Our findings reveal a number of interesting trends discussed within the context of work previously undertaken in this thesis and also among the broader ADHD neuroimaging literature.

Firstly, we note that we did not observe any meaningful differences on behavioural indicators of task performance between the low and high social jetlag groups. This is in contrast to the results reported in Chapter 3 in which we found that individuals with greater social jetlag consistently showed a faster reaction time on the CCPT which has been previously linked to predominantly impulsive and hyperactive ADHD symptoms (Hervey *et al.,* 2006; Hwang-Gu *et al.,* 2013). We suggest however that the limited sample size in the current study might yield insufficient power to detect an effect on the reaction time parameter on both tasks. Interestingly, low and high social jetlag groups showed differences in the peak latency of the P3 ERP in response to target presentations on the CPT-AX such that the peak latencies were significantly shorter in the high social jetlag group. Previously studies have indicated that the latency of the P3 component reflects cognitive processing time in cases where a task relevant stimulus is presented and has been found to be correlated with participants' reaction time (Kraiuhin *et al.,* 1989; McCarthy & Donchin, 1981) and the distance between the response button and participant (Doucet & Stelmack, 1999). According to this convention one interpretation of this effect might be that individuals with higher social jetlag spend less time preparing their response in either the selection or execution phase of the action taken. This interpretation is supported by the previously described association

between reaction time and higher levels of social jetlag in the behavioural findings reported in Chapter 3 potentially forming an index of impulsive decision making. We note however that participants average RTs on this task occurred before the average peak latencies of the P3 component and therefore this effect may not reflect selection phase of cognition as it occurred after effector action was mobilised. This suggests that the differences in P3 wave were not related to the individual's level of preparedness or mobilisation of attentional resources for target identification, but rather points perhaps to differences in post-decisional processing of events (Standburg *et al.,* 1996). This effect was also only apparent during the CPT-AX test which relies on the detection of rare 'Go' stimuli and not the CCPT during which pre-potent responding is encouraged. The possibility is raised therefore that task context may be a relevant factor involved in differential response patterns. Many of the findings describing the relatedness of the P3 component with some of the neurocognitive deficits similarly associated with ADHD have focused primarily on attention deficits rather than impulsive/hyperactive symptoms. Moreover, these studies consistently find that increased latencies rather than decreased latencies are associated with deficits in sustained attention on the continuous performance task (Strandburg *et al.,* 1996), the auditory oddball task (Hoyniak *et al.,* 2015), and the test of variables of attention (Braverman *et al.,* 2006). Therefore, our results may be rather interpreted in the converse sense that high social jetlag groups are more attentive than low social jetlag groups. In future studies replication of our effects and the design of protocols which lend themselves more readily to accurate interpretation are necessary to further explore the associations we describe here.

Concerning the amplitude of the P3 component we detected the typically described increase in the evoked potential during presentations of task relevant stimuli (*i.e.* amplitudes were greater during presentation of the infrequently presented 'Go' stimuli on the CPT-AX and during presentation of the rare 'No-Go' stimuli on the CCPT). The increased amplitude of the P3 component in response to salient stimuli is thought to index recruitment of additional attentional resources during task performance (Polich, 2007) and therefore such a pattern might be expected for appropriate task engagement. The main effects for group on

performance during both tests did not reveal any differences however on the mean P3 amplitude thus failing to recapitulate the most commonly observed findings of attenuated P3 amplitudes in adults with ADHD (Szuromi *et al.,* 2011). Interestingly, on the CCPT we observed that the amplitude of the ERP became substantially greater as the interstimulus interval between trials increased in the low social jetlag group however this effect was apparently absent among high social jetlag individuals. Previous findings support the notion that ISI moderated changes in P3 amplitude correspond with changes in the cognitive resources required as changes in task difficulty occur (Key *et al.,* 2005; Polich, 1990). Thus this finding might indicate that differences in neuroelectric activity are only detectable in groups with different levels of circadian misalignment as task difficulty scales. Gonsalvez & Polich (2002) suggest a processing resource interpretation of ISI moderated differences in evoked amplitude which is elicited by the target-to-target interval. They suggest that during short ISIs more resources are consumed in a relatively short amount of time compared to less frequently occurring events during longer ISIs. It is postulated that during longer ISI trials the P3 generation system can recover more efficiently and therefore the ERPs produced are of greater amplitude. According to this model one interpretation of the effects described here is that higher levels of functional jetlag might produce recovery deficits of the neural structures underpinning the P3 amplitude.

A number of neocortical generators pertaining to the P3 component have been described including the prefrontal cortex, parietal and temporal lobes and the temporoparietal junction, and the anterior cingulate cortex (Linden, 2005). Of these brain regions, volume differences in the anterior cingulate cortex (ACC) have been linked to reduced P3 amplitude (Araki *et al.,* 2004), and crucially activation of this structure has been linked with P3 No-Go ERPs in previous studies (Fallgatter *et al.,* 2002; Strik *et al.,* 1998). Indeed the ACC is part of a frontal circuit responsible for automatic motor inhibition and pre-potent response suppression (Albares *et al.,* 2014; Horn *et al.,* 2003; Braver *et al.,* 2001) and a role for structural abnormalities in the ACC contributing to ADHD symptom severity has been suggested (Bledsoe, Semrud-Clikeman, & Pliszka, 2013). In light of the aforementioned findings reported

here, future studies into how circadian misalignment may affect brain activity should focus on the role of the ACC as has previously been done for chronotype (Rosenberg *et al.*, 2014; Forbes *et al.*, 2012).

There are a number of limitations to this section of study that the reader should bear in mind when interpreting its findings. Firstly, we acknowledge that the findings reported here are from a preliminary phase of investigation and therefore are only intended as a formative assessment of the effects of social jetlag on neuroelectric activation during task performance. Apart from the very small sample size which was only available for this stage of analysis we did not take into consideration the time-of-day during which participants were assessed nor did we control for potential sleep restriction the night before testing. Furthermore, although we assume that the results seen as arising from differing levels of chronic circadian misalignment exposure we lack the necessary experimental design required to infer causation.

Another methodological limitation was that despite conducting a relatively high density scalp recording our analysis focused on only one electrode site. Although we had sufficient *a priori* reasons for selecting the Pz electrode position as the P3 ERP is normally greatest in parietal regions our analysis did not take into consideration other electrode sites and we could not therefore assess topographical features such as the anteriority or laterality of the components studied. A future analysis of the data might employ a clustered topographical approach selecting averages across corresponding electrodes situated in anterior, central, and posterior regions as well assessing laterality effects from left and right brain hemispheres. Furthermore, this study would benefit in the future from a robust source localisation method in order to aid identification of cerebral structures involved in the generation of the P3 component. Previously, Fallgatter *et al.* (2004) employed low resolution brain electromagnetic tomography (LORETA) to localise No-Go related continuous performance task activity to reveal a dysfunction of the ACC in children with ADHD. Given that the current experiment used a 64 channel system which provided superior topographical resolution than the aforementioned study there are a

sufficient amount of data available to compute a 3-dimesional topographical model of brain activity which may be a target of future analysis. Finally, the method used to define the amplitude and latency of ERP components focused on the peak detection of each parameter as the methods were based on the Fallgatter *et al.* (2004) and Overtoom *et al.* (1998) ADHD studies. Others more recently have highlighted drawbacks to using peak detection methods for defining component parameters instead favouring the mean amplitude and the fractional-area latency metric as both are more robust against bursts of high frequency noise in which the wave component of interest is embedded (Luck, 2005; Woodman, 2010). It is possible that other methods of defining ERP amplitudes and frequencies might produce less pronounced effects than observed in the current analysis.

Other potentially relevant factors which we did not take into account in this phase of analysis include the age and sex of participants. Previously a meta-regression conducted in the review of Szuromi *et al.* (2011) examining the effect sizes of P3 amplitude differences in adult ADHD revealed that decreases in amplitude varied as a function of age and sex. The results indicated that the decrease in P3 amplitude in ADHD became larger in older participants and was more pronounced as the proportion of females included in the sample was higher. Interestingly, according to the chronotype distributions from the MCTQ epidemiological database both of the aforementioned groups would be expected to show the least amounts of social jetlag among the rest of the population. Future studies might specifically investigate age differences of this effect and especially sex differences in electrophysiological correlates of behaviour as other have shown pronounced sex differences in circadian rhythms of mental performance (Santhi *et al.,* 2016).

In conclusion, the preliminary findings reported here describe differential patterns of neuroelectric activation in response to task demands involving sustained attention and response inhibition between groups experiencing different levels of social jetlag. These results deserve a more thorough evaluation in order to replicate these findings and in larger sized cohorts and to determine an exhaustive panel of effects which may be present other electrode sites before any firm conclusions can be

reached linking the jetlagged brain with intermediate brain phenotypes described in ADHD.

Chapter 5

Exploring associations between actigraphy derived estimates of sleep, rest-activity patterns, and symptoms of adult ADHD

Abstract

The ability to obtain accurate estimates of sleep duration, phase, and quality, as well circadian characteristics of the rest-activity rhythm is often a challenge as individuals may be prone to misperception biases using self-report methods or such variables may be beyond subjective evaluation. Furthermore, obtaining such information in naturalistic environments is of fundamental importance when attempting to understand how these systems vary between normal weekday routines. Actigraphy is a non-invasive and objective method for recording aspects of the rest-activity pattern of motor activity and sleep parameters *in situ* circumstances. In this study a subset of participants (n = 51) randomly chosen from previously described cohort in Chapter 3 wore wrist-worn actigraphs for seven consecutive days. The objective of our analysis was to explore associations between actigraphy derived sleep and circadian parameters and symptoms of adult ADHD, impulsivity, and circadian dysfunction. Results indicate medium effect size associations between ADHD symptoms and delayed phase of the activity rhythm and mid-point of sleep as well as reduced sleep duration, sleep efficiency, and subjective sleep quality. Similarly, impulsiveness showed medium effect size correlations with delays in sleep onset, sleep mid-point, and motor phase nadir, as well as reduced sleep duration and quality. Chi-squared periodogram analysis of the circadian period over the recording interval showed that a deviation of the estimated period from twenty-four hours was associated with more pronounced self-reported features of ADHD symptomatology, impulsivity, and failures of cognition. Furthermore, this difference in period was associated with decreased rhythm stability and amplitude indicating a role for possible entrainment deficits in such cases. Group-wise approaches comparing high ADHD symptom individuals with age and sex matched individuals showed elevated levels of social jetlag and poorer sleep quality in the high symptom group. Exploratory linear regression models predicting ADHD symptom levels and impulsivity revealed that actigraphy derived mid-point of sleep, sleep efficiency, and sleep duration were among the most important respective predictors of symptom

risk. These results support previous findings which show substantial sleep disturbances and circadian rhythm delays in adult ADHD and point towards a potential role for dysfunctional entrainment of the circadian system in the pathophysiology of ADHD-like traits among the general population.

5.1 Introduction

In the Chapter 3 we aimed to determine an objective assessment of symptoms relevant to ADHD by operational means. By overcoming the potential biases found in self-reported data the conclusions drawn from our study linking the operation of the circadian clock and homeostatic sleep satiation with behaviourally manifested traits such as impulsiveness, inattention, and risky-decision making, are more robust. Similar to the limitations highlighted at the beginning of chapter 3 our ability to make assumptions regarding the sleep and the circadian phenotype neurobehavioral and personality traits has thus far been restricted to self-reported data regarding sleep timing on work and free days and self-evaluation of sleep quality from which important indicators of circadian phase and sleep disturbance are estimated. In this section we utilise actigraphy recordings to provide an objective charting of sleep patterns and the rest-activity cycle in order to better approach our research question.

There are many advantages to using actigraphy for the estimation of both indicators of sleep quality and the underlying entrainment characteristics of the locomotor circadian rhythm. Firstly, actigraphy provides a convenient and *in situ* assessment of sleep characteristics that can be used to evaluate parameters involving sleep timing and quality such as the bedtime and wake time, total sleep time (TST), onset latency of the sleep episode (SOL), and the amount of wake experienced after sleep onset (WASO). Importantly such objective indictors are found to produce superior measures of sleep estimation circumventing errors of subjective report that frequently emerge in studies where participants are asked to estimate their own quality of sleep (Lauderdale *et al.,* 2009; Gerschik *et al.,* 2012). Furthermore, the aforementioned problems involving misperception of sleep appear to be more pronounced among chronic insomnia sufferers and individuals that experience poorer sleep quality, with psychological factors frequently leading to an overestimation of sleep disturbance (Harvey & Tang, 2012; Rioux, Tremblay, & Baslien, 2006; Fichten *et al.,* 2005). As we hypothesise that such individuals may be more susceptible to experiencing ADHD-like symptoms, objective monitoring of sleep patterns may aid to compensate for self-reported measures that lose specificity

the more severe the self-rating becomes. The use of actigraphy for providing measures estimating sleep and wake has previously been reported in normative samples across a diverse age profile according well with PSG derived measures of sleep and wake (Acebo *et al.*, 1999; Jean-Louis *et al.*, 2001; Sadeh *et al.*, 1991) as well as in clinical cases with confirmed diagnosis of ADHD (van der Heijen *et al.*, 2005, 2007; Singh & Zimmerman, 2015).

Regarding the estimation of circadian rhythm measures, actigraphy can also be used to validate estimates of circadian phase of entrainment using the sleep corrected mid-point of sleep on freedays from the MCTQ (Roenneberg, 2015). This measure can be reliably correlated with actigraphy-derived measures of the mid-point of the sleep phase (using algorithms to estimtate sleep onset based on motor activity) or by using similarly derived measures such as the actigraphy determined nadir of the twenty-four hour gross activity plot, both of which are strongly correlated. Furthermore, actigraphy may be used to assess other circadian rhythm entrainment characteristics that cannot be captured by self-report, such as the period of the entrained rest-activity rhythm, and amplitude of the activity rhythm, as well as the stability and variability within and between individual days (Gonclaves *et al.*, 2015). There are several computational approaches that can be used to analyse biological and behavioural circadian rhythms (reviewed in Refinetti, Lissen, & Halberg, 2007). Among the most commonly used methods to estimate the circadian characteristic of a rhythm is the consinor method in which the rhythm is fitted to a cosine curve with an assumed period of 24 h (Halberg, Tong, & Johnson, 1967). When this method is applied a number of variables can be extracted indicating the rhythmic aspects of the distribution of the data such as the amplitude of the oscillation indicating the strength of the circadian rhythm, the acrophase indicating the phase of the maximum in relation to a reference time used as a marker for the rhythms phase of entrainment, and the midline estimating statistic of the rhythm (MESOR) indicating the rhythm adjusted mean (Refinetti *et al.*, 2007). The rhythmicity of several biological parameters such as circadian rhythms in core body temperature and blood pressure for example follow such sinusoidal function and are analysed using this parametric method. In the case of the rest-activity rhythm however the issue has been raised that

such a parameter does not typically follow a sinusoidal function and might be better characterised by the use of non-parametric functions (Goncalves *et al.,* 2015; Van Someren *et al.,* 1996; Zornoza-Moreno *et al.,* 2011). The functions used in the non-parametric circadian rhythm analysis (NPCRA) method of probing the rest-activity cycle have previously been described in detail elsewhere (Van Someren *et al.,* 1996, 1997; Goncalves *et al.,* 2015). For the purposes of reader familiarisation each of the metrics will be discussed briefly here (for computation see 4.2 Methods) and their utility in clinical scenarios reviewed. The NPCRA method extracts seven variables describing the rhythm interdaily stability, intradaily variability, relative amplitude, and the mean activity count and times of onset of the most active 10 hours of the day and the least active 5 hours of the day. In several studies such variables have been shown to be disturbed in older age and are associated with specific neurological and psychiatric presentations.

The interdaily stability (IS) of the rest-activity rhythm measures the ratio between the variance of the average 24 h pattern around the mean and overall variance of the data and is a parameter which is used to indicate the strength of coupling or synchronisation between the circadian rhythm and the external environment (Van Someren *et al.,* 1996; Witting *et al.,* 1990). High IS values indicate better coupling between the 24 h cycle and low IS values might occur as a result of poor between day consistency of the rest-activity pattern due to an entrainment deficit or pressure from the social clock as demonstrated in populations on alternating shift-work schedules that show decreased rhythm stability (Rea *et al.,* 2008). Clinical findings have linked specific conditions to a lower stability of the rest-activity pattern. Most notably senile patients and those diagnosed with Alzheimer's Disease have shown an attenuated IS compared to pre-senile and control groups (Van Someren *et al.,* 1996; Hatfield *et al.,* 2004). It is thought that reduced integration of the photic zeitgeber plays a major role in the reduced circadian rhythm stability seen in these populations possibly due to a combination of reduced exposure to natural light (Harper *et al.,* 2004) and also Alzheimer's Disease related optical nerve degeneration compromising RHT signal transduction (Campbell *et al.,* 1988; Hinton *et al.,* 1986). Furthermore, the Van Someren group demonstrated increases in rhythm stability in demented and

Alzheimer's type patients after an increased indirect bright light illumination intervention except for in visually impaired groups (Van Someren *et al.*, 1997). Among psychiatric populations reduced IS has been noted in bipolar disorder (Jones, Hare, & Evershed, 2005), unipolar depression (Berle *et al.*, 2010), and in adults with Asperger syndrome (Hare, Jones, & Evershed, 2006). It is not clear whether disturbances in photic zeitgeber entrainment are implicated in these conditions however other factors related to reduced stability might be insufficient entrainment to social signals or disorganised patterns of activity as a consequence of the condition symptomatology. In the current study IS was used to measure between day consistency of rest-activity rhythms.

The intradaily variability (IV) parameter yields information about the fragmentation of the rest-activity cycle. Based on the clustered mean hourly values of activity each day subtracted from each consecutive hour which is normalised for population variance, the IV reflects transitions between long periods of rest and activity (Van Someren *et al.*, 1996). High IV values occur as a result of large hourly differences in the activity rhythm such as rest and inactivity during the normally active period (*i.e.* daytime napping, reduced mobility) or greater nocturnal activity from awakenings or other sleep disturbances. Among the most important predictors of rest-activity fragmentation is older age with several studies showing elevated IV in elderly samples (Huang *et al.*, 2002; Oosterman *et al.*, 2008; Whitehead *et al.*, 2008). Such a condition is typical of worsened sleep efficiency and poorer circadian integrity associated with senescence (Huang *et al.*, 2002) and has been linked to degeneration of peptide-expressing cells containing VIP and AVP in the SCNs of the elderly individuals producing a reduced internal coupling of oscillators decreasing the circadian drive of sleep and wakefulness (Swaab & Hofman, 1994; Harper *et al.*, 2008). Studies have shown similarly that degeneration of neurons in the SCN may be accelerated in neurodegenerative processes associated with Alzheimer's Disease (Swaab, Fliers, & Partiman, 1985; Zhou, Hofman, & Swaab, 1995) with the pathology being associated with higher IV values compared to similarly aged controls (Witting *et al.*, 1990; Hatfield *et al.*, 2004). In non-elderly clinical populations evidence for an association between greater IV and bipolar disorder has been reported (Jones *et al.*,

2005). This finding is consistent with a literature which proposes that circadian dysfunction features prominently in the disorder (Teicher, 1995, Teicher *et al.,* 1997) with episodic fluctuations in levels of motor activity specifically related to the pathophysiology of bipolar disorder (Indic *et al.,* 2011). In the current study IV was used to indicate fragmentation of the rest-activity pattern.

Non-parametric measures of circadian phase consist of the time of onset of M10 (M10o) which measures the onset of the 10 most active hours of the day and the time of onset of L5 (L5o) which measures the onset of the 5 least active hours of the day typically occurring during the subject's rest interval. Additionally, the mean value of the activity counts for M10 and L5 are used as estimates of diurnal activity and nocturnal activity respectively. In some populations a reduction in M10 has previously thought to be indicative of reduced motor capacity and a reduction of exercise and is shown to be associated with poorer performance on measures of cognition and executive function in aged individuals (Carvalho-Bos *et al.,* 2007). In institutionalised populations and patients with Lewy-body dementia reduced diurnal activity has also been noted (Van Someren *et al.,* 1996; Harper *et al.,* 2004). In younger populations it can be difficult to ascertain whether a higher M10 is indicative of pathological hyperactivity or a greater level of athletic activity however. As with M10, the L5 activity levels are frequently found to differ with older age reflective of the age related breakdown of the sleep/wake and rest-activity pattern. A low L5 value typically indicates a rest interval with few arousals and consistent with the other non-parametric circadian rhythm measures greater sleep fragmentation has been reported in Alzheimer's disease patients and Parkinson patients (Harper *et al.,* 2004; Whitehead *et al.,* 2008). Antemortum L5 also correlates with a reduction of neurotensin in the SCN of patients with dementia indicating a role of global neurodegeneration of the master pacemaker influencing this parameter (Harper *et al.,* 2008). In neurologically intact patients L5 most likely indicates sleep disturbances and would be expected to correlate highly with sleep related variable of arousal such as WASO and sleep efficiency. As L5 is calculated by the mean activity plot, higher values indicating greater sleep disturbance are likely masked by activity plots of participants with between day inconstancies in rest-activity rhythms however.

Perhaps a more revealing parameter which measures the robustness of the rest-activity pattern is the amplitude of the rhythm. Measured by finding the difference between mean activity peak and nadir, the amplitude indicates the strength of the rest-activity oscillator. The amplitude of a rhythm may be attenuated as a function of reduced diurnal activity or increased nocturnal arousal. Similar to other biological rhythms robust rhythms of locomotor activity may be in indicative of strong coupling to stable zeitgebers and may be attenuated by exposure to weakened circadian signals such as lighting during the rest phase (Gooley *et al.,* 2011). There are two methods of estimating amplitude using the NPCRA approach. The gross motor amplitude measure (AMP) simply involves the difference between M10 and L5 however as mean activity counts for L5 are small in size in comparison to M10 it has been suggested that it does not produce any additional information over that which is captured by M10 alone (Witting *et al.,*1990; Goncalves *et al.,* 2015). Furthermore, because AMP it is not normalised for different levels of mean diurnal activity expressed by the individual it obfuscates the circadian rhythm aspect of the activity rhythm and the motor activity level in between subject comparisons. Consequently, the relative amplitude (RA) is the preferred measure which examines the difference between M10 and L5 divided by the sum of the two (Van Someren *et al.,* 1996). Circadian amplitude dysregulation indexed by a lower RA is inversely correlated with indicators of sleep quality and executive function (Bromundt *et al.,* 2011; Oosterman *et al.,* 2009; Carvalho-Bos *et al.,* 2007). Attenuated rest-activity amplitude also features among different psychiatric conditions such as bipolar disorder (Faedda *et al.,* 2016), major depressive disorder (Moraes *et al.,*2013), and seasonal affective disorder (Winkler *et al.,* 2005). Here we use both M10o and L5o as measures of the circadian phase of entrainment with mean motor levels also reported to give an estimation of both daily and nocturnal activity. Furthermore, AMP and RA were assessed to determine the amplitude of the rest-activity pattern with low values suggesting weaker signal strength of the circadian rest-activity rhythm possibly reflecting poor rhythm entrainment.

Concerning the relevance of these aforementioned parameters in ADHD a number of studies have made attempts to chart the rest-activity patterns of

individuals with the disorder revealing specific sleep and circadian abnormalities associated with ADHD. Unlike the findings that emerge for neurological diseases and other psychiatric diagnoses, differences in rhythm precision, fragmentation, and amplitude are not as consistent between control subjects and those with ADHD. While some studies show elevated degree of rhythm variability (*e.g.* Van Veen *et al.,* 2010; Fasmer *et al.,* 2015) others report no differences between individuals with ADHD in addition to comorbid SOI and those without groups on IS and IV measures (Van der Heijden *et al.,* 2005b). Rather it seems the expression of circadian abnormalities in ADHD most often relates to the timing of the sleep and rest-activity rhythm more so than the coherency or robustness of the rhythm with the most consistent finding reported in the actigraphy literature on ADHD involving phase delays in the rest-activity rhythm. Numerous studies specifically report a delayed phase of sleep and a greater SOL in groups of ADHD patients (Boonstra *et al.,* 2007; Crabtree, Ivanenko, & Gozal, 2003; Gruber *et al.,* 2000; Hvolby *et al.,* 2008; Van der Heijden *et al.,* 2005b, 2006; Van Veen *et al.,* 2010; Corkum *et al.,* 2001). Furthermore, these behavioural results are in agreement with findings indicating phase delays in DLMO, skin temperature, and salivary cortisol concentrations in ADHD individuals (Van der Heijden *et al.,* 2006; Van Veen *et al.,* 2010; Bijlenga *et al.,* 2013b; Baird *et al.,* 2011). One report also suggests that the level of circadian period misalignment estimated using actigraphy was associated with a higher clinical index of symptom severity among individuals with ADHD (Baird *et al.,* 2011) perhaps reflecting an entrainment failure among individuals with the disorder. Moreover, indicators of sleep restriction and poor sleep quality are frequently noted in individuals with ADHD speaking further to a generally disturbed sleep pattern being highly co-morbid with the disorder. Actigraphy determined TST is found to be shorter in those with with ADHD (Owens *et al.,* 2009) and poorer sleep efficiency has been shown in a number of studies (Boonstra *et al.,* 2007; Dagan *et al.,* 1997; Van Veen *et al.,* 2010). Importantly, the psychological/psychiatric consequences of sleep disturbances entail a plethora of negative behavioural and cognitive outcomes in non-clinical populations that are consistent with symptoms of ADHD (Gau *et al.,* 2007; Kass *et al.,* 2003).

A number of limitations exist however on the generalisability of such findings considering the almost exclusive use of clinical samples utilised in the previously highlighted studies. While a number of reports take into consideration the ability to control for the status of psycho-active medication when designing and interpreting their work (Van Veen *et al.,* 2010; Van der Heijden *et al.,* 2005b; Owens *et al.,* 2009), this is counterbalanced by a number of studies which only report circadian phase delays in clinical groups whose ADHD is treated with stimulant medication. In childhood cases of the disorder for example methylphenidate treatment has been shown to associate with many of the same problems such as later bed times, greater SOL, and increased motor activity before bed (Boonstra *et al.,* 2007; Ironside *et al.,* 2010). Fargason *et al.* (2013) report also that among a group of adult cases of ADHD studied the condition diagnosis alone was not associated with circadian delay but a later dosing time of stimulant medication was, indicating that psychopharmacological side-affects may be behind such associations. Furthermore, it remains unascertained whether these actigraphy detected indicators of sleep and circadian rhythm disturbances are associated solely with clinically identified cases of ADHD or rather if these disturbances are apparent perhaps with a lower level of severity among 'pre-clinical' individuals or those that can be placed highly on personality dimensions associated with ADHD-like traits.

To this end this arm of the study includes objectively determined assessments of the rest-activity cycle and sleep intervals to answer the broader research question addressed in this programme of research. The outcomes of this study were twofold. Firstly, by exploring the relatedness of objective and subjective measures of estimated sleep timing and quality we hoped to validate the questionnaire-based tools used in the other chapters of this research piece. Additionally, the second and primary focus of the current study was to explore the associations between actigraphy determined measures of circadian phase, precision, fragmentation, amplitude, and period, and well as indicators of disturbed sleep, and self-reported scores on the ASRS, BIS, and CFQ scores and to conduct between groups comparisons assessing individuals with a high degree of ADHD-like traits and those that scored within the normal range.

5.2 Materials and methods

Participants

Fifty-four participants (27.6%) in total were randomly selected from the initial sample of 195 participants described in Section 3.2 of the current thesis to undergo week-long actigraphy assessment. Selection was based on device availability in the lab at the time of collecting neuropsychological data as well as fulfilling other inclusion criteria previously noted such as not being a shift-worker, or self-report of any clinical condition that would potentially affect sleep. A total of three individuals were excluded from analysis after data collection had concluded due to non-compliance with the device (n = 2) or due to technical errors during recording resulting in too few intervals being available for analysis (n = 1). The final sample size therefore consisted of 51 participants (53.8% female) and had a mean age of 23.31 years (SD = 3.61, range 19 – 34). Participants were instructed on how to wear the actigraph device and on how to fill out the accompanying sleep diary (see *Actigraphy* heading below). Written informed consent was given by each participant before commencing the experimental protocol. Ethical approval for this study was granted by the Biomedical and Life Sciences Committee at Maynooth University.

Questionnaire data

Participants completed the Adult ADHD Self Report Scale (ASRS), the Barratt's Impulsiveness Scale (BIS), the Cognitive Failures Questionnaire (CFQ), the Pittsburgh Sleep Quality Index (PSQI), and the Munich Chronotype Questionnaire (MCTQ) as described previously in Section 2.2. The ASRS score Part A and the total BIS score were used as dependent measures of ADHD-like symptoms and impulsive traits and the CFQ was used as a measure of general cognitive deficit. Subjective sleep quality was estimated using the global PSQI score. The sleep-corrected midsleep on freedays (MSF_{sc}) and level of social jetlag accrued (SJL) were variables of interest ascertained by the MCTQ.

Objective estimates of sleep-wake cycle and rest-activity rhythm

Actigraphy

Objective measures of sleep quality, timing, and 24 h rest-activity pattern estimates were obtained through week-long actigraphy recordings using the Actiwatch 2 actigraph (Philips Respironics, Murrysville, PA). The actigraphs specified used a solid-state Piezo-electric accelerometer with a sampling bandwidth range of .35 – 7.5 Hz to detect movements within the normal range of human activity. Participants wore actigraphs on their non-dominant wrist for seven consecutive days which continuously and passively measured their activity 24 h per day. Movements were recorded as activity counts by the device at a storage interval of 15 s. Participants were asked not to remove the device during the recording period except when bathing or swimming. Actigraph removals were noted in an Actiwatch removal diary given to participants and such intervals were excluded from analysis. Additionally, activity free intervals of 1 h or greater that were not indicated in the removal diary were treated as suspicious for device removal and were also eliminated from the analysis. Each morning participants also completed the Consensus Sleep Diary (CSD; Carney *et al.,* 2012) indicating their bedtimes and wake up times for that day as well as estimates of their sleep duration and time until sleep onset. All analyses were limited to a period of six consecutive 24 h intervals after excluding partial days with data not fully captured by the actigraph.

Sleep estimates

Estimates were derived from actigraph data to measure sleep start and end times, time in bed (TIB), total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SlpEff; percent of time in actually bed spent asleep), as well as parameters measuring sleep fragmentation such as the amount of awakenings after sleep onset (WASO) measured in minutes as well as the number of individual bouts of wakefulness throughout the night. Each variable was calculated using a standard algorithm in the Actiware software version 5.57 (Philips Respironics, Murrysville,

PA). Briefly, the scoring algorithm computes a weighted value which integrates previous and successive activity counts from epochs which temporally surround the scored epoch. The weighted activity value is given by the equation:

$$A = 0.04E_{-8} + 0.04E_{-7} + 0.04E_{-6} + 0.04E_{-5} + 0.2E_{-4} + 0.2E_{-3} + 0.2E_{-2} + 0.2E_{-1} + 4E_{0} + 0.2E_{+1} + 0.2E_{+2} + 0.2E_{+3} + 0.2E_{+4} + 0.04E_{+5} + 0.04E_{+6} + 0.04E_{+7} + 0.04E_{+8}$$

Where A = sum of activity counts for the 15-second scored epoch and the surrounding epochs; E ±n = activity counts of the previous, successive, or scored epoch (E_0). If the sum of these weighted data exceed a defined minimum threshold value the epoch is scored as awake otherwise it is scored as sleep. We selected a medium activity threshold (40 activity counts) as it is the default setting in Actiware and has been validated with PSG and subjective sleep ratings from sleep disordered populations (Kushida *et al.,* 2001). An interval of 10 immobile minutes below this threshold signified the sleep onset time. Actigraph estimates of sleep start and end times were validated against self-reported bedtimes and wake up times from sleep diaries to ensure accuracy and rest interval estimates were corrected as necessary. As using bedtime or wakeup times as circadian rhythm phase markers is influenced by the total sleep duration we used the midpoint of actigraphy estimated sleep intervals as a marker of sleep phase instead (MS_{ACT}).

Estimation of the twenty-four hour activity rhythm

We applied the previously described standard nonparametric circadian rhythm analysis (NPCRA) functions to the rest-activity data in order to ascertain an objective reading of the circadian rhythm of activity (Van Someren *et al.,* 1996, 1999; Goncalves *et al.,* 2015). The variables examined were as follows: interdaily stability (IS), intradaily variability (IV), the mean activity and onset of the most active consecutive 10 h interval of daily activity (M10 and M10o, respectively) and of the least active consecutive 5 h interval of daily activity (L5 and L5o, respectively), the mean

amplitude of the activity rhythm (AMP) and relative amplitude of the activity rhythm (RA) normalised for individual differences in activity count.

The IS of the rhythm provides a measure for how stable the rhythm is over the multiple days assessed indicating how similar interdaily periods of activity are over time. It varies between zero and 1 with higher values supposedly indicating the strength of synchronisation to the environmental zeitgeber (*i.e.* the light-dark cycle). It is given by the equation:

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

Where p is the total number of data per day which in this study were 24 as it is the number of hours in a day, n is the total number of data (total hours over six days = 144), $\bar{x}_h$ refer to the hourly means, $\bar{x}$ is the mean of all data, and $\bar{x}_i$ represents the individual data points.

The IV provides information about the fragmentation of the rhythm of rest and activity. Higher values indicate a greater frequency of transitions between rest and activity between all successive hours. Large hourly differences in activity as a result of daytime napping or shift-work for example produce a higher IV. It is given by the equation:

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

Where, as previously described, p is the number of data per day and n is the total number of data, $\bar{x}_h$ refer to the hourly means, and $\bar{x}$ is the mean of all data. $(\bar{x}_{h-1})$ represents the first derivative of the hourly clustered mean activity data which is the result of the previous element subtracted from the posterior element (for example the

mean hourly activity count at 23:00 h minus that at 22:00 h, then on the successive line this would be the mean hourly activity count at 00:00 h minus that at 23:00 h).

For the calculation of phase markers of the activity rhythm M10o and L5o as well as the mean activity counts for M10 and L5, activity data were resampled from 15 s intervals into 1 min aggregates in spreadsheet format. After excluding actigraph removal artefacts a composite rest-activity profile 1440 min in duration was created and double plotted from which M10, M10o, L5, and L5o parameters were computed. We examined both gross amplitude of the rhythm (AMP) which was given by the difference between the mean activity counts for M10 and L5 as well as the NPCRA variable relative amplitude (RA) which examines the robustness of the rest-activity rhythm normalised for the activity level of the individual. It is given by the equation:

$$RA = \frac{M10 - L5}{M10 + L5}$$

Where M10 and L5 refer to the mean activity count for the most active consecutive 10 hours and the mean activity count least active consecutive five hours. Factors which produce a lower RA might be deficits in locomotion (*i.e.* associated with older age, or during hospital admission) which decreases M10, greater levels of disturbed sleep which elevate L5, a combination of both which diminishes the differences between peak and through of the rest-activity rhythm. To estimate the periodicity of the circadian rest-activity rhythm we calculated the circadian period (τ) for each individuals data over at least 6 consecutive days via χ^2 periodogram using the ClockLab Analysis Circadian Toolbox (Actimetrics, Wilmette, IL) for MATLAB R2012b (Mathworks, Natick, MA). The χ^2 periodogram is an optimal method of detecting rhythmicity of event recorder data such as the activity recorded by the actiwatch between the ranges of 14 to 34 h and can precisely estimate the period of a circadian rhythm (Sokolove & Bushell, 1978).

Data analysis

A series of bivariate correlations were conducted to explore the interrelation of variables derived from questionnaires assessing sleep habits and ADHD symptoms with objective measures of sleep/wake timing, quality, and the circadian rhythmicity of the rest-activity cycle. Shapiro-Wilk tests for normality were performed to determine the distribution of the variables assessed as is most appropriate given the size of the sample. Normally distributed variables (ASRS, BIS, CFQ, MSF_{SC}, SJL, PSQI scores, IS, IV, M10o, MS_{ACT}, TIB, and the number of awakenings) were examined using Pearsons product moment correlation coefficient (r) and non-normally distributed variables (RA, AMP, L5o, L5, τ, TST, SOL, SlpEff) were assessed using Spearman's rank order correlation coefficient (r_{rho}). Furthermore, group-wise explorative analyses were conducted between high ADHD symptom individuals (designated by an ASRS score >13; Kessler *et al.,* 2007) and a comparison group consisting of participants matched for age and sex. As the proportion of scores under the threshold indicative of a likely case of ADHD far outnumbered the cases we identified, age and sex matching was achieved using the python-based Propensity Score Matching (PSM) extension for SPSS (version 1.5.0, IBM Developerworks). The PSM method balances observed covariates between two groups by carefully matching cases by their propensity score which is derived from the probability of an outcome based on its covariates (see Thoemmes, 2012). Independent samples t-tests or Mann-Whitney U tests were conducted as appropriate to ascertain differences in dependent measures between 'ADHD-likely' (Age = 22.16 ± 2.95, 50% female) individuals and the comparison group (Age = 22.92 ± 3.5, 50% female). All time data were converted into decimal time and transposed into a linear format to facilitate a meaningful analysis without relying on circular statistics. Values for the deviation of τ from T = 24 h were log-transformed as data were heteroscedastic however non-normality persisted and data were analysed using non-parametric methods. All statistical analyses were performed in SPSS 22 (IBM, Chicago, IL) with a significance threshold set at $p < .05$.

5.3 Results

Interrelatedness of subjective and objective measures of sleep and activity rhythms

Firstly, we conducted a number of correlations to examine the relatedness between self-reported measures of chronotype and sleep quality with actigraphy derived variables measuring 24 h rest-activity rhythm characteristics (Table 4.1) and sleep parameters (Table 4.2). We found that the MCTQ derived measure of circadian phase MSF_{sc} was significantly associated with objective measures of phase correlating positively with MS_{ACT} (r = .601, p < .001), SOL (r = .323, p < .05), M10o (r_{rho} = .500, p < .001) and L5o (r = .607, p <.001). Global PSQI score was not so reliably indexed by objective measures however failing to achieve any significant correlation with any of the actigraphy derived measures of sleep disturbance (*i.e.* TST, SOL, sleep efficiency, WASO). These findings are similar to other reports which show that the PSQI, when taken as a global index across all seven scale components, correlates poorly with actigraphy derived sleep measures (Grandner *et al.,* 2006; Buysee *et al.,* 2008; Beaudreau *et al.,* 2012). Most notabely it has been suggested that the final two components on the PSQI measure, 'Medication' and 'Daytime Dysfunction' subscales, show poor internal reliability with other components on the scale, and themselves may be indicators of psychological states rather than sleep distruptions (Beaudreau *et al.,* 2012; Paudel *et al.,* 2008). Subsequently we investigated whether PSQI sub-scale scores that were qualitatively similar to actigraphy measures of sleep duration, onset latency (SOL), and sleep disturbances were correlated.Results indicated that the *'Sleep Latency'* component of the PSQI (0 – 3, higher scores corresponding with longer latency) did not correlate with actigraphy determined SOL (r = .253, p = .148). However, the *'Sleep Duration'* component (0 – 3 , higher scores indicating fewer hours slept) was correlated with objectively determined total sleep time (r =-.406, p = .017) and WASO (r = .440, p = .009). Self-reported measures of sleep disruption measured by the *'Sleep Disturbances'* component (0 – 3, higher scores indicating more disturbed sleep) also agreed with the actigraphy estimated minutes of wakefulness during the sleep period (WASO; r = .487, p = .003). We note however that as the PSQI was completed before actigraphy, differences between sleep quality

the month prior to the beginning of actigraphy recordings might not account for more recent evaluation of sleep.

Concerning recording of motor activity we note a number of interesting relations among variables which measure the circadian pattern of activity. Levels of circadian rhythm variability (IV) were negatively correlated with M10 (r = -.360, p < .01) as well as gross motor amplitude (r_{rho} = -.363, p < .01) both of which are consistent with the findings suggesting that less robust circadian rhythms are more vulnerable to repeated shifts in phase. Surprisingly, however IV and SJL were not found to be related (r = -.154, p = .281). The reason for this is not clear but may be due to the length of actigraphy recording as only one weekend was captured for each individual during the 7 day recording interval. More data may be required in order to establish whether these two measures of circadian rhythm desynchrony are related.

Further to this, we did not detect any significant associations between the any of the variables and the circadian period (τ) of the rest-activity rhythm however the deviation of τ from 24 h was negatively correlated with rhythm stability (IS) (r = -.371, p < .01) and the relative amplitude (RA) of the rest-activity cycle (r_{rho} = -.280, p < .05). Among sleep variable estimates we note that a longer TST was associated with greater sleep efficiency (r_{rho} = .682, p < .001), and that a longer SOL was correlated with poorer sleep efficiency (r_{rho} = -.545, p < .001).

Table 5.1. Correlation matrix depicting correlations between actigraphy derived estimates of rest-activity rhythms and questionnaire derived self-reported measures

	ASRS	BIS	CFQ	MSF_{sc}	SJL	PSQI	IS	IV	RA	AMP	M10	M10o	L5	L5o	τ
BIS	**.683*****	-													
CFQ	**.609*****	**.550*****	-												
MSF_{sc}	.198	**.292***	.130	-											
SJL	.139	.108	.039	**.466*****	-										
PSQI	**.390****	**.290***	**.297***	.194	-.046	-									
IS	-.243	-.230	-.203	-.068	-.006	-.092	-								
IV	-.123	.016	.036	.035	-.154	.079	-.249	-							
RA	-.045	-.027	-.040	-.095	-.085	-.104	.240	.045	-						
AMP	**.281***	**.353***	.131	.008	-.109	-.152	.128	**-.363****	.141	-					
M10	**.294***	**.346***	.117	.024	-.096	-.131	-.014	**-.360****	-.014	**.970*****	-				
M10o	**.333***	.198	.174	**.500*****	.112	.123	.178	-.143	-.048	.189	.232	-			
L5	.150	.120	.073	.101	.071	.056	-.160	-.202	**-.930*****	.196	**.351***	.149	-		
L5o	**.293***	**.276***	.083	**.607*****	.115	.265	-.006	-.075	-.091	.167	.168	**.583*****	.148	-	
τ	-.195	-.163	-.132	-.011	-.114	.034	-.142	.186	-.226	-.217	-.157	.020	.151	.013	-
$\lvert\tau\text{-}24\rvert$	**.443*****	**.365****	**.306***	.134	.029	.226	**-.371****	-.018	**-.280***	-.059	-.016	.134	.250	.211	-.255

*ASRS = Adult ADHD self-report scale score; BIS = Barratt's Impulsiveness Scale total score; CFQ = Cognitive Failures Questionnaire score; MSF_{sc} = midsleep on free days corrected for sleep debt; SJL = social jetlag; PSQI = Pittsburgh Sleep Quality Index score; IS = interdaily stability; IV = intradaily variability; RA = relative amplitude; AMP = gross motor amplitude; M10 = activity counts for most active 10 h; M10o = time of onset of M10; L5 = activity counts for least active 5 h; L5o = time of onset of L5; τ = circadian period; $\lvert\tau\text{-}24\rvert$ = difference of τ from 24 h. *p < .05; **p < .01; ***p < .001*

Table 5.2. Correlation matrix depicting correlations between actigraphy derived estimates of sleep quality, duration, and timing, and questionnaire derived self-reported measures

	ASRS	BIS	CFQ	MSF_{sc}	SJL	PSQI	MS_{ACT}	TIB	TST	SOL	SlpEff	WASO
BIS	**.683*** **	-										
CFQ	**.609*** **	**.550*** **	-									
MSF_{sc}	.198	**.292***	.130	-								
SJL	.139	.108	.039	**.466*** **	-							
PSQI	**.390** **	**.290***	**.297***	.194	-.046	-						
MS_{ACT}	**.392** **	**.379** **	.229	**.601*** **	.271	.124	-					
TIB	-.140	-.244	.051	.055	.126	.144	-.142	-				
TST	**-.442*** **	**-.420** **	-.084	-.201	.109	-.012	-.228	**.649*** **	-			
SOL	.232	**.313***	.152	**.323***	.013	.284	.133	**.281***	-.258	-		
SlpEff	**-.466*** **	**-.339***	-.060	-.198	.114	-.164	-.203	.014	**.682*** **	**-.545*** **	-	
WASO	.069	.025	.120	-.196	-.058	-.150	-.077	.060	.056	**-.478*** **	-.089	-
#Wake	-.202	**-.297***	-.017	-.098	-.090	-.054	-.040	**.477*** **	**.542*** **	-.230	.205	**.326***

ASRS = Adult ADHD self-report scale score; BIS = Barratt's Impulsiveness Scale total score; CFQ = Cognitive Failures Questionnaire score; MSF_{sc} = midsleep on free days corrected for sleep debt; SJL = social jetlag; PSQI = Pittsburgh Sleep Quality Index score; MS_{ACT} = actigraphy determined average mid-point of sleep; TIB = total time in bed; TST = total sleep time; SOL = Sleep onset latency; SlpEff = Sleep efficiency; WASO = minutes awake after initial sleep onset; #Wake = number of wake bouts during sleep. $p < .05$; $**p < .01$; $***p < .001$.

Associations between circadian rhythm alterations and sleep disturbances and ASRS, BIS, and CFQ, measures

Inspection of correlation coefficients of ASRS score plotted against measures indicating circadian phase suggests that circadian phase delays and delayed sleep timing associate with greater self-reported symptom counts showing significant positive correlations with MS_{ACT} (r = .392, p < .01), M10o (r = .333, p < .05), and L5o (r = .293, p < .05), however no associations were found between ASRS score and SOL (r_{rho} = .232, p =.101) (Figure 5.1A). Similarly, inspection of variables correlated with BIS score also showed significant positive correlations with a later circadian phase of entrainment demonstrating associations with MS_{ACT} (r = .379, p < .01), SOL (r_{rho} = .313, p < .01), and L5o (r = .276, p < .05) (Figure 5.1B). These relations were not present for CFQ score which indicates general cognitive function deficits speaking perhaps to the specificity of the associations between delays in the circadian clock and symptoms of inattention and impulsivity (Figure 5.1C, Table 5.1 and Table 5.2).

Among the variables measuring sleep duration and fragmentation we found that ASRS scores were associated with reduced amount of sleep time and less efficient sleep correlating negatively with TST (r_{rho} = -.442, p <.001) and sleep efficiency (r_{rho} = -.466, p <.001) (Figure 5.2A). BIS scores showed similar relations correlating negatively with TST (r_{rho} = -.420, p <.01) and sleep efficiency (r_{rho} = -.339, p < .05) yet paradoxically was associated with fewer bouts of wakening (r = -.287, p < .05) (Figure 5.2B). As with the markers of circadian and sleep phase we did not detect that sleep disturbances or sleep duration were associated with CFQ score (Figure 5.2C).

Correlation coefficients between circadian period and questionnaires measuring ADHD symptoms, impulsivity, and cognitive failures failed to show any associations between variables with non-significant results found for ASRS score (r_{rho} = -.195, p = .170), BIS score (r_{rho} = -.163, p = .254), or CFQ score (r_{rho} = -.132, p = .356) (Figure 5.3A, C, E). Among the most consistent findings across each outcome measure however were moderate to strong correlations with the difference in τ from 24 h indicated by positive correlations noted with ASRS score (r_{rho} = .443, p = .001), BIS score (r_{rho} = .365, p = .008), and CFQ score (r_{rho} = .306, p = .029), suggesting that circadian period length

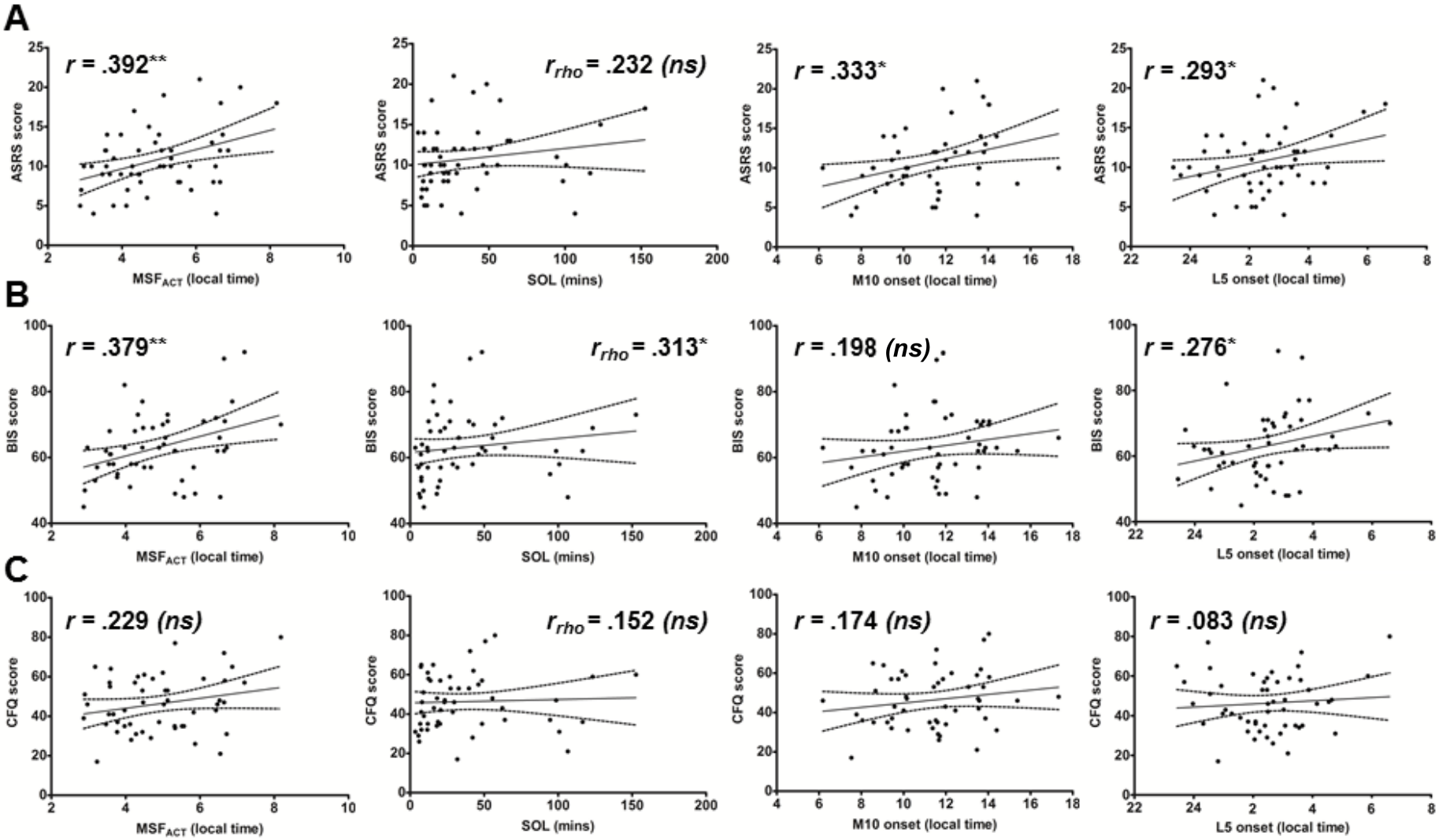


Figure 5.1 *Scatter plots depicting the relation between* ***(A)*** *ASRS scores* ***(B)*** *BIS scores, and* ***(C)*** *CFQ scores on y-axes against actigraphy determined measures of sleep and circadian phase. Panels going L-R direction indicate MS_{ACT}, SOL, M10 onset and L5 onset. p < .05; **p < .01; ***p < .001. Solid line indicates line-of-best-fit and dashed lines indicate the 95% confidence interval. ns indicates no significant differences*

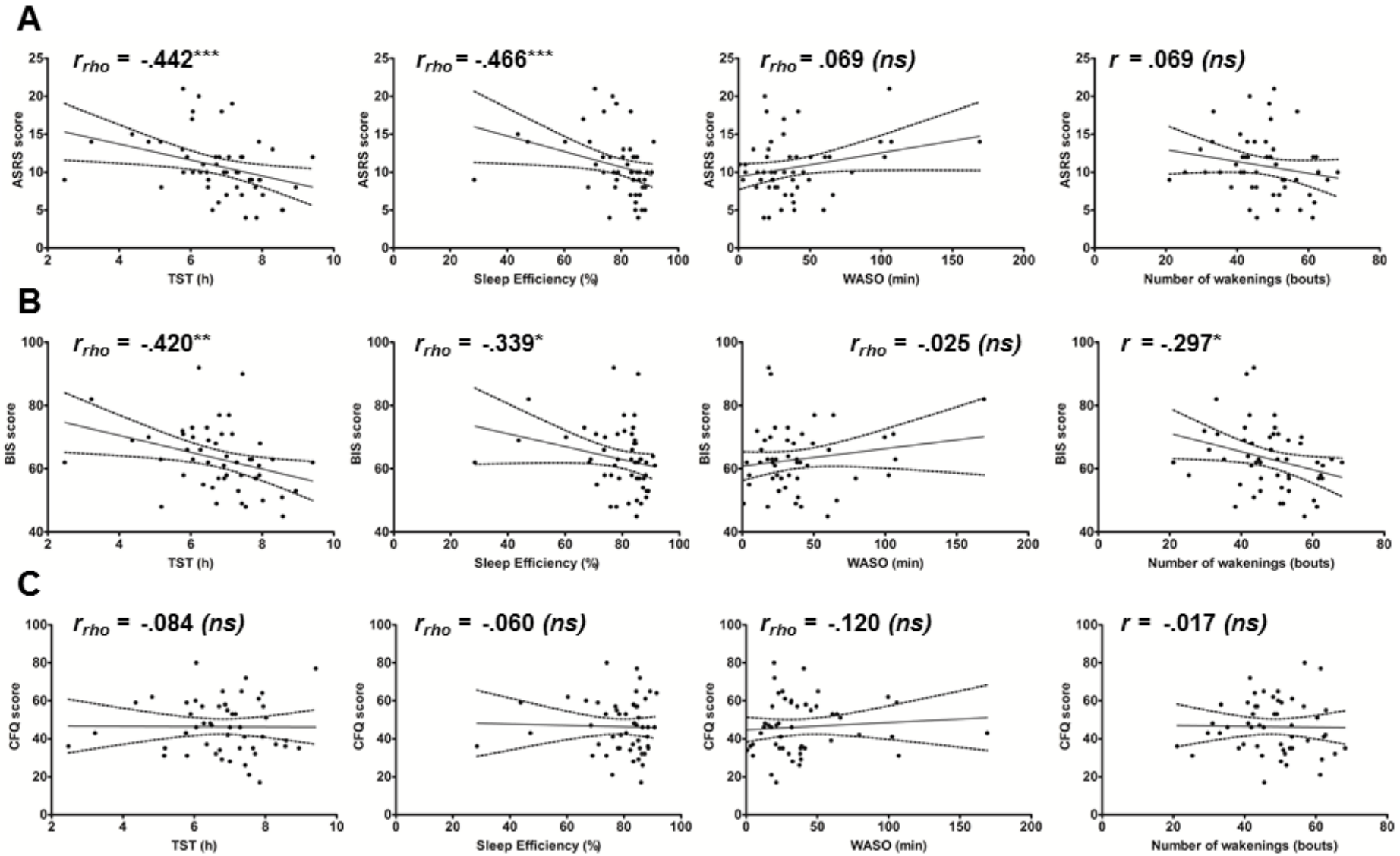


Figure 5.2 *Scatter plots depicting the relation between* ***(A)*** *ASRS scores* ***(B)*** *BIS scores, and* ***(C)*** *CFQ scores on y-axes plotted against actigraphy determined measures of sleep duration and quality. Panels going L-R direction indicate TST, Sleep efficiency, WASO, and the number of wakenings during sleep. p < .05; **p < .01; ***p < .001. Solid line indicates line-of-best-fit and dashed lines indicate the 95% confidence interval. ns indicates no significant differences*

per se was not an important covariate of ADHD-like symptoms, impulsivity, or cognitive failures but rather the deviation from the 24 h ideal was associated with each (Figure 5.3B, D, F).

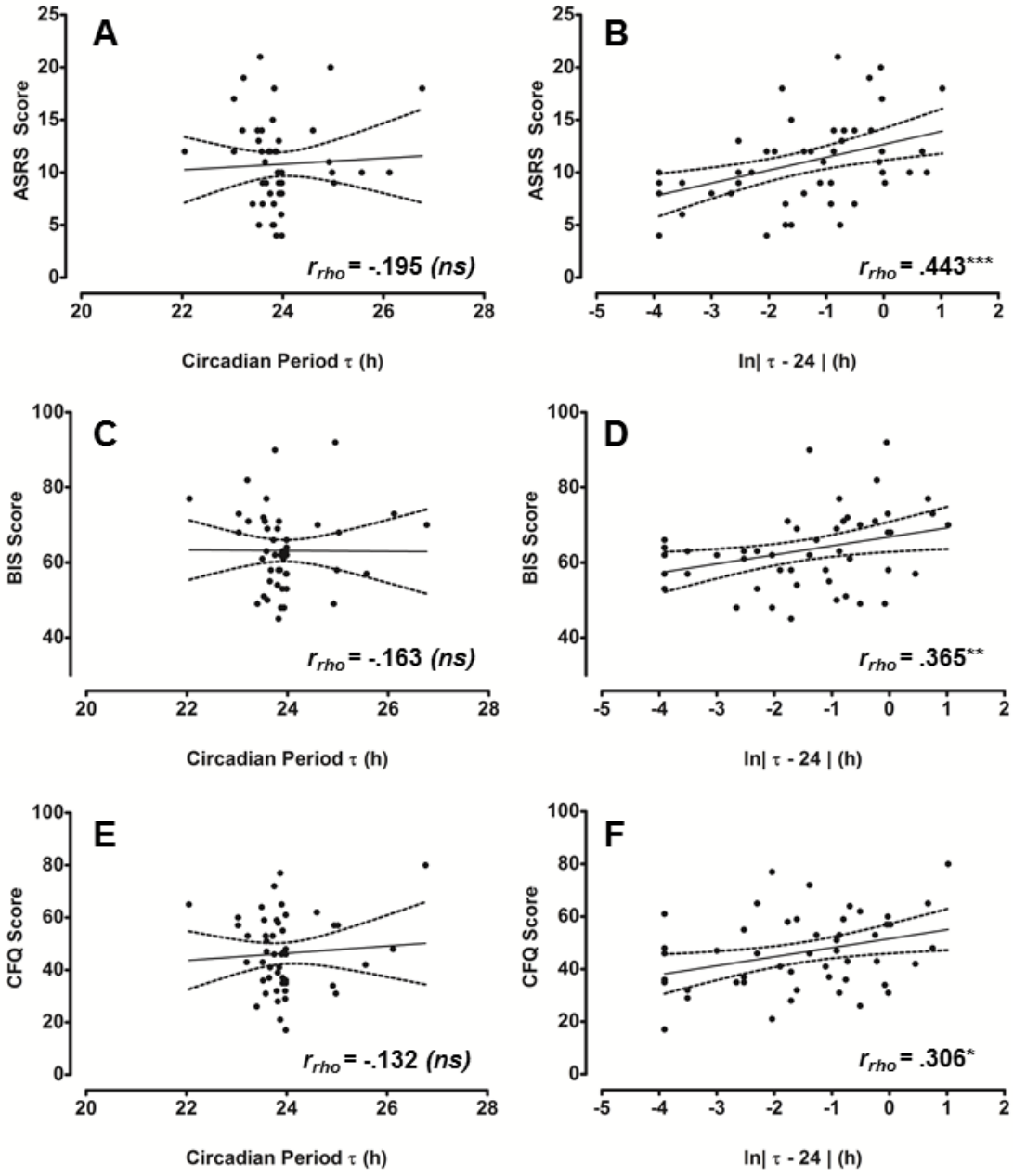


Figure 5.3 *Scatter plots depicting the correlations between outcome measures and underlying tau. Left panel shows the entrained circadian period against (A) ASRS score, (C) BIS score, and (E) CFQ score. Right panel shows the absolute difference of τ from 24 h against (B) ASRS score, (D) BIS score, and (F) CFQ. Note the non-significant relations between circadian period length, rather ADHD symptom rating, trait impulsivity, and general cognitive dyfunction are all positively related to a deviation in the entrained circadian period from the ideal 24 h. * p < .05; **p < .01; ***p < .001; ns indicates no significant differences*

Group-wise comparisons of ASRS score

Further to describing linear relationships between sleep and circadian measures and questionnaires measuring ADHD relevant domains we conducted a series of between groups comparisons selecting individuals who scored highly on the ASRS as being designated as ADHD-likely (n = 12) and selected an age and sex matched comparison group from the remaining sample. The means and SEM or median rank in the case of non-parametric tests for each group's variable score are presented in Table 5.3. Independent samples t-tests revealed significant differences in SJL and PSQI score between ADHD-likely and the comparison group with high ASRS individuals showing more SJL, $t(22) = -2.287$, $p = .032$, and poorer sleep quality $t(22) = -2.296$, $p = .033$. There was not a significant difference in MSF_{sc} between groups detected however, $t(22) = -1.325$, $p = .199$ (Figures 5.4A, B, and C).

Analysis of twenty-four hour rest-activity rhythm variable estimates did not reveal any significant between group differences for rhythm stability, $t(22) = .462$, $p = .649$ (Figure 5.5A), or variability, $t(22) = .618$, $p = .543$ (Figure 5.5B). Similarly both relative amplitude and gross motor amplitude did not differ significantly, RA: $U = 59$, $p = .695$ (Figure 5.5C), AMP: $U = 50$, $p = .325$ (Figure 5.5D). Furthermore there were not any differences detected for measures of M10 ($U = 51$, $p = .356$, Figure 5.5E) and M10 onset ($t(22) = -1.317$, $p = .202$, Figure 5.5F), or for measures of L5 ($U = 56$, $p = .566$, Figure 5.5G) and L5 onset ($U = 51.5$, $p = .379$, Figure 5.5H).

Inspection of sleep variables estimated by actigraphy found that, similar to MCTQ results, mid-point of sleep did not significantly differ between groups, $t(22) = -1.05$, $p < .306$ (Figure 5.6A). There was not a significant difference for the total time in bed measured between groups, $t(22) = .286$, $p = .778$ (Figure 5.6B), or sleep onset latency, $U = 38$, $p = .09$ (Figure 5.6D), but the ADHD-likely group did show a shorter total sleep time, $U = 29$, $p = .023$ (Figure 5.6C), and diminished sleep efficiency, $U = 19$, $p = .003$ (Figure 5.6E). There were not any differences between these groups in the total minutes of WASO, $U = 63$, $p = .880$ (Figure 5.6F), yet the comparison group did have a greater number of individual bouts of wakefulness after sleep onset had occurred, $t(22) = 2.255$, $p = .038$ (Figure 5.6G).

Similar to correlational analyses between group comparisons of τ did not find any association with ADHD symptoms, U = 49, p = .316 (Figure 5.7A), however the deviation of circadian period from 24 h was significantly greater in the ADHD-likely group, U = 27, p = .016 (Figure 5.7B).

Table 5.3 Between group comparisons for ADHD-likely individuals and age and sex matched participants

	Normal matches (*n* = 12)	**ADHD-Likely (*n* = 12)**	**Statistic (*t* / *U*)**	**Group Comparisons**
Age (years)	22.92	22.16		
	(3.5)	(2.94)		
Male/Female	6/6	6/6		
Questionnaires				
MSF_{sc} (local time)	5.5 (.37)	6.18 (.32)	t = -1.325	p = .199 (*ns*)
SJL (h)	1.44 (.256)	2.32 (.283)	t = -2.287	***p* = .032***
PSQI score	4.82 (.672)	7.6 (1.03)	t = -2.296	***p* = .033***
NPCRA				
IS	.486 (.039)	.461 (.036)	t = .462	p = .649 (*ns*)
IV	.788 (.051)	.74 (.059)	t = .618	p = .543 (*ns*)
RA	.884	.894	U = 59	p = .695 (*ns*)
AMP	352.43	347.45	U = 50	p = .325 (*ns*)

M10	361.73	374.26	$U = 51$	$p = .356$ (*ns*)
M10o (local time)	11.08 (.77)	12.38 (.59)	$t = -1.317$	$p = .202$ (*ns*)
L5	15.41	21.98	$U = 56$	$p = .566$ (*ns*)
L5o (local time)	2.48	2.82	$U = 51.5$	$p = .379$ (*ns*)
Sleep variables				
MS_{ACT} (local time)	5.01 (.357)	5.6 (.442)	$t = -1.05$	$p = .306$ (*ns*)
TIB (h)	8.55 (.296)	8.43 (.286)	$t = .286$	$p = .778$ (*ns*)
TST (h)	6.87	6.04	$U = 29$	***p* = .023***
SOL (mins)	13.71	39.71	$U = 38$	$p = .091$
Sleep efficiency (%)	84.71	70.81	$U = 19$	***p* = .003****
WASO (mins)	39.91	31.78	$U = 63$	$p = .880$
#Wakenings	53.11 (3.03)	44.72 (2.17)	$t = 2.255$	***p* = .038***
Rhythm				
Period τ (h)	23.95	23.58	$U = 49$	$p = .316$ (*ns*)
Deviation of period from 24 h	-2.18	-.51	$U = 27$	***p* = .016***

*Table shows parametric (independent t-test) or non-parametric (Mann-Whitney U test) comparisons between groups. Group means with SEM appearing in parentheses are listed where t-tests are used. Median ranks are listed where Mann-Whitneys test is applied. Age is reported with standard deviations in parenthesis. * p < .05; **p < .01; ***p < .001; ns indicates no significant differences*

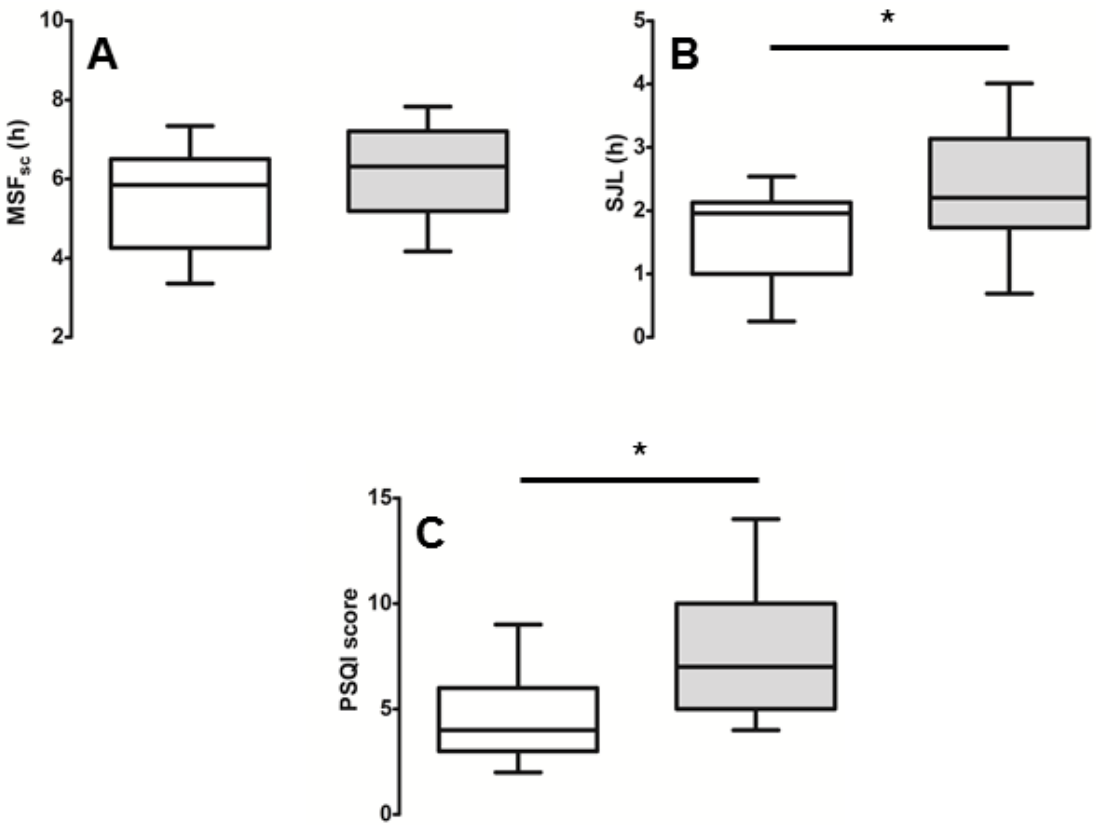


Figure 5.4 *Box-plot comparisons on questionnaire measures. Group-wise comparisons between 'ADHD-likely' (Grey boxes) cohort and 'normal matches' (white boxes). Groups compared on (A) MSF_{sc}, (B) SJL, and (C) PSQI score. * p < .05; **p < .01; ***p < .001*

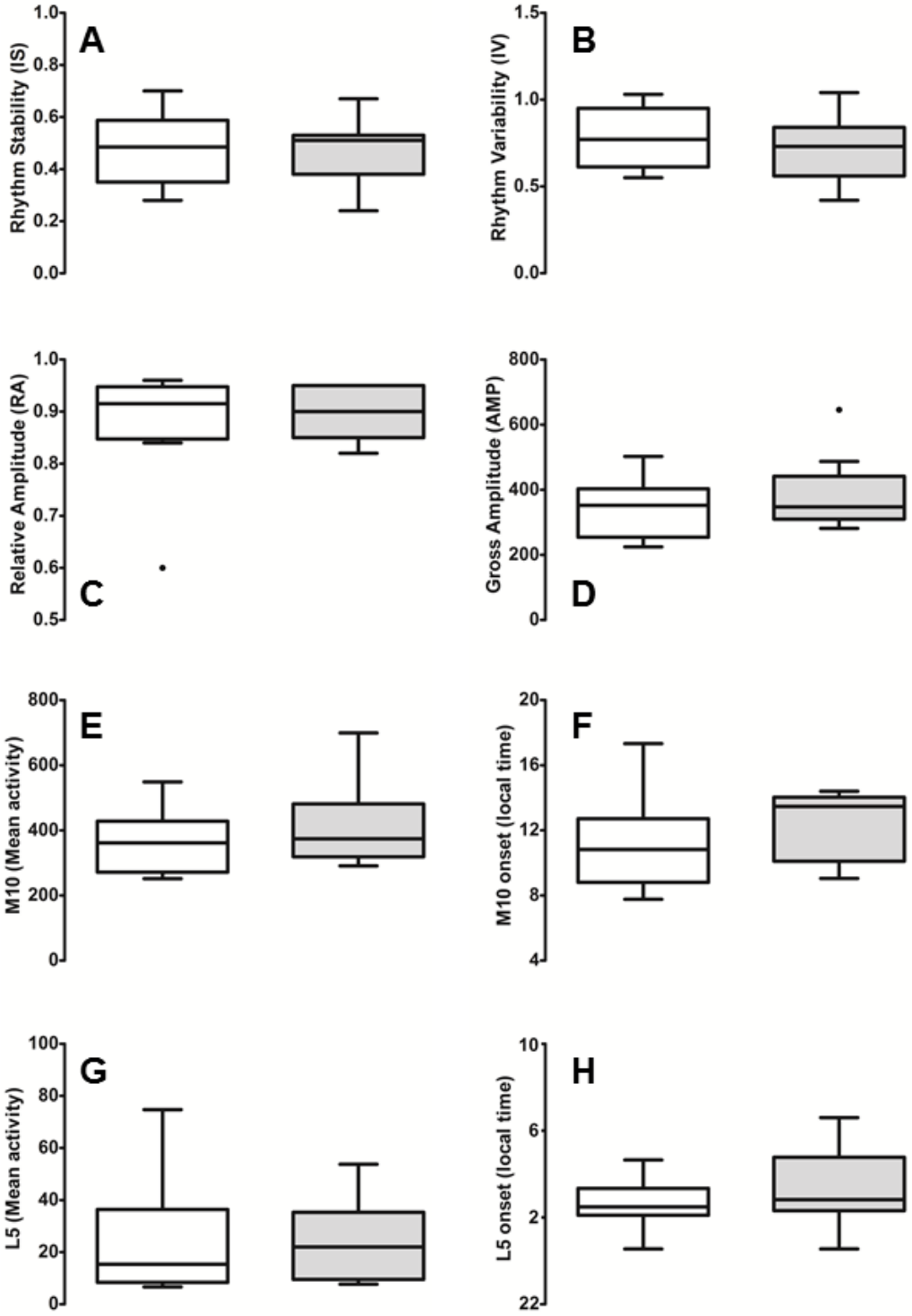


Figure 5.5 *Box-plot comparisons for NPCRA parameters. Group-wise comparisons between 'ADHD-likely' (Grey boxes) cohort and 'normal matches' (white boxes). Groups compared on (A) IS, (B) IV, (C) RA, (D) AMP, (E) M10, (F) M10o, (G) L5, and (H) L5o. * p < .05; **p < .01; ***p < .001*

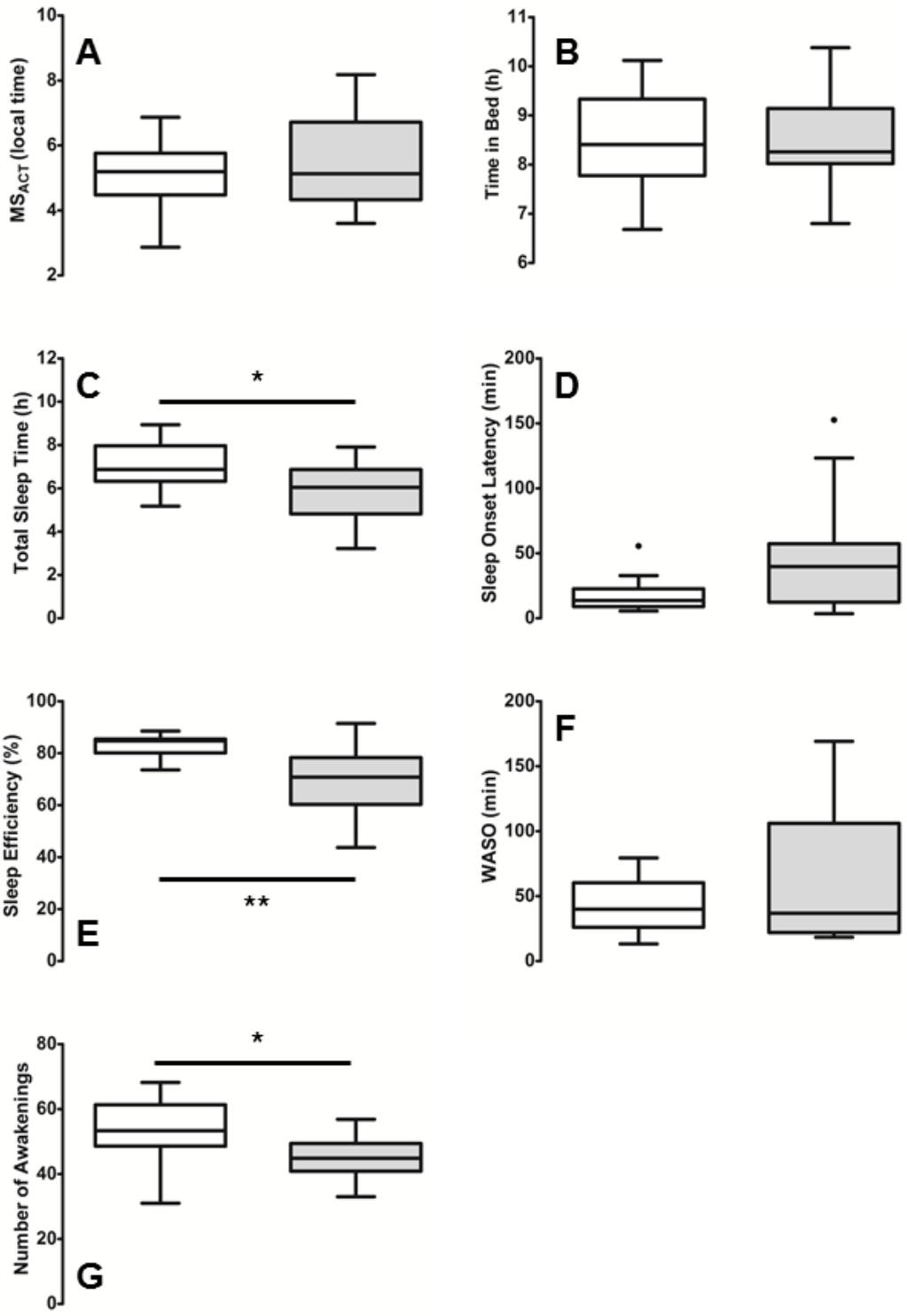


Figure 5.6 *Box-plot comparisons for actigraphy determined sleep estimates. Group-wise comparisons between 'ADHD-likely' (Grey boxes) cohort and 'normal matches' (white boxes). Groups compared on (A) MS_{ACT},(B) TIB, (C) TST, (D) SOL, (E) Sleep efficiency, (F) WASO, and (G) number of awakening bouts. * p < .05; **p < .01; ***p < .001*

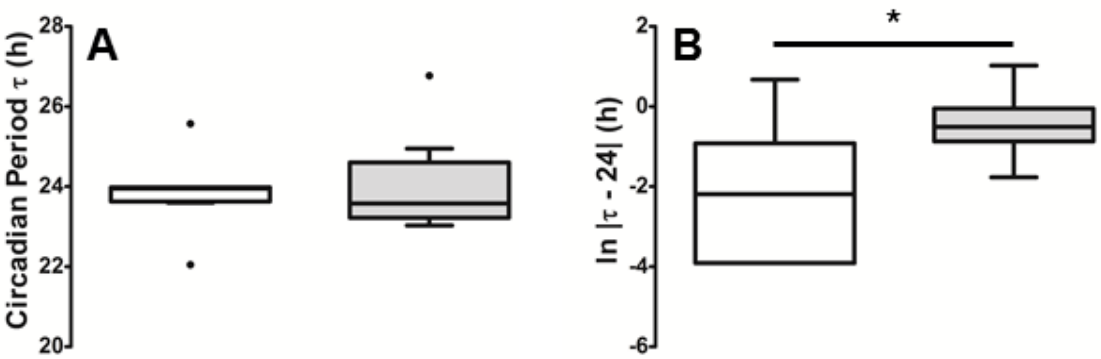


Figure 5.7 *Box-plot comparisons for circadian rhythm period. Group-wise comparisons between 'ADHD-likely' (Grey boxes) cohort and 'normal matches' (white boxes). Groups compared on (A) the entrained circadian rhythm period and (B) the deviation of the circadian period from 24 h. * p < .05; **p < .01; ***p < .001*

Regressions predicting ADHD symptoms and traits

In order to assess the relationship between rest-activity and sleep pattern estimates and measures of ADHD symptoms and impulsivity we conducted two exploratory linear regression analyses with the aim of predicting ASRS and BIS scores. Given the relatively small sample size for a regression in the present study in addition to age and sex we selected only predictors that showed a correlation coefficient of greater than .4 but also included MS_{ACT} (r = .392) as a measure of circadian phase. Inserted in the model were TST, SlpEff, MS_{ACT}, and deviation of τ from 24 h. Predictor variables were entered using a forward selection method. The final model predicting ASRS scores was comprised of two predictor variables, MS_{ACT} and sleep efficiency, and was statistically significant, $F(2, 48) = 8.905$, p = .004, accounting for approximately 21.8% of the variance in the ADHD screener score (R^2 = .249; adjusted R^2 = .218). Circadian phase held the greatest share of the variance (β = .391, sr^2 = .152, p = .003) followed by Sleep Efficiency (β = -.309, sr^2 = .095, p = .017, see Table 5.4).

The final regression model for the prediction of BIS scores was also statistically significant and was comprised of the predictors MS_{ACT} and TST; $F(2, 48) = 7.454$, p = .002, and accounted for approximately 20.5% of the variance in self-reported general

trait impulsivity (R^2 = .237; adjusted R^2 = .205). Circadian phase again held the greatest share of the variance (β = .347, sr^2 = .119, p = .009) followed by TST (β = -.307, sr^2 = .093, p = .019, see Table 5.5).

Table 5.4. Regression model predicting ASRS score using actigraphy derived sleep and rest-activity pattern estimates

Final Model	B	SE_B	β	sr^2
Constant	12.87	3.82		
MS_{ACT}	1.213	.388	.391	.152
Sleep Efficiency	-.102	.041	-.309	.095

R^2 = .249; adjusted R^2 = .218, p = .004. Predictor variables inserted in final model MS_{ACT} (local time) and Sleep efficiency (%). B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in the proportion of ASRS score accounted for by variable.

Table 5.5. Regression model predicting BIS score using actigraphy derived sleep and rest-activity pattern estimates

Final Model	B	SE_B	β	sr^2
Constant	65.90	8.76		
MS_{ACT}	2.27	.995	.347	.119
TST	-2.38	.983	-.307	.009

R^2 = .237 adjusted R^2 = .205 p = .002. Predictor variables inserted in final model MS_{ACT} (local time) and Total Sleep Time (h). B = unstandardised regression coefficient; SE_B = standard error of unstandardized regression coefficient; β = standardised regression coefficient; sr^2 = squared semi-partial statistic, measuring unique variance in the proportion of BIS score accounted for by variable.

5.4 Discussion

In the current study we describe associations between perturbed sleep patterns, and a number of measures of delayed circadian phase of entrainment, with self-reported symptom counts of adult ADHD and general trait impulsivity in a normative non-clinical population. Among the most important predictors of ADHD-like features and traits indexing impulsivity were a later mid-point of sleep and lower sleep efficiency, and a later mid-point of sleep and shorter total sleep duration, respectively. These findings are consistent with a number of studies carried out in ADHD populations and in the general population which show that delayed timing of the circadian clock and disruption to sleep duration and quality might produce or exacerbate pre-existing symptoms of inattention and impulsivity (Mahajan *et al.,* 2010; Sivertsen *et al.,* 2015; Gau *et al.,* 2007; Voinescu *et al.,* 2012; Kamphius *et al.,* 2014). In samples of clinically confirmed ADHD where objective measures of sleep estimation such as actigraphy and polysomnography have been used, lengthening of sleep onset latency, decreased sleep efficiency, and shorter bouts of uninterrupted sleep have been reported (Boonstra *et al.,* 2007; Van Veen *et al.,* 2010; O'Brien *et al.,* 2003). Such findings are strikingly similar to the sleep disturbances that we report here associated with greater symptom counts.

Interestingly, the associations described in this study seem to be specific to features found in ADHD rather than general deficits in cognitive ability as no significant correlations were found between markers of circadian phase, sleep quality or duration, and self-reported cognitive failure score. Therefore, the characteristics of the sleep and rest-activity profile which we describe here might represent a risk factor towards ADHD symptom liability over and above the general maladaptive effect of sleep and circadian rhythm disturbances on cognition and behaviour noted by others (Curcio *et al.,* 2006; Schmidt *et al.,* 2007). An important trend which has begun to emerge from the literature on this subject and is further supported by the findings of the current study is that of the link between circadian clock dysfunction and the presentation of ADHD-like symptoms which are found to associate along a dimensional axis. While a number of reports have suggested that sleep and circadian

rhythm dysfunction might be considered part of the potential pathophysiology of the disorder (Schredl *et al.,* 2007; Sobanski *et al.,* 2008), findings such as those reported here suggest that a delayed circadian phase and greater sleep onset latency might represent risk factors towards conventional ADHD-like symptoms among the general population also. Thus future studies may benefit from moving away from discrete diagnostic methods when investigating the relevance of circadian rhythm characteristics and outcomes associated with common psychiatric conditions such as ADHD. Further, the current study is one of the few which utilises objective measurement of the rest-activity profile to probe for associations with traits of impulsivity and inattention in typically developing populations. Our findings are supportive of a number of questionnaire based reports conducted among members of the general population which link later circadian typology and subjective sleep deficits with greater levels of self-reported impulsivity and attentional deficits in both children and adults (Bae *et al.,* 2010; Caci *et al.,* 2009; Gruber *et al.,* 2012).

Although a clear reason for these associations remains elusive data reported in the previous two experimental chapters suggest that circadian dysregulation which emerges from social jetlag might represent a novel mechanistic candidate driving the effects of later circadian phase and negative behavioural outcomes. Surprisingly, the current data did not show any significant relations between measures of rest-activity pattern stability or fragmentation and ASRS or BIS score. Similarly, while group-wise approaches did indicate that ADHD-likely individuals experienced greater SJL than age and sex matched volunteers, exploratory correlations did not reveal any associations between MCTQ derived estimates of SJL and objective measures of IS or IV. There are several reasons why this might be the case. Firstly, concerns the amount of days sampled during the actigraphy recording interval. In the current study participants wore the actigraph devices for seven full days however the MCTQ measure of SJL is derived from participants self-reported sleep timing behaviour on 'general' work week. This discrepancy between self-report accounts and objective metrics may arise from the possibility that the amount of data recorded by the actigraph did not faithfully capture a typical working week. Furthermore, as the actigraph could only sample data for a maximum of one weekend during the week-

long recording period and the number of interdaily transitions affecting the stability and variability of the rest-activity rhythm might not necessarily correspond with a self-reported measure of behaviour. It would have been beneficial in this regard to extract a longer recording session from participants in order to properly assess weekday-weekend transitions. Conversely, this point further raises another limitation found in the commonly held assumption in actigraphy studies that activity on weekends will differ from weekdays conforming to societal norms of organising work and free day activities. As the population in question consisted of students one limitation in our research was not ascertaining how weekly schedules influenced by the social clock (*i.e.* whether students work part-time at weekends or if they only have class on certain week days). Further study is required in order to understand the precise impact of SJL on the rest-activity interval and how it corresponds with other parameters of the rest-activity pattern that are not accessible through self-report.

One of the most consistent findings in the current study and probably the most novel amongst the pre-existing literature are the associations which we report between deviations of the entrained circadian period from 24 h and greater ASRS, BIS, and CFQ scores. Previously Baird *et al.* (2011) reported a similar association finding that a shorter circadian period of best fit of the rest-activity pattern was positively correlated more symptom severity on the DSM interview score for ADHD. Unlike the previous study we did not detect any association between symptom counts and the period of the locomotor rhythm *per se*, rather when the absolute deviation of τ from the 24 h theoretical ideal was plotted against self-reported measures, weak to moderate correlations emerged linking circadian dysfunction to greater scores of inattention and impulsivity, as well as a general higher index of cognitive errors. Such findings may be interpreted in line with what would be expected according to the *circadian resonance hypothesis* which predicts that fitness is enhanced the tighter the circadian rhythm is coupled to the environmental photoperiod (Pittendrigh & Bruce, 1959; Wyse *et al.,* 2011). The most apparent evidence illustrating this hypothesis comes from animal models of behaviour where housing under photoperiods that deviate from 24 h produces more maladaptive

health outcomes such as increased weight gain and insulin resistance (Karatsoreos *et al.,* 2011; Vilaplana *et al.,* 1995; Campuzano *et al.,* 1999) and the associations previously reported linking a greater deviation of free-running τ from 24 h and decreased lifespan (Wyse *et al.,* 2010). In the context of human behaviour it is reasonable to expect a greater degree of variability in the entrained locomotor period as control of environmental lighting might lead to being better able to tolerate departures from a precise 24 h photoperiod. However as indicated here deviations from a resonant 24 h circadian period might exacerbate deleterious neurobehavioual outcomes such as impulsiveness, risk-taking, and poor attentional control as τ drifts between days. Alternatively, individuals with compromised circadian resonance might forego entrainment as a consequence of some apparent adaptive advantage afforded by the environment. It could be speculated that temperamental and personality factors such as an increased sensation seeking behaviour among subjects might lead to deviations in circadian period through modified zeitgeber exposure and therefore reverse or exogenous causation could explain the relations noted.

Taken together the presence of a delayed circadian phase and a deviation in circadian period suggests an entrainment deficit among individuals with elevated impulsivity and inattention. This is further indicated by the weak to moderate strength negative correlations noted between deviation in circadian period and interdaily stability and relative amplitude of the rest-activity rhythm suggesting that rhythms are not tightly coupled to the environmental signal. Surprisingly, however circadian phase and period were not related despite previous indications that an earlier phase of entrainment is associated with shorter periods and later phases with longer periods (Wright *et al.,* 2005; Duffy, Rimmer, & Czeisler, 2001). Despite being seemingly independent in the current sample there are a number of overlapping factors which modify both circadian phase and period and have further been implicated with the potential role of the circadian timekeeping system in ADHD. While circadian dysfunction in certain clinical populations and older individuals has been linked to loss of neural integrity in the master pacemaker (Harper *et al.,* 2004; Whitehead *et al.,* 2008), it seems unlikely that the SCN is affected given the health status and age profile of the current sample. Rather circadian abnormalities detected

in the current study are most likely the result of inadequate zeitgeber exposure which acts as a synchroniser of behavioural circadian rhythms to the temporal environment.

The shifting potential of the phase angle of entrainment of the circadian rhythm is known to be influenced by the timing, duration, and the intensity of photic zeitgeber administration (Gronfier, Wright, & Czeisler, 2002; Gronfier *et al.,* 2004). Similarly, the entrainment of individuals with shorter intrinsic periods to match the 24 h day (Duffy & Czeisler, 2009) or to exceed it in the case of experiments conducted by (Gronfier *et al.,* 2007) is dependent on strong environmental synchronisers. Such a strong zeitgeber signal of bright days and dark nights has been perturbed by modern living arrangements with studies showing low natural exposure to bright light among city dwellers (Hébert, Dumont, & Paquet, 1998; Scheurmaier, Laffan, & Duffy, 2006). Roenneberg *et al.* (2012) illustrate the effects of this circadian interruption linking reduced time spent outdoors in natural light to a later chronotype across their European database of MCTQ scores. Furthermore, the use of artificial lighting and light emitting electronic devices such as computers, phones, and iPads/tablets reduce the darkness levels during the normal scotoperiodic phase leading to maladaptive circadian entrainment in humans (Smolensky *et al.,* 2015). It seems likely therefore that such patterns of delayed circadian phase and the departure from a resonant period seen in the current study may emerge as a result of poor entrainment to environmental synchronisers either by reduced daytime bright light exposure, excessive light at night, or a combination of both.

Moreover, these findings accord strikingly well with epidemiological reports which suggest that geographical regions and altitudes with higher levels of solar intensity are associated with lower prevalence rates of ADHD (Arns *et al.,* 2013; Huber *et al.,* 2015). The reasons for these associations are thought to be based upon a protective role of better solar circadian entrainment which is facilitated by exposure to bright natural light during the morning and early parts of the day (Arns, Swanson, & Arnold, 2015). Similarly, evening and nocturnal use of LED screen media devices by children and adolescents produces many of the same deficits noted among ADHD

patients such as delayed sleep onset and melatonin suppression (Cajochen *et al.,* 2011; Custers & Van den Bulck, 2012; Van den Bulck, 2004, Wood *et al.,* 2013). Controlled studies are required however to investigate if exposure to brighter natural light during the daytime and limitation of artificial light at night have any meaningful effect on improving impulsivity and attention scores and to confirm the hypothesis that such effects are driven primarily through the better entrainment of the circadian timekeeping system.

An alternative explanation for the later circadian phase and deviation in period observed in the current study might involve individual differences in the phototransduction circuitry that relays zeitgeber information from the environment to the SCN via dedicated retinohypothalamic pathways. Previously it has been reported that melanopsin gene variants are associated with sleep timing and chronotype (Lee *et al.,* 2014; Roecklein *et al.,* 2012). Functionality of the ipRGC phototransduction circuitry in healthy adolescents and young adults has previously been assessed by examining sustained pupil constriction after exposure to bright blue light (van der Meijden *et al.,* 2016). The post-illumination-pupil response (PIPR) measured in this manner specifically indicates the strength of non-vision forming photic responses dependent on the intrinsic melanopsin signalling which targets areas such as the master clock and the olivary pretectal nucleus (OPN). Interestingly the authors of this study found that blue-light responsiveness was associated with a delayed circadian phase of sleep timing (measured by later midsleep) suggesting that inter-individual differences in melanopsin signalling contribute to circadian clock entrainment when the dose of lighting is held constant (van der Meijden *et al.,* 2016). It is suggested that these behavioural outcomes emerge as a result of differences in sensitivity to photo induced delays of melatonin secretion which are also found to be associated with a stronger PIPR to light (Munch *et al.,* 2015). Interestingly, inspired by clinical experience in which adults diagnosed with ADHD frequently report a greater sensitivity to bright light, Kooij and Bijlenga (2014) report survey data showing a high prevalence of self-reported photophobia amongst individuals with ADHD in comparison to healthy subjects. The authors suggest that there may be a potential role for ipRGC activity leading to oversensitivity in the condition.

It has also been suggested that bright light nociception may be relayed via melanopsin-signalling pathways which project to the OPN (Digre & Brennan, 2012; Okamoto *et al.,* 2010). While melanopsin signalling to the SCN represents a separate arm of the NIF photic response to light than signalling to the OPN, the latter of which is primarily involved with pupillary light reflexes and blinking of the eyes rather than circadian regulation (Gamlin *et al.,* 2006), the implication of ipRGC functionality with both circadian entrainment and clinical reports of ADHD is a topic that warrants further investigation. It may be the case that individual differences in light-evoked responses to light involving RHT mediated signalling represents a common intermediate phenotype for both later circadian typology and adult ADHD.

In order to test whether different patterns of light exposure might mediate circadian entrainment and negatively affect ADHD symptomatology future studies should attempt to record light exposure in individuals with the disorder as well non-clinical groups such as adolescents and young adults that are at risk of elevated impulsivity and delays in sleep onset. A number of actigraph devices on the market, including the Actiwatch 2 used in this study, have the added feature of being able to passively measure environmental illuminance levels in addition to locomotor activity. Furthermore, depending on manufacturer specification some devices are also capable of detecting the spectral composition of light allowing for a more meaningful assessment of the dosage of short wavelength light (450 – 490 nm) which has the greatest impact on circadian entrainment in humans. In the current study our ability to record environmental light exposure was restricted by the very fine sample interval chosen and the charge capacity of the device's battery. Future studies should aim to collect this information in addition to studying locomotor rest-activity patterns to conduct a more thorough investigation into the role of light exposure and circadian timekeeping and psychiatric symptoms as others have done with other common health consequences linked to circadian dysfunction such as adult and childhood obesity (Reid *et al.,* 2014; Pattinson *et al.,* 2016).

We note a number of study limitations here which should be considered when interpreting the findings of the present study. Firstly, is that the associations we

report here only implicitly suggest that symptom counts of attention deficit and impulsivity are a consequence of circadian and sleep problems. While there is a reasonable amount of *a priori* evidence among the literature to speculate a cause and effect relationship our findings can only be interpreted as correlational and not causative. Similarly, a case can be made for reverse causation to apply. Higher symptom counts of hyperactivity and reduced sensitivity to social zeitgebers for example may be driving the associations with later phase and maladaptive entrainment rather than the other way around. Moreover, the observations we note are among a cohort of healthy young adults and require replication in populations with clinically confirmed ADHD. Although our approach might be advantageous considering the availability of medication-naïve subjects, there conversely may exist separate interactions between diagnosis and features of sleep and circadian disturbance not represented in our data.

In conclusion, the results of this study replicate findings which link sleep and circadian clock abnormalities with ADHD in adults. We find that objective measures of circadian phase and mid-sleep correlate with self-reported scores validating the self-report measures used to estimate circadian sleep phase in other experiments described in this work. Furthermore, we were able to assess components of circadian rhythm entrainment by actigraphy that are not readily acquired via subject report methods and describe a novel association between a deviated circadian period and higher symptom ratings. We highlight the exploratory nature of our study and advise that replication using controlled experimental designs are necessary before conclusive evidence can be generated. Future work is also required to determine if interventions targeting such dysfunctions might lead to therapeutic benefit in clinical populations and to investigate whether light or other zeitgeber entrainment moderates these relationships.

Chapter 6

Investigating the effects that common variants in core circadian genes have on shaping sleep, circadian phase and ADHD-like traits

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Abstract

Research investigating associations between common polymorphisms in genes which regulate the molecular circadian clock and human circadian phenotypes have primarily focused on the morningness-eveningness dimension of diurnal preference. Similarly, a number of studies report that common variations in circadian clock genes may confer susceptibility towards ADHD or disease related traits. Many of these studies however have used subjective measures of diurnal preference rather than actual indicators of chronotype such as the sleep phase and in the ADHD literature have focused on reported symptoms rather than objective indictors of neuropsychological performance. Here, we studied the common single nucleotide polymorphisms CLOCK T3111C and PER2 C111G, and the 54 base pair nucleotide sequence variable number tandem repeat polymorphism in PER3, and examined differences between genotypes on sleep and circadian rhythm variables as well as self-reported ADHD traits and performance on the CCPT and IGT. DNA from donated saliva samples was collected from volunteers (n = 185) from the same experimental cohort used in Chapter 3 and participants were genotyped for the three polymorphisms. Results indicate that there were no main effects of any of the genetic variants on either sleep or circadian parameters adjusting for multiple comparions; no main effects on self-reported ADHD symptoms, impulsivity, and cognitive failures; and no main effects behavioural indictors of impulsivity and risky decision making using neuropsychological tasks. Exploratory backward elimination regression models revealed significant gene × environment interaction effects for CLOCK T3111C × social jetlag on impulsivity scores; significant PER3 × sleep quality effects on ADHD symptom scores; significant PER3 × sleep quality effects on impulsivity scores; and significant PER3 × sleep quality effects on cognitive failure scores. We acknowledge the limitations of this study including a relatively small sample size for a candidate gene study and a heterogeneous cross-section of the population. Results are discussed within the context of the need for phenotypes which are closer biological indexes of the circadian system in candidate gene studies

and the additional possibility for a moderating role of the environment to be considered when examining individual differences in how chronotypes emerge or symptoms manifest.

6.1 Introduction

Attention deficit-hyperactivity disorder has been shown to be a highly heritable condition suggesting that genetic links may have a role to play in the aetiology of the disorder (Faraone *et al.,* 2005; Matthews *et al.,* 2014; Hawi *et al.,* 2015). Similarly, individual differences in the diurnal preference trait have also been shown to be heritable thus shaping research interest into how genetic variation might influence behavioural phenotypic expression of the circadian timing system (von Schantz *et al.,* 2015). Given the associations between ADHD and the circadian and sleep timing systems, interesting questions involving the potential shared genetic links between both phenomena have emerged. This is especially true where insight into such links might improve our understanding of the mechanisms which lead to the high frequency occurrences of sleep and circadian abnormalities that are present in the condition (Coogan *et al.,* 2016).

As previously discussed in the introduction to this research, the circadian rhythm expressed by the master clock in the SCN and by peripheral oscillators is maintained by the 24 h oscillation of transcription feedback loops of the core 'clock genes'. This group of molecular circadian regulators consist of several genes including *Pers 1/2/3, Crys 1/2, Clock, and Bmal1,* which interact with each other and regulate their own activation and inhibition throughout the circadian cycle (Ko & Takahashi, 2006; Reppert & Weaver, 2001). Previous genome-wide association studies (GWASs) have implicated elements of the circadian clock, specifically clock gene polymorphisms in *PER1* and *PER2* as being associated with incidence of childhood and adolescent ADHD (Lasky-Su *et al.,* 2008; Brookes *et al.,* 2006). Similar large scale GWASs have recently suggested that a number of the same genes involved in the molecular circadian clockwork are implicated in measures of human chronotype and diurnal preference (Kalmbach *et al.,* 2016; Jones *et al.,* 2016; Lane *et al.,* 2016). Possible relations between these novel genetic variants and psychiatric conditions where circadian dysfunction is prevalent have yet to be explored however.

Associations between circadian clock genes and ADHD have been further supported by functional differences noted between wild-type and knockout/mutant

subjects in animal studies. Experiments involving animal models of ADHD have shown increased attention deficit, hyperactivity and impulsive behaviours in *PER1b* zebrafish and *PER1* mouse knockouts (Huang *et al.,* 2015). Earlier experiments also show that mice carrying a mutation in the *CLOCK* gene display a mania-like phenotype which includes substantial overlap with ADHD-like symptoms with behavioural pattern of hyperactivity, decreased sleep, and hyper-sensitivity to reward such as sucrose availability and cocaine administration (Roybal *et al.,* 2007; Coyle, 2007). Furthermore, mutation of *PER1* and *PER2* in a mouse model of alcohol reinforcement has shown increased ethanol intake and reinforcement from reward potentially linking function of these circadian components with a dysfunction reward circuit in mammals (Gamsby *et al.,* 2014).

While genome-wide studies have the necessary power to detect genetic effects that are significant after correcting for several comparisons their drawbacks include potentially missing significant associations which are lost after such correction. Additionally, specificity over the phenotype in question is sacrificed when such large cohorts are utilised and the limitations involving the use of categorical data or diagnosis as an interpretable phenotype have been highlighted previously (Meyer-Lindenberg & Weinberger, 2006). Furthermore, translating behavioural findings from animal work to resemble a representative picture of human mental illness presents more complex challenges of interpretation and replication in a human scenario. In the last number of years several candidate gene studies have reported potential associations between polymorphisms in multiple canonical clock genes and behavioural features of sleep and circadian rhythm regulation as well as common diseases and mental health problems (Voinescu, 2009). The roles of such variants have also been linked to impulsivity and ADHD-like phenotypes and reward circuit modulation (Forbes *et al.,* 2012). Single nucleotide polymorphisms (SNPs) are among the most common of all DNA sequence variations reported in the literature. A SNP refers to a single point mutation in the base-pair sequence of a gene which defines two alleles, with each one from each homologous chromosome. For example, a single base substitution $T \rightarrow C$ produces three possible genotypes where individuals among a population may be homozygous for two T-alleles, two C-alleles, or heterozygous

for both, possessing one copy of each allele at that point on either chromosome (*i.e.* T/T, C/C, or C/T respectively). Another type of gene polymorphism is known as a variable number tandem repeat sequence (VNTR) in which a nucleotide sequence pattern is repeated a number of times directly adjacent to each other. An example of such is the VNTR in the dopamine D4 receptor gene (DRD4), implicated with differential transmission of the neurotransmitter among mesocortical pathways, where it has previously been shown that the 7-repeat allele confers a heighted risk towards ADHD diagnosis (Faraone *et al.,* 2001).

One of first clock gene association studies was that in which delayed circadian phase in humans was linked to a common variant in the CLOCK T3111C SNP (*rs1801260*) reported by Katzenberg *et al.* (1998) in which the authors found an association between the minor C-allele and increased evening diurnal preference. These results are since shown to be controversial however with some groups successfully replicating the findings of the original study (Mishima *et al.,* 2005; Friedman *et al.,* 2009) but a larger number of studies have not been able to corroborate the association reporting null findings (*e.g.* Robilliard *et al.,* 2002; Joahansson *et al.,* 2003; Iwase *et al.,* 2002; Pedrazzoli *et al.,* 2007; Choub *et al.,* 2011; Barclay *et al.,* 2011). Furthermore, using endocrine and core body temperature parameters as objective markers of delayed circadian entrainment in addition to self-reported morningness-eveningness scores, Chang *et al.* (2011) failed to show any association with the purportedly risky C-allele. Studies have also shown an association between other CLOCK gene variants and sleep duration (Allebrandt *et al.,* 2010) and the CLOCK T3111C SNP has been associated with shorter sleep duration and insomnia in psychiatric populations (Benedetti *et al.,* 2007; Serretti *et al.,* 2003). However, findings from the Barclay *et al.* (2011) study did not show that this SNP predicted sleep quality in members of the general population.

Interestingly, an association between CLOCK T3111C and adult ADHD has been consistently replicated by a number studies indicating that the polymorphism conferred risk towards the disorder (Kissling *et al.,* 2008; Xu *et al.,* 2010; Jeong *et al.,* 2014). In two of the studies carried out among forensic and general male cohorts,

individuals carrying the T-allele had elevated symptoms of ADHD (Xu *et al.,* 2010; Jeong *et al.,* 2014). Similarly, group-wise approaches using ADHD diagnosis as a phenotype found a transmission bias for the T-allele among ADHD subjects (Kissling *et al.,* 2008). Data reported by Cao *et al.* (2012) also find that the T3111C SNP in CLOCK is associated with ADHD in children although contrary to previous findings the authors of this study found that the C-allele confers risk. Given the contrasting and inconclusive patterns of association between this SNP and behavioural outcomes, further investigation and more precise phenotyping methods are required in future work. Moreover, the functional consequence of the CLOCK SNP at a molecular level or how it may influence CLOCK protein expression is currently unknown although given that the polymorphism is present in the 3'-untranslated-region of CLOCK it has been suggested it might act upon mRNA stability and translation (Xu *et al.,* 2010; Coogan *et al.* 2016).

Another common polymorphism which has been associated with circadian typology is the C111G SNP in the *Per2* gene. Carpen *et al.* (2005) described the PER2 C111G *(rs2304672)* polymorphism in a study concerning five different PER2 SNPs and potential links between advanced sleep phase syndrome (ASPS). The authors found that the G-allele of this polymorphism associated significantly with extreme morningness indicated diurnal preference in members of the general population. Another group reported that the PER2 C111G SNP was associated with extremely high morningness in two Japanese ASPS families (Satoh *et al.,* 2003). Non-replications of these results have been reported by others however that find no associations between the PER2 C111G SNP and diurnal preference (Choub *et al.,* 2011). Further, Lee *et al.* (2011) report that while other SNPs identified in the PER2 gene were associated with significant differences in diurnal preferences in a Korean population, the C111G SNP was not. Interestingly, other behavioural associations with PER2 C111G in obese individuals involve greater probability of dropping out of dieting interventions, extreme snacking, and eating when bored (Garaulet *et al.,* 2010) potentially indicating an association between this polymorphism and impulse control or delay-gradient deficits. Additionally, Forbes *et al.* (2012) investigated the effects of this genotype on responses to reward in adolescents using fMRI and found

that G-allele carriers showed reduced mPFC activation relative to C/C homozygotes. To our knowledge no overt association between this SNP and ADHD exists but given the findings reported in the latter two aforementioned studies it could be speculated that PER2 C111G is a candidate gene for ADHD risk. Though the functional significance of this polymorphism is unknown as the SNP resides in the 5'-untranslated-region of PER2 it is suggested that its functional role might involve exerting effects upon mRNA structure (Garaulet *et al.,* 2010).

The final polymorphism to be discussed in this study is a VNTR in exon 18 of the PER3 gene in humans which is expressed as a 54-bp sequence arranged in tandem consisting of either 4 copies of the repeat in the short version of the allele or 5 copies of the repeat in the long version (Ebisawa *et al.,* 2001). Possible genotypes for this polymorphism consist of individuals homozygous for the short repeat version ($PER3^{4/4}$) or long repeat version ($PER3^{5/5}$), and heterozygotes ($PER3^{4/5}$). Previously studies have found the 4-repeat allele to be associated with eveningness and delayed sleep phase syndrome (DSPS) and the 5-repeat allele to be associated with increased morningness circadian typology (Archer *et al.,* 2003; Ebisawa *et al.,* 2001; Jones *et al.,* 2007; Ellis *et al.,* 2009; Lázár *et al.,* 2012). These findings are also contrasted by a study conducted by Pereira *et al.* (2005) which found that the longer allele was the one conferring risk towards DSPD in a Brazilian cohort, while other studies have reported no associations between either alleles or genotypes and diurnal preference (Voinescu & Coogan, 2012; Goel *et al.,* 2009; Osland *et al.,* 2011). A closer inspection of the sleep architecture patterns associated with the VNTR shows differential homeostatic drive towards sleep and wakefulness between genotypes with $PER3^{5/5}$ individuals showing shorter sleep latency and greater and earlier slow wave sleep (Viola *et al.,* 2007). Furthermore, following sleep deprivation a compensatory increase in slow wave sleep is noted in $PER3^{5/5}$ individuals at the expense of REM sleep during recovery periods (Viola *et al.,* 2007; Dijk & Archer, 2010). Noteworthy here is the similarity of the sleep profile in $PER3^{5/5}$ individuals and that of early types suggesting that the purported link between PER3 and earlier chronotype might be mediated by an accelerated increase of sleep pressure (Gaggioni *et al.,* 2014). A protective role of the 4-repeat allele against drowsiness and cognitive dysfunction

during sleep restriction has been noted previously also with PER3$^{4/4}$ individuals showing a slower increase of Θ/α waking EEG signal and less slow eye-movements in comparison to PER3$^{5/5}$ individuals (Viola *et al.,* 2007; Cajochen *et al.,* 1999). Thus it may be the case that because PER3$^{5/5}$ individuals are less robust to the effects of homeostatic sleep pressure on performance than PER3$^{4/4}$ individuals. Consequently, the latter group may be more inclined to prolong wakefulness possibly explaining the apparent evening preference noted in relation to the long genotype variant.

In relation to ADHD, although the PER3$^{5/5}$ genotype is typically associated with morningness and ADHD is associated with a later chronotype and delayed circadian timing, interesting neurobehavioural deficits have been observed among 5-repeat homozygotes. Maire *et al.* (2014) note a greater time-on-task decrement during performance on the psychomotor vigilance task (PVT) which was genotype dependent with PER3$^{5/5}$ individuals showing poorer performance. The PVT is classic test used to assess sustained attention which is a component also affected in ADHD. Further, González-Giraldo *et al.* (2015) showed that PER3$^{4/4}$ individuals performed better than carriers of at least one 5-repeat allele on the Tower of London task, a common test used to measure cognitive planning which the authors suggest might be an important intermediate phenotype for ADHD. Conversely, the alerting effects of short-wave length light are more pronounced among PER3$^{5/5}$ individuals especially during early waking hours (Chellapa *et al.,* 2014) which on one hand points potentially to protective effect against inattentiveness while on the other possibly suggests that typically delayed phase PER3$^{4/4}$ individuals might be more susceptible to ADHD-like symptoms. At the time of writing only one study exists examining if the PER3 VNTR genotype was associated with ADHD and comorbid sleep onset insomnia and found no significant effect (van der Heijden *et al.,* 2005a).

Taken together the literature reviewed here on candidate gene studies which explore associations between circadian clock genes and circadian phenotypes, as well as between circadian clock genes and phenotypes potentially related to ADHD, has not presented unequivocal findings. As the circadian phenotype is a multifactorial trait influenced by factors such as age, sex, social scheduling as well as exposure to

light to list a few, it is not surprising that straightforward genotype-phenotype relations remain elusive or fraught with replication failure. Furthermore, the links which may exist between circadian genes and circadian timing of the activity cycle are likely of small magnitude effect size and owing to the observation that chronotype is a behaviourally complex phenotype it is most likely under the influence of multiple genes as many other complex behaviours are (Glazier *et al.,* 2002; Meyer-Lindenberg & Weinberger, 2006). As previously noted by others one manner in which the power to detect meaningful genotype-phenotype relations might be improved is by optimising phenotyping methods to record a more precise confound-free measure of circadian entrainment (Allebrandt & Roenneberg, 2008). Among the majority of the aforementioned studies listed the authors have used the Horne-Ostberg Morningness Eveningness Questionnaire (MEQ) as the primary outcome variable of interest. The MEQ conceptualises the circadian phenotype in terms of a spectrum of diurnal preference based on a self-reported and subjective *'feeling best rhythm'* and while it is commonly used in the field of human chronobiology given its correlation with several biological parameters (Di Milia *et al.,* 2013; Bailey & Heitkemper, 2001; Griefahn et al., 2002), it is inherently a psychological metric rather than an index of behaviour (Roenneberg, 2015; Levandovski, Sasso, & Hidalgo, 2013). Limitations to this approach of phenotyping the chronotype trait involve the failure to account for the modifying role of the social clock through work day influences upon sleep timing and for sleep debt accumulated during the working week which is known to mask chronotype on free days (Roenneberg *et al.,* 2007). The MSF_{sc} measure derived from the MCTQ which estimates the circadian phase of entrainment of the sleep phase has instead been proposed as a more suitable index of chronotype in studies investigating genetic associations between polymorphic variants and behaviour (Allebrandt & Roenneberg, 2008, Levandovski *et al.,* 2013). A similar issue potentially leading to non-replication among studies phenotyping for ADHD is the manner in which outcome is defined. Many of the studies which examine the association between circadian gene variants and ADHD use categorical/diagnostic approaches to identify phenotypes leading to possible loss of power in detecting gene-phene associations.

Instead inattention and impulsivity may be expressed on an interval scale which allows for comparison as a continuously distributed trait among different genotypes (*i.e.* additive dosage of a risky allele might be expected to produce a linear increase in impulsiveness rather than the allele merely being found in a higher frequency in 'impulsive' individuals).

Consequently, the objective of this component of the study was to attempt to both replicate existing, and to potentially demonstrate novel, geneotype-phenotype associations between the polymorphisms CLOCK T3111C, PER2 C111G, and PER3 VNTR, and outcomes involving circadian phase, sleep quality, and ADHD relevant traits in adults. The use of the CCPT and IGT neuropsychological tasks were also employed here to give an objective estimation of performance measuring attention, impulsivity, and risk-taking. Furthermore, given that behavioural outcomes are more often the product of gene-environment interactions (G×E) the effects which may only manifest given adequate environmental exposure to maladaptive factors (Moffitt, Caspi, & Rutter, 2005) we conducted exploratory analyses into the moderating effects of aspects of sleep disturbance and circadian misalignment. In the context of the current study it might be the case that a gene variant confers susceptibility towards worsened symptoms of inattention or impulsivity, but only in the presence of a significant interruption to sleep or circadian rhythm function. To this end we explored G×E moderated associations selecting measures of sleep disturbance and social jetlag as candidate environmental risk factors as we have previously shown (Chapter 2) that these variables predict symptom risk.

6.2 Materials and methods

Participants

Individuals recruited in the initial experimental sample consisting of 195 participants (described in Section 3.2) were at the end of the behavioural experimental protocol invited to partake in a genetic association study which they were informed aimed to further explore the role of common circadian clock gene variants on predicting self-reported sleep behaviour. After the previously described exclusion criteria were applied and participants who had recently eaten or smoked were ruled out due to concerns over oral sample contamination, a total of 185 individuals volunteered to take part. The final sample consisted of 90 males and 95 females (48.6% and 51.4% of the sample respectively) and had a mean age of 22.38 years (*SD* = 3.65; range 18 – 38). Donated saliva samples were obtained on site using Oragene DNA OG-500 Collection Kits (DNA Genotek, Neapan, ON, Canada) and were subsequently kept stored at room temperature between 15 – 30 °C or refrigerated according to manufacturer's instructions until later genotyping could take place. Written informed consent was given by each participant before commencing the experimental protocol which included the option to donate a salivary sample if they wished to volunteer in the genetic component of the experiment. Ethical approval for this study was granted by the Biomedical and Life Sciences Committee at Maynooth University.

Questionnaires and objective measures

A number of MCTQ derived measures previously described in Section 2.2 were included in our analyses. Namely, chronotype and delays in sleep phase were estimated using the MSF_{sc} measure as well as self-reported sleep onset latency (SOL) on free days. Average weekday sleep duration was calculated as well as separate durations for free (SDf) and workdays (SDw) used. Participants completed the PSQI which was used to estimate general sleep quality. The ASRS, BIS, and CFQ scores were also used to measure self-reported ADHD symptom counts, general trait

impulsivity, and cognitive failure frequency. The CCPT and IGT were administered and scored as previously described (Section 3.2).

DNA extraction procedures

Isolation and purification of human DNA from salivary samples was performed using DNeasy Blood and Tissue Kits (Qiagen). Cell lysis and precipitation of genetic material was achieved according to kit manufacturer's instructions. First, a 1 mL sample of saliva was transferred from the Oragene OG-500 collection kit to a 2 mL micocentrifuge tube, adding 20 µl of proteinase K followed by 200 µl of Buffer AL, mixing by vortex between steps. Samples were incubated at 56 °C for 10 min using an Eppendorf Thermomixer compact 5350 (Sigma-Aldrich). 200µl ethanol (at 96-100% concentration) was added to samples post-incubation and the mixture transferred into DNeasy mini spin columns placed over a 2 mL collection tube for centrifugation.

All centrifugation steps were carried out at room temperature (15-25 °C) using the Eppendorf Centrifuge 5430 R (Fisher Scientific). The solution was first centrifuged for 1 min at 8000 rpm before adding 500 µl of Buffer AW1 before centrifuging again for 1 min at 8000 rpm. 500 µl of Buffer AW2 then was added and the sample centrifuged for 3 min at 14000 rpm. Between steps supernatant flow-through was discarded and spin columns were transferred to new collection tubes to avoid contamination of the membrane containing the sample pellet with waste product. After a final centrifugation at 14000 rpm for 1 min DNA was eluted by adding 50 µl of Buffer AE to the centre of the spin column membrane and centrifuged for 1 min at 8000 rpm. This step was repeated a second time for increased DNA yield in the elution product. DNA was quantified using the spectrophotometry method with the Multiskan Go Microplate Spectrophotometer (Thermo Scientific).

Polymerase Chain Reaction (PCR) protocols

CLOCK T3111C (rs1801260)

A total of 50 ng of genomic DNA was mixed with 5 pmol of each PCR primer in a total volume of 25 μL containing 1× PCR buffer (200mMTris–HCl pH 8.4, 500mM KCl), 1.5mM magnesium chloride, 0.2 mM of each deoxyribonucleotide triphosphate, and 0.5 U of DNA polymerase (GoTaq G2 Hot Start Polymerase, Promega). The primers 5′-TCCAGCAGTTTCATGAGATGC-3′ (forward) and 5′-GAGGTCATTTCATAGCTGAGC- 3′ (reverse) were used to obtain products of 221 bp size. The reaction mixture was cycled as follows in a DNA thermal cycler: Denaturation at 94 °C for 3 min was followed by 35 cycles at 94 °C for 45 s, 55 °C for 45 s, and 72 °C for 45 s, and a final extension at 72 °C for 7 min. A 20 μL aliquot of the PCR product was then submitted to restriction reaction at 37 °C for 16 h with BSPI286I restriction enzyme (New England Biolabs). Fragments were separated by electrophoresis on 3 % agarose/synergel gel.

PER2 C111G (rs2304672)

A total of 50 ng of genomic DNA was mixed with 5 pmol of each PCR primer in a total volume of 25 μL containing 1× PCR buffer (200mMTris–HCl pH 8.4, 500mM KCl), 1.5mM magnesium chloride, 0.2 mM of each deoxyribonucleotide triphosphate, and 0.5 U of DNA polymerase (GoTaq G2 Hot Start Polymerase, Promega). The primers 5′-GTGCGTGTGCTTGTTAATGC-3′ (forward) and 5′-TCCTTGGTGGGGTTACTGG-3′ (reverse) were used to obtain PCR products of 114 bp size. The reaction mixture was cycled as follows in a DNA thermal cycler: Denaturation at 94 °C for 3 min was followed by 35 cycles at 94 °C for 45 s, 55 °C for 45 s, and 72 °C for 45 s, and a final extension at 72 °C for 7 min. A 20 μL aliquot of the PCR product was then submitted to restriction reaction at 37 °C for 16 h with HpyCH4V restriction enzyme (New England Biolabs). Fragments were separated by electrophoresis on 3 % agarose/synergel gel.

PER3 4-5 repeat VNTR (rs57875989)

A total of 50 ng of genomic DNA was mixed with 5 pmol of each PCR primer in a total volume of 25 μL containing 1× PCR buffer (200mMTris–HCl pH 8.4, 500mM KCl), 1.5mM magnesium chloride, 0.2 mM of each deoxyribonucleotide triphosphate, and 0.5 U of DNA polymerase (GoTaq G2 Hot Start Polymerase, Promega). The primers 5′-CAAAATTTTATGACACTACCAGAATGGCTGAC-3′ (forward) and 5′-AACCTTGTACTTCCACATCAGTGCCTGG-3′ (reverse) were used for the reaction. The reaction mixture was cycled as follows in a DNA thermal cycler: Denaturation at 94 °C for 3 min was followed by 35 cycles at 94 °C for 45 s, 55 °C for 45 s, and 72 °C for 45 s, and a final extension at 72 °C for 7 min. A 20 μL aliquot of the PCR product was then submitted to restriction reaction at 37 °C for 16 h with NCoI restriction enzyme (New England Biolabs). Fragments were separated by electrophoresis on 2 % agarose gel.

Data analysis

Differences in allele frequencies and verification that genotype distributions were consistent with Hardy-Weinberg equilibrium were assessed using χ^2 analyses. To assess differences in sleep timing and duration as well as differences across ASRS, BIS, and CFQ scores, between group comparisons were conducted for the different genotypes using separate ANCOVA models which controlled for the effects of age and sex (dummy coded 0 = males, 1 = females). ANCOVAs were conducted to examine differences in MSF_{sc}, average sleep duration, self-reported sleep onset latency, self-ratings of chronotype (on a seven-point scale ranging from extreme early type to extreme late type as included in the original MCTQ; Roenneberg *et al.,* 2003), as well as ASRS and CFQ score and scores on each of the BIS subscales (attentional impulsivity, motor impulsivity, and non-planning impulsivity). Each set of analysis was conducted three times, once for each genetic variant assessed. In order to correctly interpret explorative findings and consider misleading results due to family-wise error rates we separated our analyses into hypothesis driven/replication

questions and those that were exploratory in nature. In the former group of research aims, to protect against type I errors due the number main effects in each of the hypotheses tested (m = 30) we used the false discovery rate (FDR) to adjust the critical α used for each significant effect detected (Hochberg & Benjamini, 1990; Benjamini & Hochberg, 1995). Exploratory hierarchical regressions were performed to assess whether G×E interactions predicted ASRS scores, BIS scores, or CFQ scores in three separate multiple regressions. The interaction products between each genotype and social jetlag, and each genotype and sleep quality assessed PSQI score were inserted together with age and sex in a backward elimination model. In the latter set of analyses that were of an exploratory nature we considered $p < .05$ to be statistically significant.

6.3 Results

Excluded and missing data

After inspecting DNA quality derived from samples provided and PCR results a total of five individuals were eliminated from the analysis due to quality control failure leaving a final sample of n = 180 available for analysis. Further, we inspected responses for missing questionnaire data and found a small number of individual questionnaires that had not been returned (ASRS: n = 2, PSQI: n = 3). These participants were retained in our sample rather than discarded and analyses performed normally though the total number of data available for these specific questionnaire measures was slightly reduced.

Genotype distributions

The genotype distribution frequency for our sample was in Hardy-Weinberg equilibrium (HWE) for the PER2 C111G (χ^2 = 2.36, p > .05) and for PER3 VNTR (χ^2 = .036, p > .05) however CLOCK T3111C deviated from the expected HWE genotype distribution (χ^2 = 19.91, p < .05). The distribution of genotypes was as follows: for CLOCK T3111C we detected that 51.7% of the sample were homozygous for the T-allele and 48.3% were classified as C/T heterozygotes, while none of the individuals were C/C homozygous. For PER2 C111G we found that 85.4% were C/C homozygous, 12.9% were C/G, while only around 1.7% (n = 3) were homozygous for the G/G genotype. For PER3 approximately half the sample (50.6%) were homozygous for the short repeat $PER3^{4/4}$, 41.1% carried one of the long and short repeats $PER3^{4/5}$, and 8.3% were long-repeat homozygotes $PER3^{5/5}$. Due to the absence of C/C individuals for the CLOCK SNP, groups were instead analysed by comparing T/T homozygous individuals with those that carried a C-allele (*i.e.* individuals were compared by allelic group). Similarly, due to the scarcity of G/G individuals in the PER2 SNP we conducted between group comparisons using the G/G group compared against individuals that carried at least one C-allele.

Investigating the effects of genotype on measures of sleep and circadian disruption and ADHD-like symptom domains

CLOCK T3111C

A summary list of all genotype effects are presented in Table 6.1. Age and sex controlled between group comparisons on variants in the Clock T3111C SNP showed no significant differences between T/T homozygous individuals compared with C-allele carriers for MSF_{sc} scores, $F(1, 175) = .018$, $p = .892$, $\eta_p^2 < .001$ (Figure 6.1A), or for self-reported chronotype score, $F(1, 175) = .369$, $p = .544$, $\eta_p^2 = .002$. The mean mid-sleep time of T/T homozygotes was 5.65 ± .128 h was nearly identical to that of C-allele carriers which was 5.67 ± .132 h. We found that T/T homozygotes had a significantly greater self-reported SOL (30.93 ± 2.51 min) however when compared to C-allele carriers (23.13 ± .258 min), $F(1, 175) = 4.68$, $p = .032$, $\eta_p^2 = .026$, but this effect was not present after correcting for multiple comparisons (Figure 6.1B). There were no significant differences in sleep duration, $F(1, 175) = .066$, $p = .798$, $\eta_p^2 < .001$, (T/T: 7.86 ± .118 h, C-allele carriers: 7.82 ± .122 h), or sleep quality detected between genotype groups, $F(1, 172) = .403$, $p = .526$, $\eta_p^2 = .002$ (Figure 6.1C+D). Associations between the Clock mutation and self-reported ADHD symptom counts were not found with no differences detected between the two genotype groups detected, $F(1, 173) = .489$, $p = .485$, $\eta_p^2 = .003$ (Figure 6.1E). When we assessed multidimensional impulsivity using the BIS subscales we found no significant differences on the attentional impulsiveness scale, $F(1, 175) = .341$, $p = .56$, $\eta_p^2 = .002$ (Figure 6.1F), or on the non-planning scale, $F(1, 175) = .469$, $p = .464$, $\eta_p^2 = .003$ (Figure 6.1H). There was a small magnitude significant effect detected on the motor impulsiveness subscale however showing that C-allele carriers had a higher level of motoric impulsivity compared to T/T individuals, $F(1, 175) = 4.82$, $p = .029$, $\eta_p^2 = .027$ (Figure 6.1G). This finding did not survive correction for multiple comparisons however. Finally, the main effect of genotype predicting CFQ score was not found to be statistically significant either, $F(1, 175) = .003$, $p = .958$, $\eta_p^2 < .001$ (Figure 6.1I).

Table 6.1 Effects of genotype on sleep variables and questionnaire measures of ADHD-like symptoms, impulsivity and cognitive failures

	CLOCK T3111C			PER2 C111G			PER3 VNTR		
	F(df)	*p*	η_p^2	*F(df)*	*p*	η_p^2	*F(df)*	*p*	η_p^2
MSF_{sc} (h, local time)	.018 (1, 175)	.892	.001	.024 (1, 175)	.876	.001	1.01 (2, 174)	.366	.011
Self-reported CT	.369 (1, 175)	.544	.002	.828 (1, 175)	.364	.005	.419 (2, 174)	.658	.005
SOL (min)	4.68 (1, 175)	.032	.026	.227 (1, 175)	.599	.002	.575 (2, 174)	.564	.007
SD	.066 (1, 175)	.798	.001	.003 (1, 175)	.955	.001	1.112 (2, 174)	.331	.013
PSQI	.403 (1, 172)	.526	.002	.391 (1, 172)	.538	.002	.784 (2, 171)	.433	.009
ASRS	.489 (1, 173)	.485	.003	1.647 (1, 173)	.201	.009	.599 (2, 172)	.551	.007
BIS- Attention	.341 (1, 175)	.56	.002	.077 (1, 175)	.782	.006	.057 (1, 174)	.944	.001
BIS- Motor	4.82 (1, 175)	.029	.027	1.09 (1, 175)	.298	.006	.587 (1, 174)	.557	.001
BIS- NP	.469 (1, 175)	.464	.003	.365 (1, 175)	.547	.002	1.218 (1, 174)	.298	.014
CFQ	.003 (1, 175)	.958	.001	.530 (1, 175)	.530	.003	.105 (1, 174)	.900	.001

Table illustrates main effects of genotype on summary measures derived from questionnaires after controlling for age and sex. MSF_{sc} = corrected midpoint of sleep on free days, SOL = sleep onset latency, SD = sleep duration. Questionnaire measures assessed are PSQI, ASRS, BIS and associated subscales, and CFQ

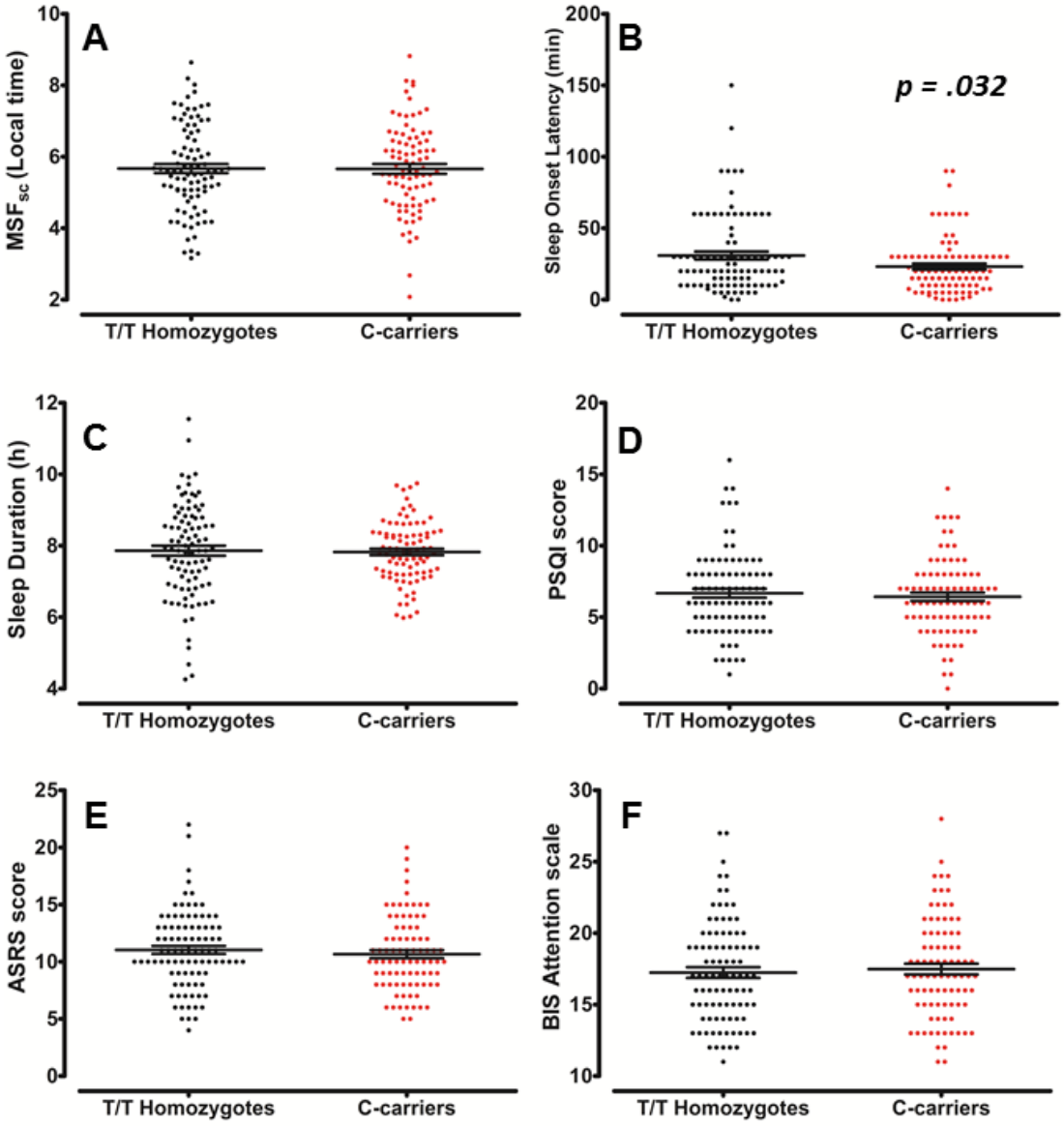

Figure 6.1. Effect of CLOCK T3111C SNP predicting sleep phase, duration, and quality, and neubehavioural dimensions associated with ADHD.

Comparisons between rs1801260 T/T Homozygotes (black circles) and C-allele carriers (red circles) on dependent measures: (A) MSF$_{sc}$ (B) sleep onset latency, (C) average sleep duration, (D) sleep quality, (E) ASRS score, (F) BIS attention impulsivity subscale. (Continued overleaf).

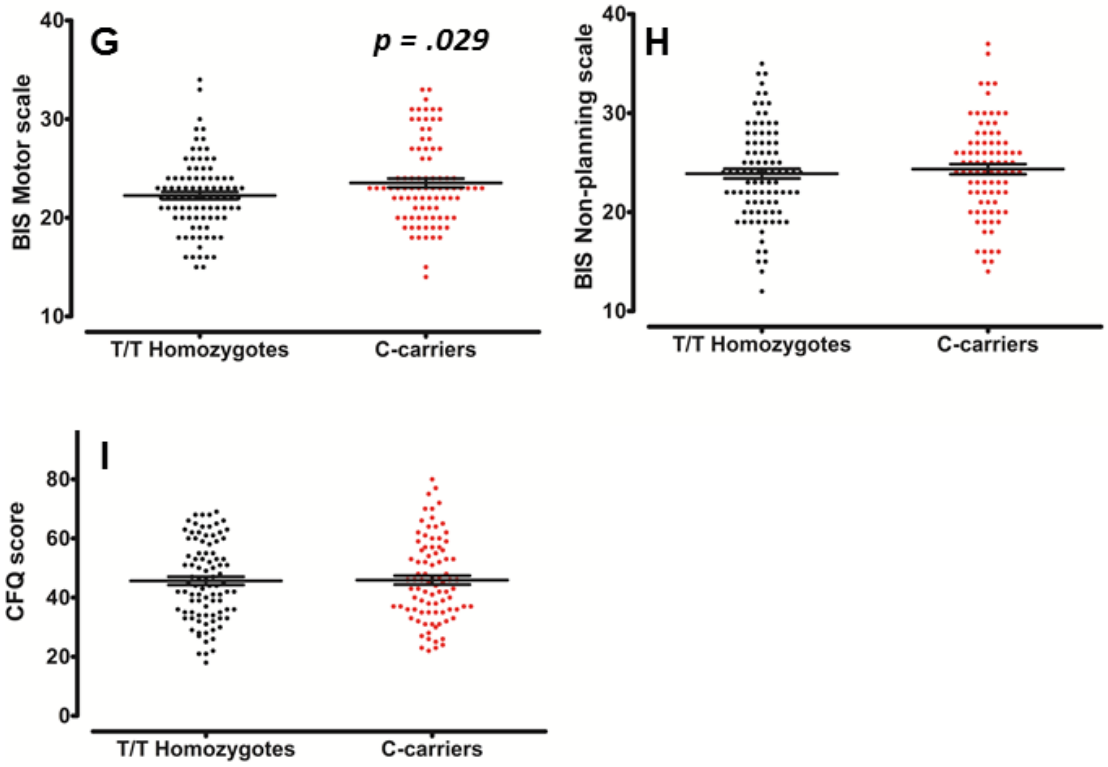

Figure 6.1. Effect of CLOCK T3111C SNP predicting sleep phase, duration, and quality, and neubehavioural dimensions associated with ADHD (cont.).

Comparisons between rs1801260 T/T Homozygotes (black circles) and C-allele carriers (red circles) on dependent measures: (G) BIS motor subscale (H) BIS non-planning impulsivity subscale, (I) CFQ score.

PER2 C111G

Next we examined the ANCOVA main effects for the PER2 C111G on the same outcome measures. We report no significant differences between C/C homozygotes and those carrying a G-allele for MSF_{sc} scores, $F(1, 175) = .024$, $p = .876$, $\eta_p^2 < .001$ (Figure 6.2A), or self-reported chronotype, $F(1, 175) = .828$, $p = .364$, $\eta_p^2 = .005$, or delays in sleep onset time, $F(1, 175) = .227$, $p = .599$, $\eta_p^2 = .002$ (Figure 6.2B). The mean mid-sleep time of individuals with the C/C genotype was 5.07 ± .11 and was 5.63 ± .24 h for the G-allele. The SOL for the C/C group was 27.54 ± 1.97 min and was 24.79 ± 4.82 min for the G-carrier group. Similarly, there were no significant differences in sleep duration, $F(1, 175) = .003$, $p = .955$, $\eta_p^2 < .001$, (C/C: 7.84 ± .092 h, G-allele carriers: 7.85 ± .225 h), or sleep quality detected between genotype groups, $F(1, 172) = .391$, $p = .538$, $\eta_p^2 = .002$ (Figure 6.2C+D). We did not find any significant main effects for genotype on any of the self-reported behavioural and trait indexes assessed. ASRS score did not differ meaningfully between groups, $F(1, 173) = 1.647$, $p = .201$, $\eta_p^2 = .009$ (Figure 6.2E), nor did any measures of impulsivity: attentional subscale [$F(1, 175) = .077$, $p = .782$, $\eta_p^2 = .006$], motor subscale [$F(1, 175) = 1.09$, $p = .298$, $\eta_p^2 = .006$], non-planning subscale, [$F(1, 175) = .365$, $p = .547$, $\eta_p^2 = .002$ (Figure 6.2F-H). Further, there were no differences in CFQ score detected between genotype groups either, $F(1, 175) = .530$, $p = .467$, $\eta_p^2 = .003$ (Figure 6.2I).

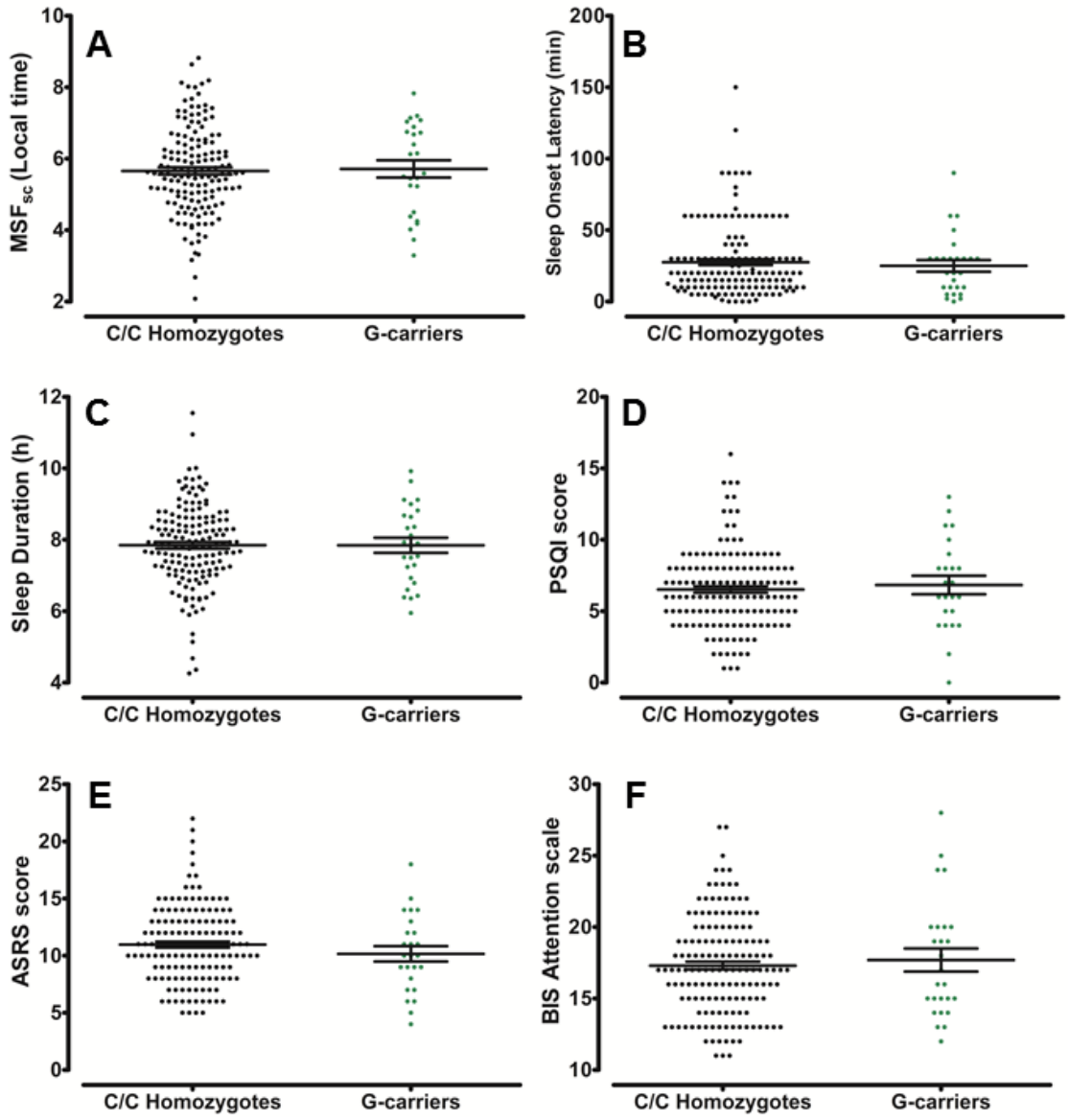

Figure 6.2. Effect of PER2 C111G SNP predicting sleep phase, duration, and quality, and neurobehavioural dimensions associated with ADHD.

Comparisons between rs2304672 C/C Homozygotes (black circles) and G-allele carriers (green circles) on dependent measures: (A) MSF$_{sc}$ (B) sleep onset latency, (C) average sleep duration, (D) sleep quality, (E) ASRS score, (F) BIS attention impulsivity subscale. (Continued overleaf).

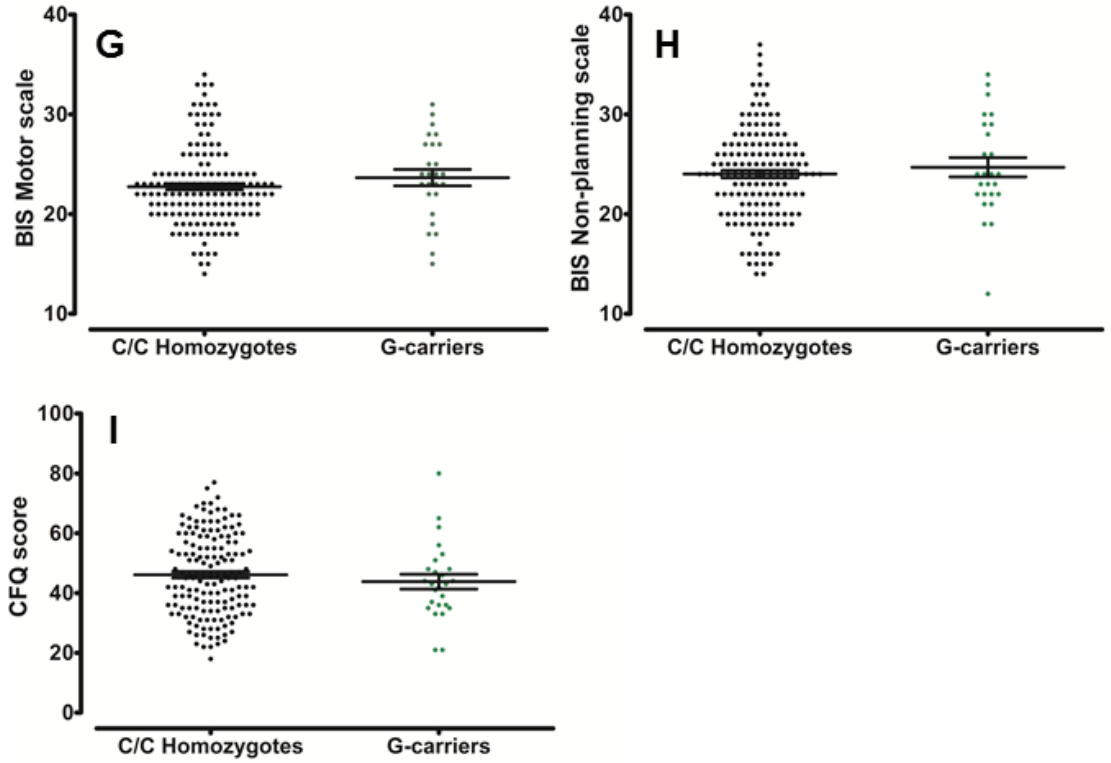

Figure 6.2. Effect of PER2 C111G SNP predicting sleep phase, duration, and quality, and neurobehavioural dimensions associated with ADHD (cont.).

Comparisons between rs2304672 C/C Homozygotes (black circles) and G-allele carriers (green circles) on dependent measures: (G) BIS motor subscale (H) BIS non-planning impulsivity subscale, (I) CFQ score.

PER3 VNTR

Finally, we assessed if associations existed between the PER3 VNTR polymorphism and measures of chronotype, sleep timing, duration and quality, as well as the other behavioural outcomes measured. The independent factor genotype consisted of three groups, individuals homozygous for either the 4/4 or 5/5 genotype respectively, or 4/5 heterozygotes which contained one of each repeat variant. Controlling for age and sex we did not find any significant main effect of genotype predicting MSF_{sc} , $F(2, 174) = 1.01$, $p = .366$, $\eta_p^2 = .011$ (means: 4/4 = 5.65 ± .130 h; 4/5 = 5.76, ± .143 h; 5/5 = 5.26 ± .319 h) (Figure 6.3A). Similarly, no effects were found when comparing self-reported chronotype, $F(2, 174) = .419$, $p = .658$, $\eta_p^2 = .005$, or sleep onset latency, $F(2, 174) = .575$, $p = .564$, $\eta_p^2 = .007$, (means: 4/4 = 27.05 ± 2.57 min; 4/5 = 28.49 ± .2.83 min; 5/5 = 21.06 ± 6.33) (Figure 6.3B). Similarly, we failed to detect any significant differences in sleep duration, $F(2, 174) = 1.112$, $p = .331$, $\eta_p^2 = .013$, or sleep quality, $F(2, 171) = .784$, $p = .433$, $\eta_p^2 = .009$, between the groups (Figure 6.3C+D). Individuals with the 5/5 genotype slept an average of 8.03 ± .294 h per night, followed by 4/4 individuals with an average of 7.94 ± .12 h, and finally by heterozygous 4/5 individuals who slept 7.7 ± .131 h per night. Furthermore, we did not find any significant main effects for the PER3 VNTR on ASRS score, $F(2, 172) = .599$, $p = .551$, $\eta_p^2 = .007$ (Figure 6.3E), BIS scores, attentional subscale [$F(1, 174) = .057$, $p = .944$, $\eta_p^2 = .001$] (Figure 6.3F), motor subscale [$F(1, 174) = .587$, $p = .557$, $\eta_p^2 = .001$] (Figure 6.3G), non-planning subscale, [$F(1, 174) = 1.218$, $p = .298$, $\eta_p^2 = .014$](Figure 6.3H), or the CFQ measure, $F(2, 174) = .105$, $p = .900$, $\eta_p^2 = .001$ (Figure 6.3I).

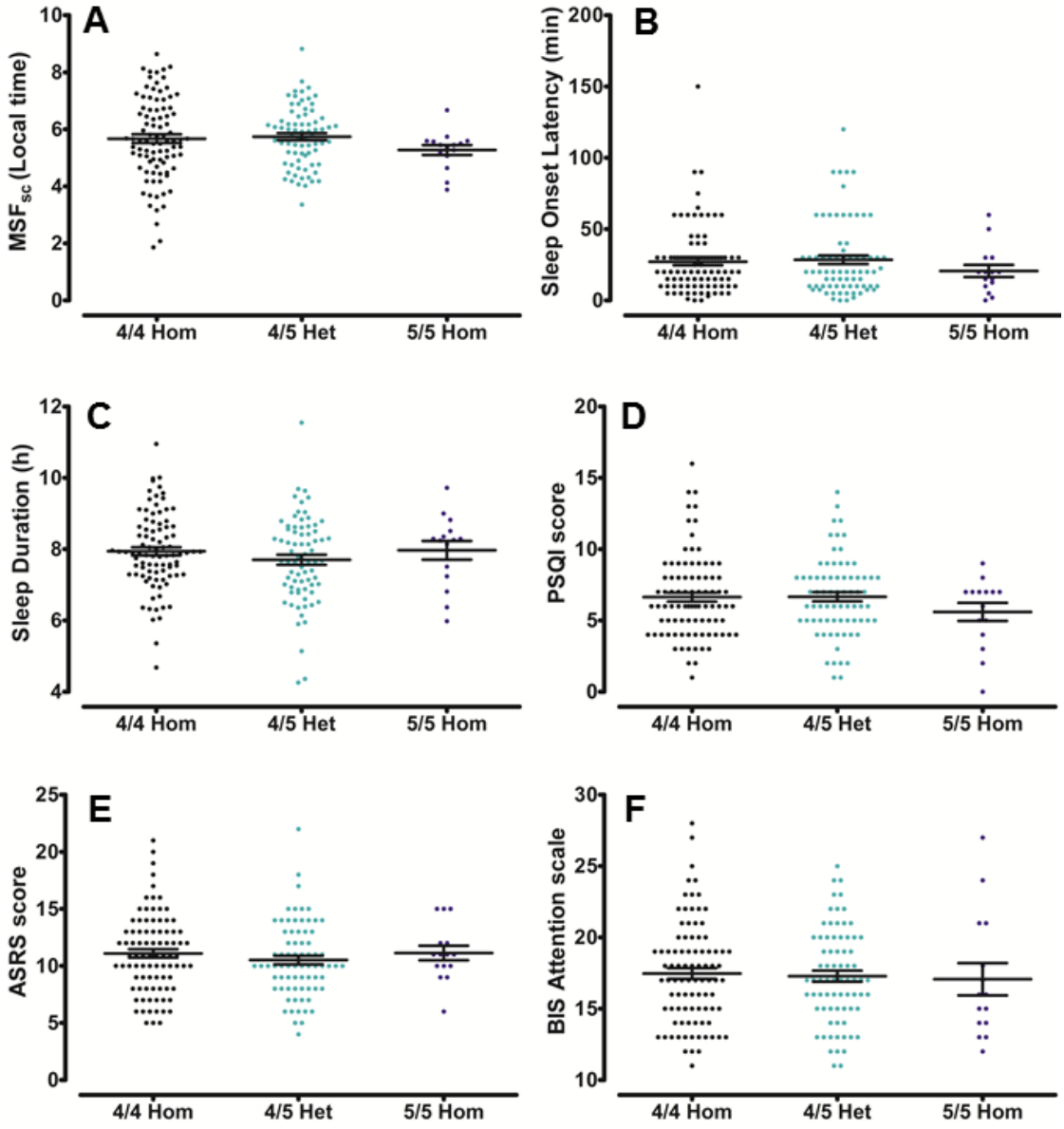

Figure 6.3. Effect of PER3 VNTR mutation predicting sleep phase, duration, and quality, and neubehavioural dimensions associated with ADHD.

Comparisons between three PER3 VNTR genotypes PER3$^{4/4}$ (black circles), PER3$^{4/5}$ (cyan circles), and PER3$^{5/5}$ (blue circles) on dependent measures: (A) MSF$_{sc}$ (B) sleep onset latency, (C) average sleep duration, (D) sleep quality, (E) ASRS score, (F) BIS attention impulsivity subscale. (Continued overleaf).

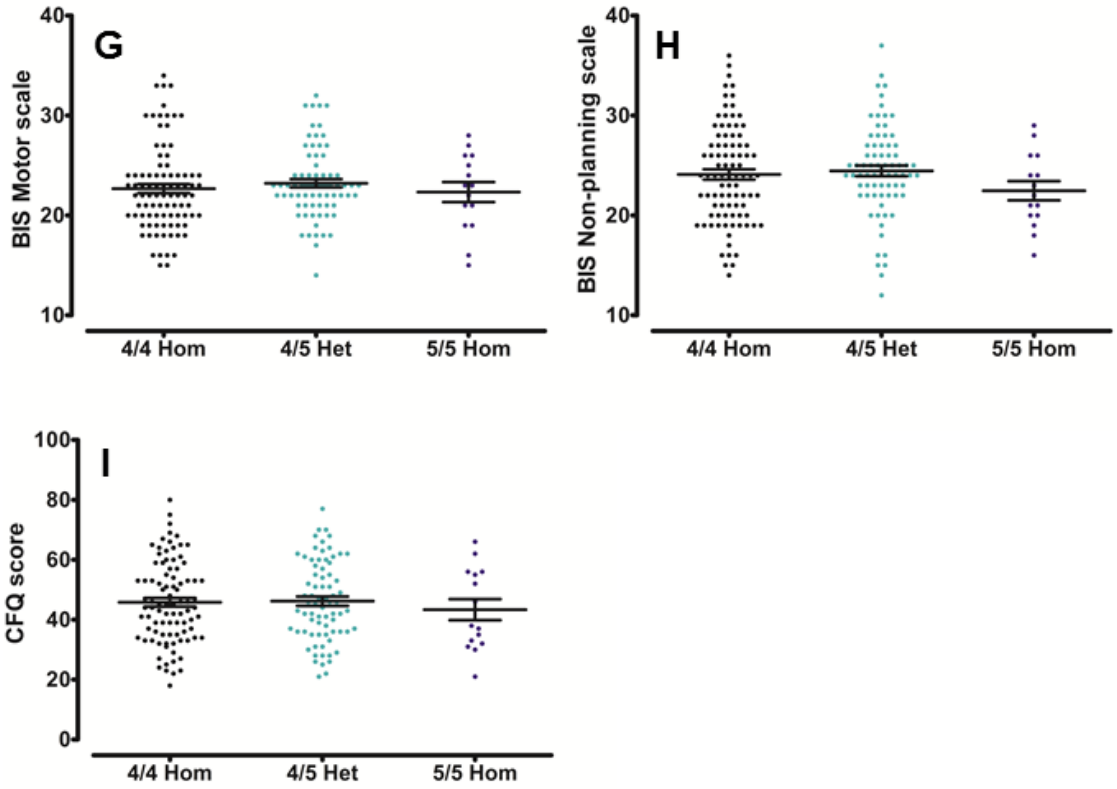

Figure 6.3. Effect of PER3 VNTR mutation predicting sleep phase, duration, and quality, and neubehavioural dimensions associated with ADHD.

Comparisons between three PER3 VNTR genotypes $PER3^{4/4}$ (black circles), $PER3^{4/5}$ (cyan circles), and $PER3^{5/5}$ (blue circles) on dependent measures: (G) BIS motor subscale (H) BIS non-planning impulsivity subscale, (I) CFQ score.

Investigating if genotype effects are apparent in the 'extreme' responders

In line with previous studies in which genotype associations have been described relating to the 'extremes' of chronotype (Barclay *et al.,* 2011; Satoh *et al.,* 2003), we undertook an analysis focusing on the extremes of behaviour to investigate whether genotype effects may only be detected when a categorical approach is applied. We partitioned the sample based on MSF_{sc} into eight separate binned groups and examined genotype distributions between the upper and lower 12.5% of the cohort (*i.e.* extreme 'late' types versus the extreme 'early' types) as others have similarly divided groups for the purpose of such analyses (7-10% of the sample *e.g.* Archer *et*

al., 2003; Barclay *et al.,* 2011). We failed to detect any differences in the genotype/allele frequency distribution among late and early groups for CLOCK T3111C (χ^2 = .206, p = .658), PER2 C111G (χ^2 = 1.665, p = .202), or PER3 VNTR (χ^2 = 2.18, p = .336). Furthermore, this convention of analysis was applied to self-reported ADHD scores where subjects were partitioned into low likelihood of ADHD and highly-likely for ADHD (ASRS score > 13; Kessler *et al.,* 2007) and similarly no differences in genotype distribution were detected between groups for CLOCK T3111C (χ^2 = .008, p = .928), PER2 C111G (χ^2 = .037, p = .847), or PER3 VNTR (χ^2 = .165, p = .921). We note however that previous studies which have segmentated such extreme manifestations of chronotype and found genetic associations with these polymorphisms have done so in larger sample sizes (*i.e.* Archer *et al.,* 2003).

Investigating if genotype effects are present using objective measures of impulsivity and inattention

Further to the analyses we conducted in Chapter 3 which utilised measures from the CCPT and IGT to provide an objective assessment of impulsivity and inattention we investigated in main effects for genotype carrier status were present on parameters from these tests. On the CCPT we included factors of primary interest which consisted of the test summary measures of error rates and reaction times as we did not detect any significant interaction effects for secondary factors such as ISI or block in the broader analysis conducted in Chapter 3. As deck selection over time was a variable of interest in the IGT we used mixed ANOVAs to examine the main effects of genotype group with block as a repeated measure.

For the CCPT independent samples t-tests did not reveal any significant differences between CLOCK 3111 T/T homozygous individuals and C-allele carriers on omission error rate (t = .676, p = .5, Figure 6.4A), commission error rate (*Welches* t = -.157, p = .118, Figure 6.4B), mean RT (t = -.354, p = .723, Figure 6.4C), or RTSD (t = .965, p = .336, Figure 6.4D). Results from the ANOVA examining IGT score found a statistically significant main effect for test block, $F(4, 640) = 29.61$, $p < .001$, η_p^2 = .406,

but did not show a significant main effect for genotype, $F(1, 160) = .110$, $p = .741$, $\eta_p^2 = .001$, or the 'genotype × block' interaction effect, $F(4, 160) = 1.85$, $p = .176$, $\eta_p^2 = .011$ (Figure 6.4E).

For the CCPT measures independent samples t-tests did not reveal any significant differences between PER2 111 C/C homozygous individuals and G-allele carriers on omission error rate ($t = -.211$, $p = .833$, Figure 6.5A), commission error rate ($t = -.114$, $p = .910$, Figure 6.5B), reaction time ($t = -.958$, $p = .339$, Figure 6.5C), or RTSD ($t = -.297$, $p = .767$, Figure 6.5D). Results from the ANOVA examining IGT score found a statistically significant main effect for test block, $F(4, 640) = 11.357$, $p < .001$, $\eta_p^2 = .066$, but did not show a significant main effect for genotype, $F(1, 160) = .027$, $p = .870$, $\eta_p^2 = .001$, or the 'genotype × block' interaction effect, $F(4, 160) = .507$, $p = .731$, $\eta_p^2 = .003$ (Figure 6.5E).

For PER3 VNTR genotype we conducted four one-way ANOVAs to examine if there was a main effect for genotype ($PER3^{4/4}$, $PER3^{4/5}$, or $PER3^{5/5}$) on CCPT performnance. The results did not show a significant main effect for omission errors [$F(2, 176) = .404$, $p = .668$, $\eta_p^2 = 005$), Figure 6.6A], commission errors [$F(1, 176) = .373$, $p = .689$, $\eta_p^2 = .004$, Figure 6.6B], mean RT [$F(2, 176) = .111$, $p = .895$, $\eta_p^2 = 001$, Figure 6.6C] or RTSD [$F(2, 176) = .1.808$, $p = .167$, $\eta_p^2 = 020$, Figure 6.6D]. In the ANOVA model we used the dichotomised PER3 variable ($PER3^{4/4}$ versus 5-repeat carriers) due to a similarity in behavioural outcomes for both genotypes (González-Giraldo *et al.*, 2015). Results from the ANOVA examining IGT score found a statistically significant main effect for test block, $F(4, 640) = 29.98$, $p < .001$, $\eta_p^2 = .158$, but did not show a significant main effect for genotype, $F(1, 160) = .004$, $p = .952$, $\eta_p^2 = .001$, or the 'genotype × block' interaction effect, $F(4, 160) = 1.604$, $p = .172$, $\eta_p^2 = .010$ (Figure 6.6E).

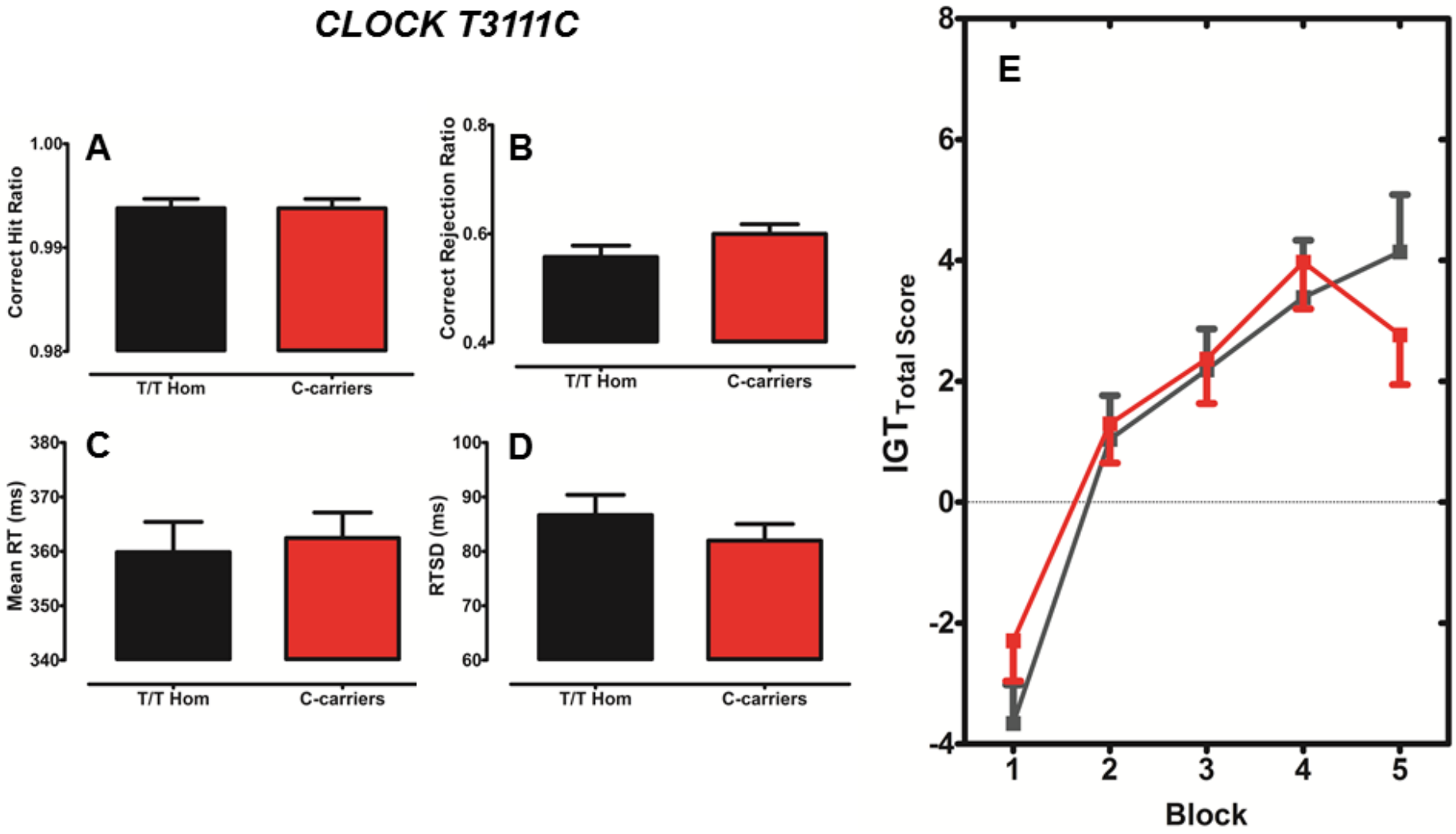

Figure 6.4. ANOVA results for the effect of CLOCK T3111C genotype on neurobehavioural tests

CCPT variables: Accuracy rates for (A) omission errors and (B) commission errors, (C) mean reaction time (D) reaction time variability. Results on the IGT summarised in section (E). T/T Hom(ozygotes) appear in black, C-allele carriers appear in red. No significant main effects for genotype were present.

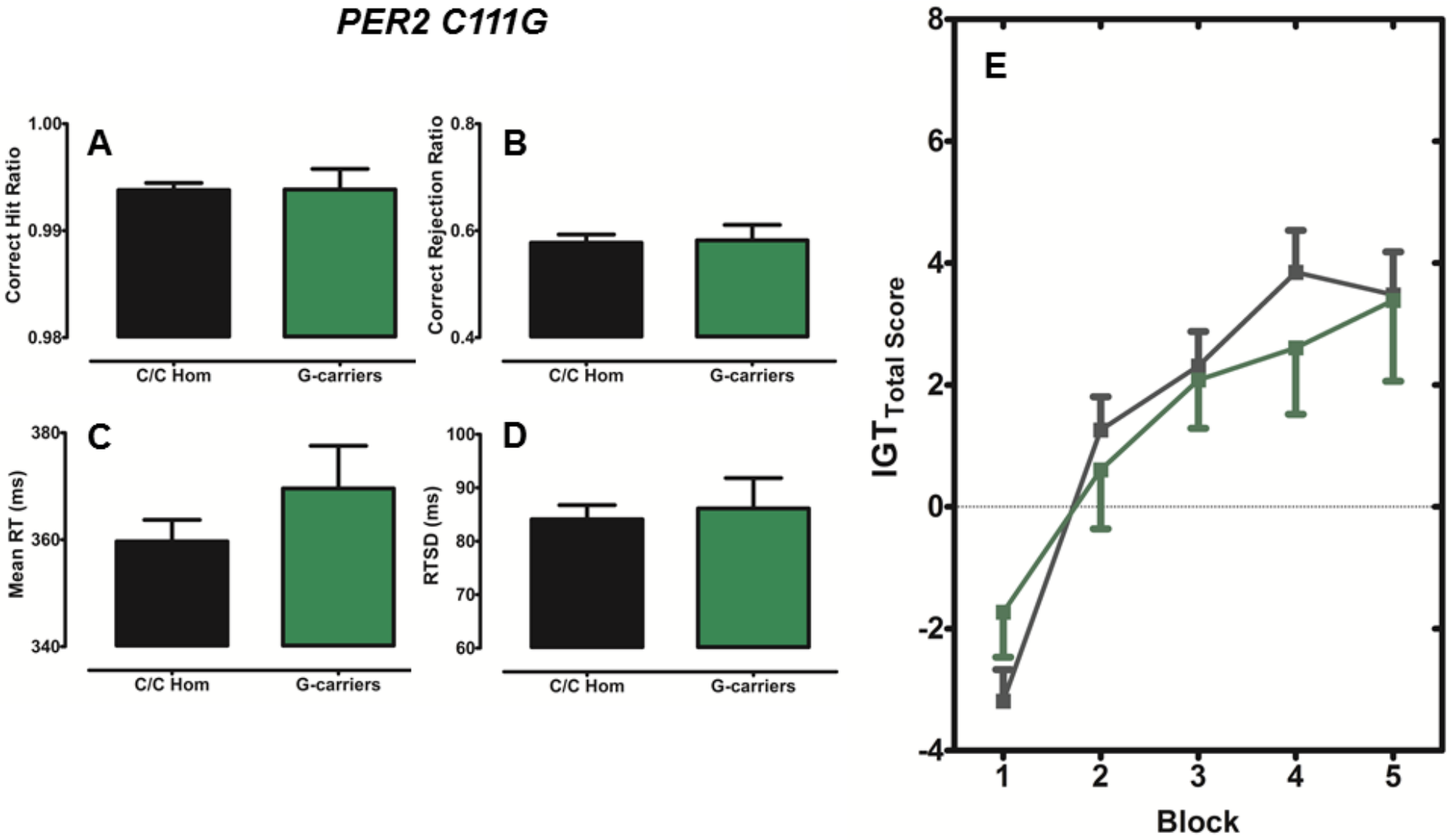

Figure 6.5. ANOVA results for the effect of PER2 C111G genotype on neurobehavioural tests

CCPT variables: Accuracy rates for (A) omission errors and (B) commission errors, (C) mean reaction time (D) reaction time variability. Results on the IGT summarised in section (E). C/C Hom(ozygotes) appear in black, G-allele carriers appear in green. No significant main effects for genotype were present.

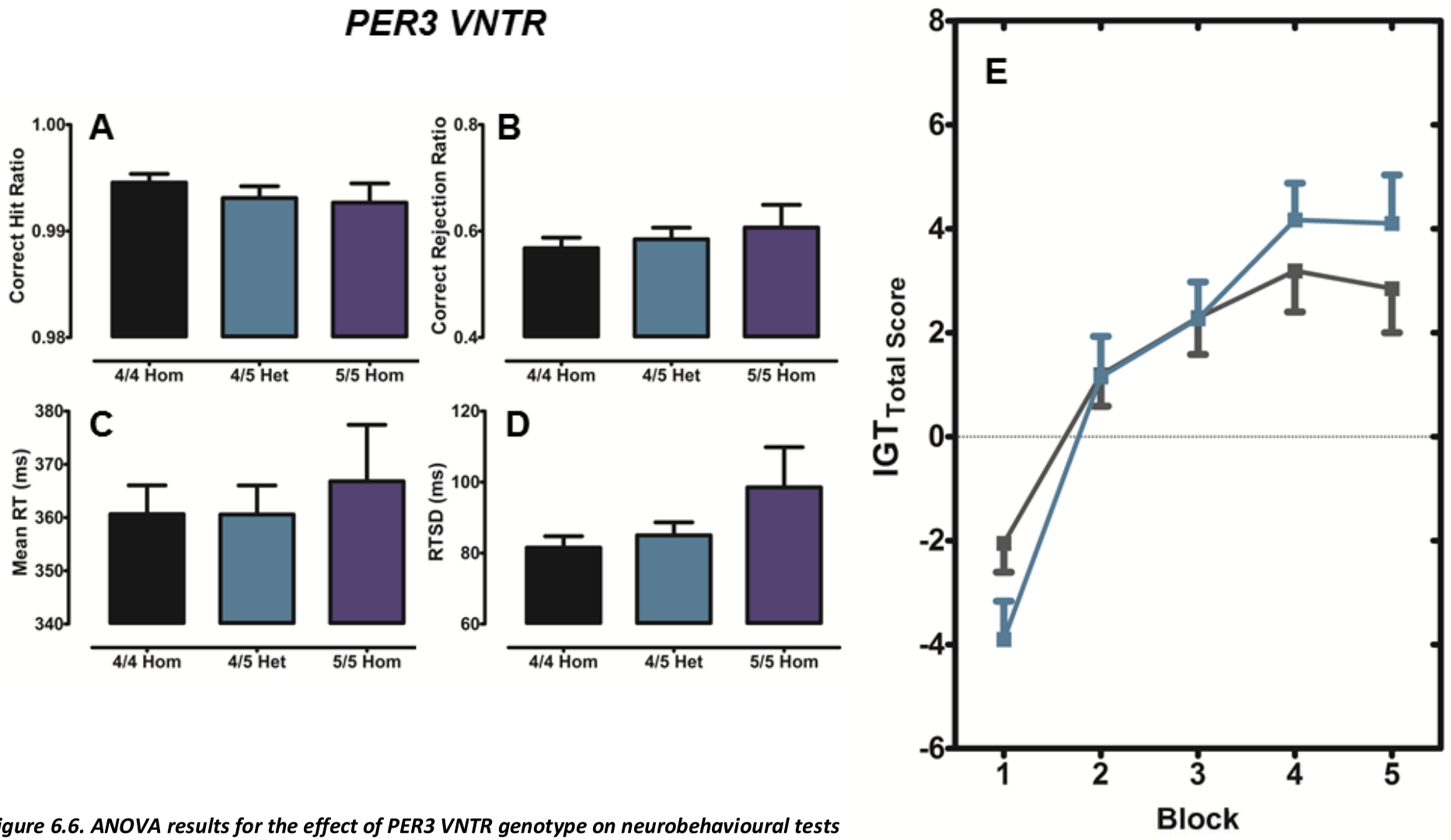

Figure 6.6. ANOVA results for the effect of PER3 VNTR genotype on neurobehavioural tests

CCPT variables: Accuracy rates for (A) omission errors and (B) commission errors, (C) mean reaction time (D) reaction time variability. Results on the IGT summarised in section (E). 4/4 Hom(ozygotes) appear in black, 4/5 Het(erozygotes) appear in blue, 4/4 Hom appear in purple. No significant main effects for genotype were present.

Exploring gene × environment interactions in predicting symptom risk

To test whether a possible association between the candidate genes described here and measures of ADHD-like traits might be moderated by environmental influences we conducted exploratory regression analyses which incorporated two previously identified risk factors of symptom risk; sleep quality and social jetlag (whose associations have been described in Chatper 2). The reason for this being that our failure to describe a genotype association ignores the possibility that genotype differences may only manifest given that a meaningful degree of sleep or circadian rhythm disturbance is already present. Here we conducted three separate linear regressions using a hierarchical backward elimination procedure as the most statistically parsimonious model to predict ASRS score, total BIS score, and CFQ score. Predictors were the genotype × environment interaction terms between the three gene variants and two continuous measures calculated by finding the product between each genotype and the mean centred environmental variable yielding a total of six predictors (*i.e. 'CLOCK × PSQI score', 'CLOCK × social jetlag', 'PER2 × PSQI score', 'PER2 × social jetlag', 'PER3 × PSQI score', 'PER3 × social jetlag'*). Genotypes were dichotomised using an additive model of trait penetrance where the major allele was considered the referent category (dummy coded = 0) which the slope of the minor allele carriers (dummy coded = 1) was compared against. Additionally, the potential confounding effects of age and sex (males = 0, females = 1) were controlled for by entering these variables as covariates each of the models.

Results indicated that for ASRS score the final backward elimination model was significant, $F(1, 174) = 13.708$, $p < .001$, $R^2 = .073$, adjusted $R^2 = .068$, inspection of which revealed only one independently significant predictor '*PER3 × PSQI score*' ($\beta = .270$, $p < .001$). This trend suggests that individuals in the current sample carrying at least one longer PER3^5 repeat are modestly more susceptible to the maladaptive effects of poor sleep quality on ADHD symptoms (Figure 6.7).

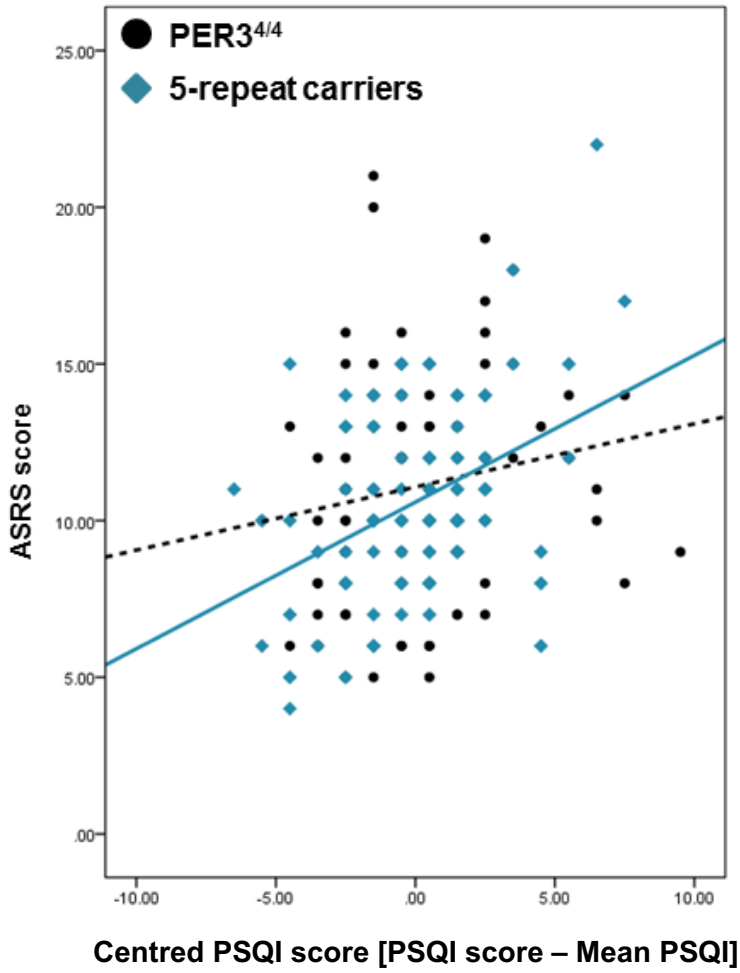

Figure 6.7 Linear associations between sleep disturbances and ASRS score labelled by PER3 genotype

Black circles and dashed line indicate referent PER3$^{4/4}$ genotypes, cyan diamonds and filled line indicate 5-repeat carriers

The final backward elimination regression model predicting total BIS score was also statistically significant, $F(2, 174) = 4.85$, $p = .009$, $R^2 = .053$, adjusted $R^2 = .042$. Inspection of regression coefficients in the final model revealed two significant predictors, *'CLOCK × social jetlag'* ($\beta = .153$, $p = .040$) and *'PER3 × PSQI score'* ($\beta = .170$, $p = .022$). Results indicated that the linear association between social jetlag and impulsivity was moderated by the CLOCK T3111C polymorphism with the C-allele conferring risk towards increased self-reported symptom ratings (Figure 6.8A) and the linear association between poor sleep quality and impulsivity was moderated by the PER3^5 variant (Figure 6.8B) similar to the effects seen on ASRS score.

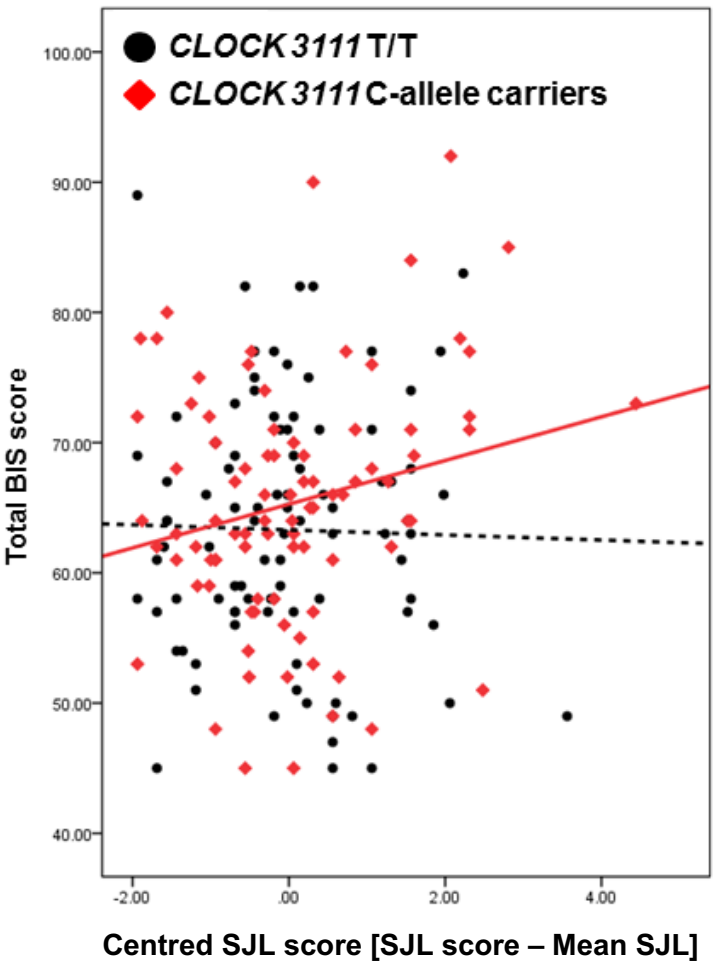

Figure 6.8 (A) Linear associations between sleep disturbances and BIS score labelled by CLOCK genotype

Black circles and dashed line indicate referent T/T *genotypes, red diamonds and filled line indicate C-allele carriers*

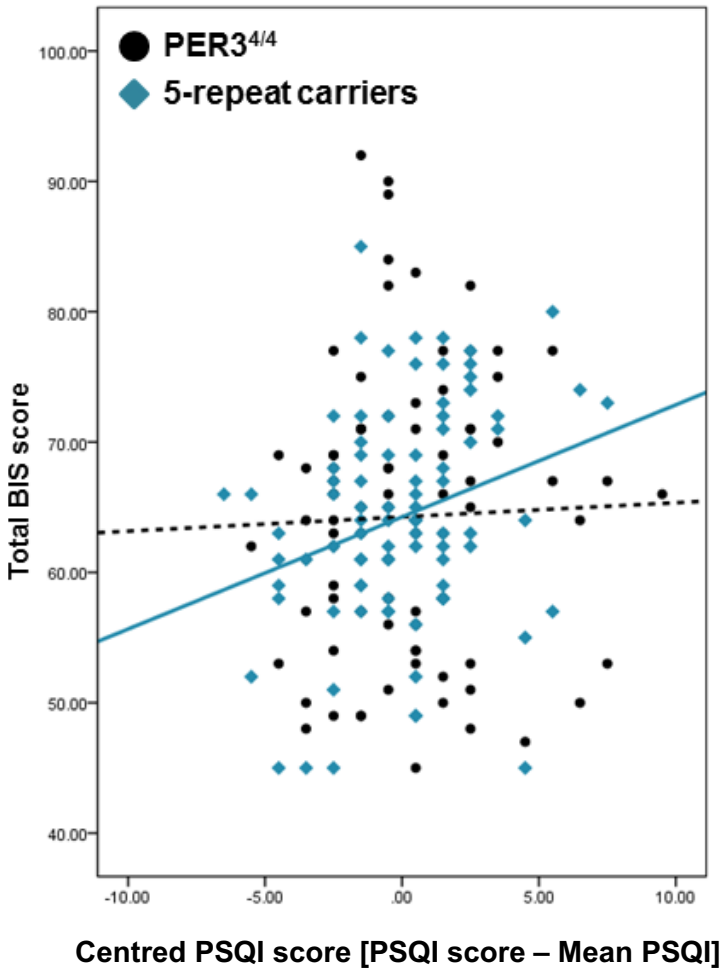

Figure 6.8 (B) Linear associations between sleep disturbances and BIS score labelled by PER3 genotype

Black circles and dashed line indicate referent PER3$^{4/4}$ genotypes, cyan diamonds and filled line indicate 5-repeat carriers

Finally, we found a significant effect for the final backward elimination regression model predicting CFQ score, $F(2, 174) = 9.12$, $p < .001$, $R^2 = .095$, adjusted $R^2 = .085$. Inspection of regression coefficients in the final model revealed two significant predictors, sex ($\beta = .186$, $p = .011$) and *'PER3 × PSQI score'* ($\beta = .258$, $p < .001$), where PER3^5 carrying individuals had a significantly greater increase in CFQ score in the presence of poor sleep quality relative to PER3$^{4/4}$ inidividuals (Figure 6.9).

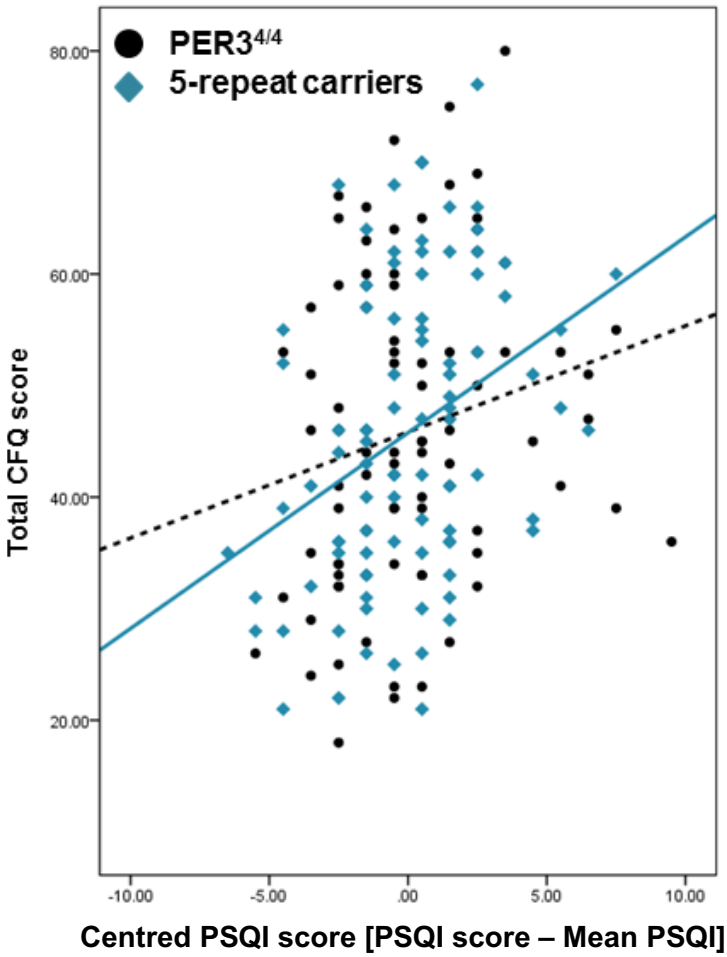

Figure 6.9 Linear associations between sleep disturbances and CFQ score labelled by PER3 genotype

Black circles and dashed line indicate referent PER3$^{4/4}$ genotypes, cyan diamonds and filled line indicate 5-repeat carriers

6.4 Discussion

The purpose of the present study was to investigate to what degree CLOCK T3111C, PER2 C111G, and PER3 VNTR polymorphisms were associated with both sleep quality and delayed circadian phase in a general young adult population. Given prior associations described between these variants and diurnal preference we used the MCTQ derived MSF_{sc} as a corrected behavioural measure of circadian phase of entrainment as our primary phenotyping outcome. Furthermore, as a number of these polymorphisms have been associated with ADHD diagnosis, or traits and indicators of performance related to ADHD, we aimed to investigate associations between self-reported ADHD symptoms, impulsivity, and cognitive dysfunction as well as objective measures of such gleaned from the CCPT and IGT. In this study we found no evidence for a main effect of any of the polymorphisms examined on sleep quality, sleep duration, or markers of circadian phase, and also failed to detect any associations between these gene variants and ASRS score, BIS scores, or CFQ scores, and no associations with outcomes on either of the neurobehavioural tests. Preliminary findings do point to a moderating role for these variants however, suggesting that the genotypes studied here may interact with other factors such as sleep disturbance and circadian misalignment to produce worsened symptoms of ADHD and impulsivity in a young adult population.

Regarding CLOCK T3111C, our failure to detect an association between this polymorphism and differential timing of sleep phase on free days between T/T individuals and C-allele carriers is contrary to reports which suggest that C-allele carriers show a greater diurnal preference for evenings (Katzenberg *et al.,* 1998; Misima *et al.,* 2005). The current findings are in agreement with several other groups however that have also found no association between this polymorphism and either diurnal preference on the MEQ scale (Robilliard *et al.,* 2002; Joahansson *et al.,* 2003; Pedrazzoli *et al.,* 2007; Choub *et al.,* 2011) or more objective biological indicators of circadian phase (Chang *et al.,* 2011). Similarly, we did not find differences in sleep duration or quality to be associated with this SNP which is in agreement with the null findings reported by Barclay *et al.* (2011) for this genotype. Other studies have

shown perturbed sleep quality and delayed sleep onset to be associated with the C-allele of CLOCK T3111C in samples of clinically depressed or bipolar patients (Serretti *et al.,* 2003; Benedetti *et al.,* 2007) indicating that effects of this genetic variant might only become evident where psychiatric diagnosis is also present. While we did detect a small magnitude main effect for CLOCK T3111C on sleep onset latency it showed that instead that the T-allele was the risk-conferring variant with T/T individuals showing an onset latency that was approximately 10 mins later than C-allele carriers, this effect was not significant after correction for multiple comparisons. Concerning ADHD symptomatology and traits related to the disorder, before corrective measures for multiple comparisons were employed we detected differences between T/T genoyptes and C-allele carriers on the motor impulsiveness subscale of the BIS with the C-allele conferring greater risk towards motor impulsivity. As both of these associations were made using subjective report measures it may be the case that more accurate phenotyping techniques are required to accurately probe for such associations. As sleep onset latency and general motor hyperactivity can both be assessed by actigraphy, future studies might attempt to further study associations between this polymorphism and these traits using objective measures of sleep and motor activity. While our findings do not support the hypothesis of an effect of CLOCK T3111C variant on sleep timing or quality in healthy adults, we highlight that potential effects may have been too small to identify within our sample and the deviation of this genotype from HWE limits the generalisability of our findings to wider populations.

Regarding PER2 C111G, we found no evidence for an association with the sleep or circadian rhythm variables assessed and failed to find any main effect of this genotype predicting scores on the ASRS, BIS, or CFQ assessments. The findings of the current study contribute to the list of studies investigating associations between this polymorphism and diurnal preference which report null findings (Lee *et al.,* 2011; Choub *et al.,* 2011). Previous studies describing an association between this gene variant and circadian phenotype do so with respect to extremes of behaviour however with the aim of investigating circadian rhythm sleep disorders such as ASPS in adults (Carpen *et al.,* 2005; Satoh *et al.,* 2003). We cannot rule out the

possibility that genotype differences may manifest in population extremes as discussed in the Barclay *et al.* (2011) study which also failed to associations for CLOCK T3111C and PER3 VNTR with diurnal preference and sleep quality. When we compared the genotype frequencies between extreme groups categorised by upper and lower percentiles of MSF_{sc} distribution we did not find any significant differences for this gene variant (the CLOCK and PER3 variants were compared in the same way and also found no differences). In the present sample therefore the hypothesis that this gene variant is associated with circadian related timing of sleep phase is not supported. As the G-allele of this polymorphic variant has previously been associated with poorer self-control and differential reward circuit activation (Garaulet *et al.,* 2010; Forbes *et al.,* 2012) this prompted us to examine if associations between neurobehavioural traits associated with ADHD were present. While we failed to describe any significant associations between outcome measures and PER2 C111G, as was formerly highlighted, we cannot rule out that such an association may become apparent in the extremes of the population (*e.g.* in individuals with a confirmed diagnosis of ADHD). The possibility of other moderating factors such as age also merits discussion here as the Forbes *et al.* (2012) study which linked this gene variant to hypoactivation of the mPFC in response to reward did so in an adolescent sample. As reward relevant brain activation and faculties mediating impulse control are known to differ among adolescents as in adults (Casey, Jones, & Hare, 2008), it may be the case that the any PER2 C111G association is dependent on the development trajectory of the individual. Further study is necessary therefore in order ascertain whether an association between PER2 C111G and ADHD relevant behaviours exists among children, adolescents, and adults.

Regarding the PER3 VNTR mutation, our findings surprisingly do not support the hypothesis replicated by several others indicating that the longer repeat of this allele, specifically among $PER3^{5/5}$ homozygous individuals, is associated with earlier diurnal preference and therefore an earlier phase of entrainment (Archer *et al.,* 2003; Ebisawa *et al.,* 2001; Jones *et al.,* 2007; Ellis *et al.,* 2009; Lázár *et al.,* 2012). Null findings have also been reported by other groups however (Voinescu & Coogan, 2012; Goel et al., 2009; Osland et al., 2011) indicating that further clarification of the effect of this

genotype on circadian phase of entrainment in humans is needed. While these initial reports suggest that a transmission bais for the homozygous variant of the longer allele is detected among morning typologies, this does not necessarily implicate that the reverse scenario, *i.e.* that the shorter allele is predictive of eveningness/later phase *per se*, would pertain. Interestingly, in a Brazilian sample an inverse association has been described where PER3$^{5/5}$ was associated with delayed circadian phase suggesting that the effects of this polymorphism may differ according to the population in which it is studied (Pereira *et al.,* 2005). The authors of this study suggest two alternative hypotheses for this association: (i) that latitude may have an effect upon the observed differences of the genotype frequency or its function in a given population or (ii) that differences in photoperiod variability and as a function of latitude or zeitgeber strength which vary by season may interact with genotypes to produce a differential phase of entrainment depending on habitat. Concerning the first hypothesis, support is found in animal studies which have demonstrated variations in the *Period 3* gene in *D. melanogaster* dependent upon latitudinal cline (Costa *et al.,* 1992) implicating a role for factors such as temperature and change in photoperiod to select for genetic variation (Majercak, Chen, & Edery, 2004). Attempts to look at the patterns of allele frequencies between indigenous human populations however did not find an association with latitude suggesting that the PER3 VNTR is not influenced by selective pressure from day-length variation (Nadkarni *et al.,* 2005). Rather, others have concluded that it is unlikely that a pattern of natural selection has shaped the evolutionary process of many common circadian clock gene polymorphisms suggesting that chance factors such as genetic drift may be involved (Ciarlegio *et al.,* 2008). As the genotype frequencies of this variant in our sample are similar to those reported by other populations from Northern Europe (*e.g.* Archer *et al.,* 2003; Osland *et al.,* 2011) it seems unlikely that the presence of this variant is remarkably different among an Irish population.

The reasoning for the second alternative hypothesis stems from the observation that most studies which report an association between PER3 VNTR and diurnal preference have been conducted among Northern hemisphere populations whereas the Brazilian cohort reported in the Pereira *et al.* (2005) study were recruited from

cities more proximally located to the equator. The argument here being that a more variable seasonal variation in daylight exposure encountered in the upper Northern hemisphere might give way to the phenotype manifesting whereas closer to the equator the effect of this gene variant on circadian phenotype is not apparent. Indeed, animal models have pointed towards differential entrainment characteristics and activity rhythms in *Per3*$^{-/-}$ knockout mice compared to wild-types when they are both transferred to and maintained on long photoperiod conditions (Pereira *et al.,* 2014) thus supporting a role for behaviour being moderated by gene-photoperiod interactions. Previous studies have also shown that light exposure differentially affects behavioural outcomes dependent on the presence of PER3 VNTR variants (Vandewalle *et al.,* 2011). The studies discussed here which show an association between the PER3 VNTR polymorphism and diurnal preference or circadian phase in other populations of a Northern European background have mostly been conducted among samples recruited in the United Kingdom (Archer *et al.,* 2003; Jones *et al.,* 2007; Lázár *et al.,* 2012). Contradiction of findings from the current study in an Irish cohort and other null findings in a reported from a Norwegian study (Osland *et al.,* 2011) suggests that latitude does not mediate the relationship as each is either of equivalent or more northerly in latitude to a region in which the effects are found. Nevertheless, improvements to the design of the current study may be made in future investigations by taking into account the season during which data collection occurs which also effects photoperiod and zeitgeber strength. In the current study we collected data continuously from March 2013 to March 2016 and did not account for seasonal differences in subject concentration (*i.e.* during teaching semester or holidays). Thus it may be the case that circadian gene-phene relations are only apparent when analysis is restricted to long or short photoperiod times of the year or during periods when the circadian rest-activity cycle is unmasked from social factors which is a hypothesis worthy of exploration in future studies.

Focusing on the subjectively reported neurobehavioural outcomes assessed our findings do not support the hypothesis that variants of the PER3 VNTR genotype are associated with symptoms of ADHD, dimensions of impulsivity, or cognitive dysfunction in a young adult population, and further do not predict different task

performance. These findings are not in agreement with previous demonstrations of executive function and vigilance deficits in 5-repeat carriers and homozygotes when compared to $PER3^{4/4}$ genotypes (González-Giraldo *et al.,* 2015; Maire *et al.,* 2014). Possible reasons for this involve time-of-day effects and the interaction with healthy sleep profiles in individuals as previous reports have shown divergence between PER3 VNTR genotypes on neurocognitive performance is dependent on whether participants are tested in the morning versus the evening (Vanderwalie *et al.,* 2009) or whether participants have experienced acute sleep loss the preceding night (Viola *et al.,* 2007; Groeger *et al.,* 2008). As the outcome measures used here were meant to serve as indicators of relatively stable habitual traits rather than momentary measures of performance which may interact with environmental factors this may explain why effects were not observed. Previously, Artioli *et al.* (2007) described an association between the $PER3^{5/5}$ genotype and the 'novelty seeking' trait of impulsivity in a large cohort of major depressed and bipolar patients. As these conditions in and of themselves include maladaptive behaviours such as increased impulsivity and poor decision making it might be the case that associations with this polymorphic variant are only manifested given prior vulnerability to these traits. Reasons for the lack of association described here may be the absence of a precipitating psychiatric diagnosis. Thus we do not rule out the possibility that future studies might find an association between this genotype and those traits in clinical groups for example in ADHD.

Interestingly, we report preliminary findings indicating differential expression of symptoms of impulsivity and ADHD –traits that are associated with CLOCK T3111C and social jetlag, and the PER3 VNTR and sleep quality, which significantly predict symptom risk among a normative sample. In particular, we observed that social jetlag combined with the CLOCK C/T heterozygous variant was associated with greater global impulsivity score than when combined with the T/T genotype. Additionally, we report that the association between poor sleep quality and symptoms of ADHD, impulsivity and cognitive dysfunction, was moderated by the presence of at least one PER3 5-repeat allele such that a steeper increase in these outcomes was present among $PER3^{5}$ carriers compared to $PER3^{4/4}$ homozygotes. A

point of interest here is that similar studies have demonstrated that the association between clock genes and maladaptive health outcomes depend upon other mediating risk factors. Ruiz-Lozano *et al.* (2016) recently report for example that the association between chronotype and obesity was significantly moderated by the presence of the C-allele variant of CLOCK T3111C. Another study conducted by Viena *et al.* (2016) from earlier the same year showed that a reduced sleep duration combined with the $PER3^{4/4}$ genotype was associated with greater mood disturbances and increased state anxiety among women, but no interactions were present among long allele carriers. Thus our findings contribute to a recent literature which suggests that the previously reported associations between genetic variants in circadian clock genes and adverse mental health outcomes are more complex in their nature. It is suggested by these findings that these gene variants produce a differential susceptibility to environmental factors which in turn are related to neurobehavioral symptoms. We note however the exploratory nature of these associations, the absence of stringent significance correction, and the need for replication from other research groups before firm conclusions can be drawn. Presently we suggest that these relations might be a target for future work in the area.

There are several limitations to this study which should be acknowledged when interpreting its findings. The first speaks more generally to the practice of candidate gene studies which attempt to describe associations between common genetic variants and behavioural and psychometric traits that are continuously distributed throughout the population. It seems likely that complex phenotypes such as human behavioural traits are not influenced to a significant degree by single point mutations but rather multiple variants of very small effect sizes that are only detectible within a population *en masse*. Furthermore, the effects of such genes on behaviour may be subject to environmental modification and to epistatic effects through gene-gene interactions (Geschwind & Flint, 2015). To reiterate a problem frequently cited in studies concerned with the genetic of psychiatric diseases, the more behavioural a phenotype is the less directly it will be predicted by a genotype (Meyer-Lindenberg & Weinberger, 2006). Given the paucity of unanimous consensus regarding the associations described between genes and psychiatric/circadian related phenotypes it

might be suggested that the outcomes predicted by these genes are more subtle than that which can be detected by self-report instruments.

Recently, for example, functional approaches to understanding the role of the CLOCK T3111C polymorphism have demonstrated that differential expression of the CLOCK protein is mediated by glucocorticoid exposure and sex which is dependent on the presence of carrier status of the C or T alleles (Shi *et al.,* 2016). The authors suggest that this mechanism may influence the risk of circadian disruption and mood disorders associated with the CLOCK gene. Furthermore, another recent study which employed diffusion tensor imaging to detect white matter microstructure integrity in patients with bipolar disorder found structural differences indicative of disrupted myelination among different CLOCK T3111C and PER3 VNTR genotypes (Bollettini *et al.,* 2016). Furthermore, previously cited work from another group have detected a role for the PER3 mutation in influencing homeostatic sleep pressure and REM sleep microarchitecture (Gaggioni *et al.,* 2014; Viola *et al.,* 2007). These phenotypes might have important effects upon sleep quality and the entrainment of the sleep-wake cycle however they cannot be readily assayed by simple self-report methods. We suggest therefore that replication problems concerning the association between genotype and self-reported diurnal preference and chronotype may arise from a failure to select an adequate phenotype. It seems that effects on behaviour arise rather at the level of the intermediate phenotype which in turn influences behavioural trait and symptom penetrance at the population level where effects are more difficult to detect.

We also note that the study was limited by the relatively small sample size available for a candidate gene study. As the effect sizes reported by others that have studied these polymorphisms were small it is possible we were unable to detect any main effects for genotype given the size of our sample. Despite this our study is comparable in sample size or contains more subjects than other published reports (Carpen *et al.,* 2005; Voinescu & Coogan, 2012; Choub *et al.,* 2011; Kissling *et al.,* 2008). Future studies with larger sample sizes are required in order to confirm or contest our findings. Finally, another limitation may concern the population selection

methods of the sample. While previous groups have attempted to include participants only of certain ethnic origin (*e.g.* Italians in Choub *et al.,* 2011) several others have reported populations of mixed ethnicity (*e.g.* Pedrazzoli *et al.,* 2007; Katzenberg *et al.,* 1998) and many do not report such data (*e.g.* Archer *et al.,* 2003; Robilliard *et al.,* 2002). Difficulties concerning the ambiguity of genetic associations in ethnically heterogeneous populations have been discussed in perspective pieces looking at human genetic variation in circadian clock components (Allebrandt & Roenneberg, 2008). While we are confident that the subjects recruited in this study were predominantly of an Irish background we did not restrict participation based on ethnicity (small numbers of other European ethnicities and South American nationals were present in the sample) and we cannot rule out genetic admixture in those self-reported as Irish. Future studies might attenuate replication failure by focusing data collection from ethnically homogenous groups.

In conclusion, data reported in the current study contributes to a frequently controversial literature investigating genetic associations between circadian clock components and chronotype, sleep, and traits relevant to psychiatry. We did not find any evidence supporting the hypotheses that polymorphic variants in CLOCK T3111C, PER2 C111G, or PER3 VNTR were associated with self-reported sleep phase, duration, and quality, or with ADHD related symptoms in a healthy young adult population. Our preliminary findings instead suggest that there may be subtler interactions between these polymorphisms and human sleep patterns which predispose individuals towards symptoms of inattention and impulsivity. It remains to be seen whether these findings are of clinical relevance and highlight that future studies might explicitly focus on the role of social jetlag and sleep quality when studying G×E effects in relation to the circadian clock and ADHD.

Chapter 7

General Discussion

7.1 Summary of findings presented in this thesis

The objective of this research was to examine how sleep and circadian rhythm disturbances among the general population contribute to symptoms of impulsivity and impaired attention with the aim of improving the understanding of such system deficits in adult ADHD. We first addressed the previously described associations relating the morningness-eveningness circadian typology trait with personality traits such as impulsiveness, risk taking, and sensation seeking in normative samples, as well as with the diagnosis of ADHD itself. In the current work we used an alternative chronotyping procedure distinct from the diurnal preference output generated by the MEQ instrument. We approached the question from the perspective of expressing the individual differences in chronotype as an estimate of the underlying circadian phase of entrainment which was measured using the mid-point of sleep obtained from the Munich Chronotype Questionnaire. Furthermore, as individuals who show higher eveningness are often also at risk of significant sleep restriction and impaired sleep quality as a result of pressure from the social clock (Roenneberg *et al.,* 2007) we examined associations with subjective sleep quality and the social jetlag measure of circadian misalignment also. In doing so, we found evidence supporting the hypothesis that it is not the inherent diurnal preference characteristic of an individual in and of itself that is a risk factor for ADHD related traits and behaviours but rather the degree of functional circadian misalignment and sleep disturbances experienced by individuals that best predicts symptom risk (Chapter 2).

Additionally, we demonstrated differential performance on neuropsychological tasks designed to measure cognitive and behavioural deficits associated with ADHD in individuals with high levels of social jetlag and disturbed sleep. Notably we found that individuals experiencing greater social jetlag showed faster pre-potent response reaction time than those in the low social jetlag group, and that those with poor self-reported sleep quality made risker choices on an experimental task commonly used to resemble gambling (Chapter 3). Importantly on both behavioural tests we were able to recapitulate performance deficits on these tasks frequently seen in ADHD in individuals experiencing sleep and circadian rhythm disturbances (Luman *et al.,*

2008; Toplak, *et al.,* 2005). Moreover, these effects were not demonstrated when individuals' self-reported chronotype was used to compare performance differences. Taken together the findings from the first two experimental chapters of this thesis illuminate the previous observations linking later diurnal preference and circadian phase delays of sleep with ADHD in adults and children and point to a role for circadian misalignment and sleep deficits in potentially underlying such associations.

In order to provide an objective estimation of the 24 h rest-activity cycle and the quality of individuals' sleep participants were assessed using wrist-worn actigraphs for one week to get a picture of their usual schedules of activity (Chapter 5). This component of study revealed a number of correlations between indicators of delayed circadian phase, sleep deprivation, and sleep disturbances, with heighted symptoms of ADHD and impulsivity. Thus our findings accord well with previous reports of delayed behavioural rhythms in clinical populations with ADHD (Boonstra *et al.,* 2007; Van der Heijden *et al.,* 2005b; Van Veen *et al.,* 2010). We also highlight that these associations were not apparent for other domains of cognitive impairment, indicating a specific association between disturbances in these parameters and ADHD relevant traits and behaviours. Of the associations noted we found that later sleep phase and impaired sleep quality and duration were the most important predictors of ADHD symptoms and impulsivity respectively, representing a possible future target of therapeutic interventions to address such deficits which in turn might ameliorate or help control symptoms of ADHD in adults (see section 7.2). Finally, in this chapter we also describe novel associations between individuals' circadian period and worsened symptoms of ADHD, impulsivity, and cognitive dysfunction. The findings suggest that a deficit in the entrainment properties of the circadian timing system to a 24 h period might contribute to the pathophysiology of ADHD in adults. Thus it remains to be seen whether efforts to improve circadian resonance may also lead to symptom remission or improvement (see section 7.2).

In Chapter 6 we aimed to replicate previous associations between the chronotype trait in humans as well as ADHD-like traits and symptoms, with common genetic variants in a number of candidate clock genes. Using the mid-point of sleep as a

marker of circadian phase rather than the previously utilised diurnal preference dimension we did not detect any significant effect for the genotypes studied. Furthermore, self-reported measures of symptomatology and objective indicators of performance on the neuropsychiatric tests used did not differ between genotypes. Our exploratory findings revealed differential susceptibility to adverse effects of social jetlag and poor sleep quality in different genotype carriers however. Accordingly, future studies might consider how these environmental factors interact with genotypes to confer risk towards certain deleterious cognitive outcomes and behavioural traits, especially with respect to ADHD.

Furthermore, a supplementary experiment described in Chapter 4 revisited the neurobehavioral findings described in Chapter 3 which showed that social jetlag had an effect upon continuous performance task performance. This was done in part in an attempt to explore established neural correlates of performance previously shown to be disrupted in ADHD. Comparison of high and low social jetlag groups showed evidence of a reduced P3 latency and amplitude evoked by stimuli on the CPT-AX and CCPT versions of the continuous performance task respectively. Results suggest that continuous circadian misalignment might perturb optimal brain function during response inhibition and sustained attention tasks which in turn may have implications for previous chronotype specific structural brain changes and diminished activation.

7.2. Implications for understanding and treating attention-deficit/hyperactivity disorder and general public health considerations

Presently, an extensive literature exists detailing the high prevalence of sleep disturbances (Cortese *et al.,* 2009; Hvolby, 2015) and circadian abnormalities in ADHD (see Section 1.10; Coogan *et al.,* 2016; Coogan & McGowan, 2017). It has been argued that these alterations may constitute a risk factor of the disorder; a symptom of the disorder; or reflect a common factor predicting both sleep and circadian rhythm disturbances as well as comorbid core pathophysiological features of ADHD

(Cassoff, Wiebe, & Gruber, 2012). Indeed many of the symptoms associated with ADHD emerge in non-clinical populations as a by-product of sleep deprivation (Corkum *et al.,* 1998; Wulff *et al.,* 2010) and longitudinal studies have indicated that ADHD diagnosis may succeed given a prior history of sleep complications and sleep onset insomnia in childhood (Gregory & O'Connor, 2002; O'Callaghan *et al.,* 2010). Sleep and circadian rhythm disturbances might therefore be considered a potential enhancer of pre-existing symptoms or might precipitate *de novo* symptom liability in predisposed individuals. One of the major patterns revealed in this study, both by actigraphy and self-reported means, is that later sleep phase, sleep onset latency, and impaired sleep quality represent common risk factors associated with impulsivity and inattention in the general adult population. Thus the commonality of the current findings with previous reports indicating of sleep disturbances, circadian rhythm delays, and eveningness based diurnal preference in ADHD, raises the possibility for sleep targeted interventions and *'chronotheraputic'* approaches to be utilised to treat the condition and limit symptom severity.

Previously, treatment of co-occurring parasomnias such as restless leg syndrome (dopamine agonists, iron supplementation) as well as sleep apnea (surgical intervention) has resulted in symptom improvements in ADHD in children (Walters *et al.,* 2000; Cortese *et al.,* 2008; Huang *et al.,* 2007). Moreover, in the Huang *et al.* (2007) study primary treatment of associated sleep disturbances were found to be more beneficial than the group treated for ADHD using stimulants (methylphenidate; Mph) or the group receiving no intervention, highlighting that clinical improvements can be derived from focusing on the alleviation of sleep impairments. In adults, successes treating other common psychiatric conditions such as major depression have been noted using cognitive behavioural therapies for co-morbid insomnia (CBT-I) as reported in a recent meta-analysis focused on CBT-I efficacy (Ballesio *et al.,* 2017). In one such study a combination of CBT-I with pharmacotherapy was more effective than treatment with the anti-depressant medication alone, achieving higher remission rates for depression (Manber *et al.,* 2008). Furthermore, it has been shown that cognitive behaviour therapy for sleep disturbances may outperform mainstays of medical treatment for insomnia such as

benzodiazepine and non- benzodiazepine hypnotic drugs (Mitchell *et al.,* 2012). As far as we are aware there currently do not exist any studies examining the effects of such interventions in ADHD therefore its efficacy in treating the symptoms of the condition remains unascertained. Given the successes noted in treating other psychiatric conditions by focusing on sleep disturbances however, as well as the associations that we, and others (Mahajan *et al.,* 2010), have described linking poor sleep quality and ADHD-like symptoms, the implementation of CBT-I and other cognitive behavioural interventions focusing on disturbed sleep in ADHD represents an exciting target for future research in understanding how ADHD symptoms might be better managed. Furthermore, if support is indicated for the use such behavioural therapies this might lead to less reliance on stimulants that are typically used to manage symptoms in ADHD but may also cause side effects that are counter-productive to treating sleep disturbances.

Concerning the consistent presence of delayed circadian phase in ADHD, and the links between later activity phase/mid-point of sleep and symptoms of impulsivity and inattention which here we recapitulate in a large cohort of healthy individuals, interesting questions emerge regarding how treatment of these phenomena might be of clinical importance. A number of studies have been published involving interventions which target circadian timing in ADHD, treatment of which in turn might help to treat the condition by bringing timing within a normal range. Much of the work previously conducted has focused on the use of melatonin to adjust the phase of the circadian rhythm or as a soporific agent in the treatment of insomnia. The ability to phase advance sleep onset time and DLMO in individuals with ADHD has been demonstrated previously (Van der Heijden *et al.,* 2007) as well as the efficacy of melatonin treatment before bedtime to treat insomnia in childhood ADHD (Tjon Pian Gi *et al.,* 2003). In terms of improving the core symptoms of the disorder a small number of studies have revealed mixed effects. Promising findings from Hoebert *et al.* (2009) show that long-term melatonin treatment for managing chronic sleep onset insomnia in ADHD was effective for improving sleep quality in 88% of cases and ADHD related behaviours in 71% of cases. Another novel pharmacological option might be the anti-depressant agomelatine due to its unique mechanism of

action as a melatonergic agonist distinguishing it from other anti-depressant classes. A small scale randomised placebo-control trial of agomelatine was found to be effective in treating symptoms of ADHD (Niederhofer, 2012) and more recently it has been demonstrated that agomelatine was no different in its efficacy versus methylphenidate treatment with the additional bonus of a trend for less insomnia in the agomelatine treated group of patients (4% compared to 24% Mph) (Salardini *et al.,* 2016). Additionally, Mohammadi *et al.* (2012) found that co-administration of Mph and melatonin may lead to clinical benefits in managing shorter sleep latency but outside of these effects they found that melatonin treatment was not successful in treating ADHD symptoms. While there is future potential for the implementation of chronotheraputic agents and such as agomelatine administration and melatonin supplementation in the treatment of ADHD and associated sleep and circadian rhythm disturbances, at this stage it seems evidence is too scant to support their use in the treatment of ADHD beyond an adjunctive role. Future studies should focus on improving the state of the art of treating sleep problems and circadian entrainment challenges in ADHD with the purpose of deriving clinical benefits. In this respect combined approaches may be necessary to bolster maximal benefit as demonstrated by others showing that co-administration of melatonin and sleep hygiene produced the greatest clinical improvements to sleep in ADHD (Weiss *et al.,* 2006).

A novel finding reported in the actigraphy component of this study was that of an apparent entrainment deficit in which it was indicated that individuals with a circadian period different from twenty-four hours experienced more symptoms of ADHD and impulsivity. Previously Baird *et al.* (2012) described a similar pattern with the authors showing that shorter periods were associated with higher DSM symptom severity ratings in adults with ADHD. Such departures from circadian resonance most likely emerge as a result of inadequate zeitgeber strength which entrains the internal rhythm to the solar day. Indeed, our findings might be considered supportive of data showing that geographic solar intensity is a predictor of regional ADHD prevalence (Arns *et al.,* 2013, 2015) which is hypothesised to arise as a result of diminished zeitgeber strength leading to challenges to circadian entrainment. Furthermore, shortening of the photoperiod in winter has been found

to produce increased nocturnal agitation and motor activity in ADHD supporting a role for entrainment difficultly leading to worsened symptoms (Langevin & Ramde, 2012). It might be suggested therefore that schedules involving maximal exposure to light during the day and limited exposure to light during late part of the evening and night would help to manage ADHD symptom risk in individuals with the condition as well as in healthy subjects. Moreover, future ADHD interventions might exploit the synchronising properties of light in an effort to mitigate symptom risk. Initial small test trials such as that of Rybak *et al.* (2006) report that morning bright light therapy was associated with improvements in ADHD symptoms indicating a potential role for its future therapeutic application as a strategy to manage the condition. Recalling the previously described association between later circadian phase and symptom severity, the authors found that phase advances of the circadian rhythm associated with bright light therapy were the most important predictors of beneficial clinical outcome (Rybak *et al.,* 2006). It remains to be seen however whether timed exposure to light in such a fashion can improve deviant circadian periods in ADHD. A related strategy concerning the improvement of zeitgeber quality involves the shielding of the deleterious effect of artificial light during the late evening and night-time in patients with ADHD. As previously highlighted the effects of short wavelength light in particular are the most activating upon RHT-SCN phototransduction mediated circuitry having powerful phase shifting effects on individuals' rhythms of activity (van der Meijden *et al.,* 2016). The use of blue-light-blocking amber lens glasses has been successful in treating insomnia in ADHD as well as advancing sleep phase and lowering anxiety in adult ADHD (Fargason *et al.,* 2013). It remains to be demonstrated however that the core symptoms of the condition can be treated in this fashion but recent reports have shown successful management of manic symptoms in bipolar disorder with additive blue blocking glasses intervention in combination with pharmacotherapy (Henriksen *et al.,* 2016) suggesting that combined with traditionally indicated treatment strategies such interventions might be appropriate. Future studies would also require several nights of actigraphic assessment in order to demonstrate a correction of period in any intervention given as has previously been shown for phase advancing or delaying

the circadian rhythm (Rybak *et al.,* 2006; Faragason *et al.,* 2013). In the interim, less sophisticated methods of limiting blue light exposure might be practiced by individuals by reducing the use of laptops, e-reader/tablets and phones in the late evening and before the desired bedtime.

From a general health perspective, it has previously been noted that inadequate exposure to sunlight during the day, and overexposure to artificial light at night vis-à-vis insufficient zeitgeber signal, might be an important risk factor for numerous detrimental health effects (Smolensky, Sackett-Lundeen, & Portaluppi, 2015). Repeated circadian desynchrony and exposure to light at night has been linked to the development of cancers (Davis & Mirick, 2006; Chau, West, & Mapedzahama, 2014; Haim & Portov, 2013), and cognitive performance deficits in healthy male particpants (Cajochen *et al.,* 2011). Notwithstanding the effects of light on the entrainment of the circadian timing system we acknowledge that other mechanisms might also be at play such as the suppression of nocturnal melatonin synthesis, sleep deprivation, and NIF photic influence on arousal/alertness. Future studies should therefore also attempt to parse out which elements germane to circadian entrainment are risk factors for the behavioural and cognitive traits we describe here and elucidate other mechanisms which might be influencing behaviour.

One of the major findings from the current work was that of the consistent association of higher levels of social jetlag with greater ADHD symptom likelihood and increased impulsivity measured both by subjective self-report and by objective assessments. Furthermore, higher and lower social jetlag groups showed differences in patterns of neuroelectric activation during continuous performance task completion. Here we highlight the novel nature of these findings and suggest that previous reports which describe relations between later chronotype/diurnal preference and symptoms and traits associated with ADHD may actually be better explained by the effects of functional jetlag arising from the misalignment between the circadian and the social clock. Previous studies linking differential circadian clock function to other mental health problems such as low mood and major depression, and increasing epidemics such as obesity and diabetes, have suggested that social

jetlag might underpin the associations between these conditions and chronotype (Levandovski *et al.,* 2011; Parsons *et al.,* 2015; Roenneberg *et al.,* 2012). In the case of explaining ADHD symptoms among the broader population, this hypothesis is further spoken to by our data implicating similar patterns of ERP activation in individuals with high social jetlag as are found in clinical cases of ADHD which may in turn have implications for previous brain imaging studies which report main effects for chronotype groups (*e.g.* Hasler *et al.,* 2013; Reske *et al.,* 2015). To recapitulate, we suggest that chronic circadian misalignment may be an important risk factor for the emergence of ADHD-like symptoms in adults and its estimation using the social jetlag index of sleep behaviour represents a crucial consideration in future studies linking the circadian timing system with ADHD as well as other psychiatric disorders. That a meaningful level of circadian disturbance, and not simply a later chronotype might be a risk factor for deficits in motor inhibitory control, but not necessarily an individual's propensity to delay reward or sensitivity to reinforcement, aids in the discovery of which aspects of executive function are shaped by the circadian misalignment. Given recent findings however pertaining to other constitutional traits separate from morningness-eveningness, the canonical index of circadian typology, that influence an individuals preferred pattern of activity, and therefore circadian phase, other factors such as an individual's temperament, time perspective, and ability to delay gratification might feedback to shape the circadian phenotype also (Jankowski, 2014; McGowan *et al.,* 2017). Future studies may also consider the psychological mechanisms associated with circadian typology and social jetlag to further investigate whether to what extent the predicted outcomes associated with each are moderated by other, likely correlated, factors.

Considering the aforementioned argument pertaining to social jetlag and its associated outcomes in the current work, interesting questions emerge regarding how or if steps taken to limit social jetlag might aid in the management of ADHD symptoms as well as curtailing many of the previously described associations between social jetlag and health and cognitive performance (Roenneberg *et al.,* 2012; Parsons *et al.,* 2015; Haraszti *et al.,* 2014). Firstly, the present findings suggest that sleep hygiene protocols which cater to the production of an earlier phase of

entrainment on free days would help to alleviate the typical scenario of forced advancing of the sleep/wake cycle on work days. Prioritising earlier sleep times on free days and thereby lessening the severity of the weekend/weekday phase shift might serve to temper the worsened symptoms of impulsivity and inattention associated with social jetlag. In clinical scenarios this outcome is neatly reconciled within a broader treatment strategy of improving sleep quality and optimal entrainment to the 24 h solar day by means of light therapy or the chronobiotic interventions discussed in this section. Furthermore, in attainment of this goal occupational patterns which promote social jetlag such as recurring schedules of rotating shift-work should be avoided. Progress has been made however in understanding how the improved design of shift-work schedules might better accommodate the entrainment of circadian clock (Juda, Vetter, & Roenneberg, 2013; Fischer *et al.,* 2016). In general, it has been previously illustrated that worker fatigue may be circumvented and performance might be enhanced. Thus, implementation of social schedules designed to limit social jetlag may have wider implications for worker safety by reducing the amount of work place accidents that are more frequent among shift-workers that experience the highest levels of circadian desynchrony (Folkard & Tucker, 2003; Machi *et al.,* 2012; Rajaratnam *et al.,* 2011).

Despite initial successful attempts at circumventing the social jetlag and impaired sleep associated with such occupational schedules uptake among wider society remains disappointingly slow. Although we only studied an adult population in the current work, our findings linking social jetlag with deleterious cognitive and behavioural outcomes may have implications for other groups such as childhood and adolescent cohorts, which typically have higher prevalence rates of ADHD than adults. In adolescence in particular the circadian clock is becomes substantially delayed in its entrained phase (Roenneberg *et al.,* 2004; Carskadon, 2011) and as a result during this developmental period individuals are most affected by social jetlag (Roenneberg *et al.,* 2012; recall Figure 1.10). There are also data which might suggest that individuals differ in their sensitivity to the maladaptive effects of social jetlag as a result of their sex, with females' school performance in more adversely affected than males (Diaz-Morales & Escribano, 2015). Suggestions to overcome this

desychrony between biological time and social time have been to delay school starting times to later in the day with the aim of improving behavioural outcomes and attention during class (Kelley *et al.,* 2014). Currently there is a paucity of information regarding the success of such modifications to societally entrenched times which are difficult to change in part due to parents' typical work schedules as well as educators'. A recent meta-analysis of such delayed start time studies found only six studies which used experimental protocols with delayed start times in the 25 – 60 minute range (Minges & Redeker, 2016). Findings from these studies suggested that increased sleep duration and improvements to health, performance, and in class behaviour were attained (Boergers, Gable, & Owens, 2014; Lufi, Tzischinsky, & Hadar, 2011). It remains to be investigated however whether such outcomes might help to control impulsiveness in adolescents and young adults. Findings which potentially might lead to progress in this area are gleaned from road accident reports among older adolescents and young adults in which incidents of car crashes on school days were dramatically reduced when school start times were delayed in school districts in Kentucky (Danner & Phillips, 2008) and Virginia (Vorona *et al.,* 2011). As impulsivity and novelty seeking are known determinants of risky driving (Scott-Parker *et al.,* 2013; Pearson *et al.,* 2013) and adolescents with ADHD are at increased risk of road traffic accidents (Narad *et al.,* 2013) the impact of adjusting school/occupational schedules to more appropriately fit biological time cannot be understated. The associations described in the current work linking worsened ADHD symptoms with social jetlag support the evidence from the existing literature indicating that efforts taken to resolve circadian misalignment might in the future lead to improved mental and physical health outcomes.

7.3 Limitations of the current study

We highlight a number of limitations in the current work which might limit the generalisability of the findings reported as well as a number of methodological caveats which should be borne in mind when interpreting these findings. Firstly, throughout this research we treated the symptomatic features of ADHD as traits that

which are distributed continuously among the broader population. In approaching the research question we included only members of the general population and did not conduct a comparison study of effects in clinically confirmed cases of ADHD. The epistemology of this approach was broadly discussed in the introduction section to this research and is supported by several other accounts which relate the condition epiphenomena to extremes of behaviour that are normally distributed within groups of individuals (Levy *et al.,* 1997; Martin *et al.,* 2004). It is assumed that the findings we report will have translational implications for the emergence and treatment of the condition however we highlight that our results deserve replication in actual clinical populations with adult ADHD before firm conclusions can be drawn. We raise the possibility that the effects noted here may be more pronounced in actual cases of ADHD and suggest that there may be interaction effects present between diagnosis and sleep and circadian rhythm disturbances, which may further exacerbate behavioural outcomes in at risk individuals than could be replicated in the normal population. Among the features present in clinically confirmed ADHD which might further lead to circadian clock and sleep disruption and that are omitted are the frequent use of stimulant medications in managing symptoms (Boonstra *et al.,* 2007; Ironside *et al.,* 2010) and high prevalence rate of other psychiatric disorders (Kessler *et al.,* 2006). We also note that one of the primary considerations in assessing ADHD in adults is the retrospective presence of the condition in childhood (American Psychiatric Association, 2013) whereas in the current study we were unable to determine the chronicity of symptoms using the ASRS and BIS instruments. For these reasons more research is necessary to assess to what degree our findings are replicable in the condition.

Another limitation which should be considered is the manner in which circadian misalignment was estimated throughout our experiments via the social jetlag output from the MCTQ. As this metric functions by determining the difference in sleep phase between workdays and free days, a number of assumptions are made regarding the organisation of human behaviour on both respective days. Unlike with the school timetable and majority of jobs where standard working hours are issued the idea of a *'workday'* becomes more ambiguous and variable throughout the week

when applied to a full-time university attending sample. For example, due to class scheduling constraints the morning start times of the week may vary more dramatically throughout the week and thereby the pressure of the social clock may be variable depending on the week day assessed. Furthermore, students may work a weekend job leaving few free days among the typical college week and in instances where students may elect the scheduling of tutorials/seminars, particularly later chronotypes may be biased towards a schedule which unburdens their typical sleep/wake habits even on *'workdays'*. Previous applications of the MCTQ to a university dwelling sample revealed that the association between social jetlag and poorer academic performance dissipates once the lecturing semester finishes and the exam semester begins (Haraszti *et al.,* 2014). Moreover, the application of the MCTQ to produce a measure of social jetlag might not necessarily be appropriate in certain clinical groups such as ADHD where increased levels of unemployment are present (Küpper *et al.,* 2012). Recently progress has been made developing new methods of quantifying and visualising circadian misalignment from outputs such as actigraphy or sleep diaries using the recently described *'Composite Phase Deviation'* method (Fischer, Vetter, & Roenneberg, 2016). Future application of such measures will likely reveal more about how the circadian clock is affected by social schedules giving way to better understanding how circadian misalignment might occur.

Our methodology might be further improved by incorporating longer actigraphy recording intervals in order to objectively assess circadian misalignment as the current protocol captured only one transition between the weekend and weekday. Additionally, our interpretation of entrainment deficits indicated by a period less than or greater than 24 h might be further investigated using actigraphs which have the ability to measure light exposure. By extracting information about how the circadian clock entrains to the strength of the photic zeitgeber, better models of circadian entrainment might be generated and the risk factors for health conditions better understood as demonstrated in Reid *et al.* (2014). Finally, we acknowledge also that the MSF_{sc} measure of circadian phase is an estimate of the biological phase of the circadian clock and different associations from the ones we describe may emerge by using a different phase marker such as core body temperature of hormone secretion.

Indeed previous experiments between MEQ score and metrics of risk taking did not find any associations (Berdynaj *et al.*, 2016; Ingram *et al.*, 2016) however when the phase of the circadian clock was estimated using RNA expression of rhythmic circadian proteins associations between circadian phase and behaviour emerged (Ingram *et al.*, 2016). We suggest therefore that depending on output parameter of the circadian clock used to estimate the phase/period of the endogenous clock, reports of their links to human health may differ.

7.4 Concluding remarks

The work reported in this thesis provides an in-depth analysis of the contribution of circadian clock dysfunction and impaired sleep to worsened symptoms of impulsivity and attention deficit in adults. We have highlighted that chronic circadian misalignment rather that delayed entrained phase in and of itself may be a risk factor for the development of symptoms associated with ADHD. Thus our results might clarify a causal mechanism for the frequently noted later chronotype/eveningness associations in individuals with ADHD. Furthermore, we conclude that poor circadian resonance and reduced sleep quality, and onset latency may exacerbate or predispose individuals to greater levels of trait impulsiveness and reduced attention and cognitive functioning. We also demonstrated that common mutations in genes which underpin the circadian timing system might interact with the aforementioned risk factors to engender further negative health consequences. Finally, we demonstrate that links between high levels of habitual social jetlag and attenuated neuroelectric activation resemble that of imaging studies of brain function in ADHD. These findings might be important in shaping future strategies to manage ADHD symptoms in clinical groups as well as circumventing negative mental health outcomes in the general population also.

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Appendix A

Participant information and consent form

Assessing sleep timing and impulsive decision making and behaviour

The experiment you are being asked to participate in wishes to examine to what extent morning people differ from evening people on computer tests which measure impulsivity and inattention.

You are asked to complete five questionnaires: two which ask about general sleeping habits and three which ask about your self-assessed levels of impulsive decision making, attention, forgetfulness, and traits similar to those found in adult attention-deficit hyperactivity-disorder. Two computer tasks will ask you to respond to instructions using the mouse/keyboard. Total time of this part of experiment will take approximately 25 mins.

At the end of the experiment you will be asked to provide a sample of your saliva into test tubes provided. The purpose of this is to investigate if a biological marker (a common mutation in the genes which regulate sleep) can predict whether an individual is a morning or evening person and is more likely to have impulsive tendencies.The genetic test we carry out cannot diagnose or predict any known medical disorder and cannot be used to assess ancestry. Furthermore results will not be able to identify individual participants.

All data collected during this project will be kept confidential. For the purpose of publishing findings from this study participants will not be individually identified but only represented as part of a larger research sample (approximately 200 participants in total). Should you wish to withdraw your participation or access your data from this study at any time you may do so by contacting either the research student Mr. Niall McGowan or the project supervisor Dr. Andrew Coogan, whose contact details are provided below.

Further, none of the tests used in this study are diagnostic. Should your participation in this study raise health/medical concerns for you we strongly advise talking to your primary healthcare provider.

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To participate in this study we ask that you complete your signature on this consent form indicating that you understand the conditions of this experiment and that you are satisfied that you may withdraw your participation and data at any time up until the publication date.

Signature of participant:

_____

Please retain a copy of this form for your own records. If you have any health concerns regarding the topics covered in this project please contact the medical centre, north campus NUIM on +353 1 7083878.

If during your participation in this study you feel 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 research.ethics@nuim.ie or +353 (0)1 708 6019. Please be assured that your concerns will be dealt with in a sensitive manner.

Appendix B

Adult ADHD Self-Report Scale – PART A Screener tool (Kessler *et al.*, 2005, 2007a)

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date					
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.			Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?							
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?							
3. How often do you have problems remembering appointments or obligations?							
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?							
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?							
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?							

Part A

Appendix C

Barratt's Impulsiveness Scale (Patton *et al.*, 1995)

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

Appendix D

Cognitive Failures Questionnaire (Broadbent *et al.,* 1982)

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 you 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

		Very often	Quite often	Occasion-ally	Very rarely	Never
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 E

Munich Chronotype Questionnaire (Roenneberg *et al.*, 2003, 2007)

Munich ChronoType Questionnaire (MCTQ)

Please enter your age, gender, etc.. This information is important for our evaluations

Age: _____ **female** **male** **Height** _____ **Weight** _____

On work days ...

I have to get up at... _____o'clock
I need... _____min to wake up
I regularly wake up... before the alarm with the alarm
From... _____o'clock I am fully awake
At around... _____o'clock, I have an energy dip
On nights before workdays, I go to bed at _____o'clock...
... and it then takes me... _____min to fall asleep
If I get the chance, I like to take a siesta/nap ...
correct I then sleep for..._____ min
not correct I would feel terrible afterwards

On free days (please only judge normal free days, i.e., without parties etc.) ...

My dream would be to sleep until... _____o'clock
I normally wake up at... _____o'clock
If I wake up at around the normal (workday) alarm time, I try to get back to sleep...
correct not correct
if I get back to sleep, I sleep for another... _____min
I need ... _____min to wake up
From... _____o'clock I am fully awake
At around... _____o'clock, I have an energy dip
On nights before free days, I go to bed at... _____o'clock...
... and it then takes me... _____min to fall asleep
If I get the chance, I like to take a siesta/nap ...
correct I then sleep for..._____ min
not correct I would feel terrible afterwards

once I am in bed, I would like to read for ... _____ min, ...
... but generally fall asleep after no more than ... _____ min.

I prefer to sleep in a completely dark room correct not correct
I wake up more easily when morning light shines into my room correct not correct

How long per day do you spend on average outside (really outside) exposed to day light?
On work days: ___ hrs. ___min. On free days: ___ hrs. ___min.

Page 1

Self assessment

After you have answered the preceding questions, you should have a feeling to which chronotype (time-of-day-type) you belong to. If for example, you like (and manage) to sleep quite a bit longer on free days than on workdays, or if you cannot get out of bed on Monday mornings, even without a Sunday-night-party, then you are more a late type. If, however, you regularly wake up and feel perky once you jump out of bed, and if you would rather go to bed early than to an evening concert then you are an early type. In the following questions, you should categorise yourself and your family members.

Please tick only one possibility!

Description of categories:

extreme	early type = 0
moderate	early type = 1
slight	early type = 2
	normal type = 3
slight	late type = 4
moderate	late type = 5
extreme	late type = 6

I am...	0	1	2	3	4	5	6
as a child, I was ...	0	1	2	3	4	5	6
as a teenager, I was ...	0	1	2	3	4	5	6
In case you are older than 65: in the middle of my life, I was ...	0	1	2	3	4	5	6
My parents are/were...							
Mother ...	0	1	2	3	4	5	6
Father ...	0	1	2	3	4	5	6
My siblings are/were ... (please underline Brother or Sister)							
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
My partner (girl/boy friend, spouse, significant other) is/was ...	0	1	2	3	4	5	6

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Appendix F

Pittsburgh Sleep Quality Index (Buysee *et al.,* 1989)

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐

(j) Other reason(s), please describe

_____

_____

How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

PSQI Page 1

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

Appendix G

Stanford Sleepiness Scale (Hoddes *et al.,* 1973)

Using the 7-point scale below pick what best represents how you are feeling and note the corresponding number on the chart below.

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not fully alert	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

Appendix H

Participant information and consent form (University of Wuppertal)

Lehrstuhl für Allgemeine
und Biologische Psychologie

BERGISCHE
UNIVERSITÄT
WUPPERTAL

Examing social jetlag and the neural correlates of impulsivity

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Einverständniserklärung zur Versuchsteilnahme am Lehrstuhl für Allgemeine und Biologische Psychologie, Bergische Universität Wuppertal

Sie nehmen an einem Experiment am Lehrstuhl für Allgemeine und Biologische Psychologie der Bergischen Universität teil. Das Experiment untersucht **„Examining social jetlag and the neural correlates of impulsivity“** Während des Experiments wird die elektrische Aktivität Ihres Gehirns mittels Elektroenzephalogramm (EEG) gemessen. Dazu wird Ihnen eine EEG-Elektrodenkappe auf den Kopf gesetzt, welche die elektrische Aktivität Ihres Gehirns bei der Bewältigung der geforderten Aufgabe misst. Dieses Verfahren ist sicher, nicht-invasiv und nicht-schmerzhaft; es beinhaltet keine Ausstrahlung von elektrischen Signalen, Röntgenstrahlen magnetischen Feldern oder anderer gefährlicher Elemente. Das Verfahren können Sie sich in etwa so ungefährlich wie die Messung der Herzrate oder des Blutdrucks vorstellen. Die Messung erfordert die Vorbereitung der Kopfhaut mit einem leitenden Elektroden-Gel, welches uns hilft ein klares Signal des Gehirns zu erfassen. Deshalb sollten Sie sich nach dem Versuch die Haare waschen. Die nötigen Utensilien, wie z.B. Shampoo oder Handtuch, werden Ihnen von uns bereit gestellt. Da Augenbewegungen das EEG-Signal beeinflussen und stören, werden Ihnen zudem vier EOG-Elektroden im Gesicht angebracht, die Augenbewegungen messen. Technisch messen diese Elektroden genauso wie die EEG-Elektroden und sind von daher auch genauso unbedenklich und ungefährlich.

Der Versuch wird insgesamt ca. **120** Minuten dauern.

Der spezifische Hintergrund der Untersuchung wird Ihnen erklärt sobald sie das Experiment abgeschlossen haben. Die Aufzeichnungen und Ergebnisse jeder Versuchsperson werden

strengstens vertraulich behandelt und in den Räumlichkeiten des Lehrstuhls für Allgemeine und Biologische Psychologie sicher und eingeschlossen aufbewahrt. Die Ergebnisse Ihrer Teilnahme werden nur durch eine Versuchspersonennummer dokumentiert. Keine Namen oder Informationen, durch die Ihre Person identifiziert werden könnte, werden aufgezeichnet oder ausgewertet. Mit Ausnahme der involvierten Versuchsleiter/-innen, wird keine andere Person die individuellen Ergebnisse Ihrer Person sehen oder diskutieren. Ihre individuellen Ergebnisse werden mit denen vieler anderer Versuchsteilnehmer kombiniert und zu Durchschnittswerten zusammen gerechnet. Werden die Ergebnisse in einer Arbeit (z.B. Bericht, Thesis) oder einem Artikel (wissenschaftliches Journal) berichtet, so werden keine individuellen Ergebnisse und nur Gruppenergebnisse präsentiert. Ihre persönlichen Ergebnisse können nur Ihnen und keinen anderen Personen zur Einsicht zur Verfügung gestellt werden. Sie können zu jeder Zeit und ohne Angabe von Gründen die Untersuchung abbrechen oder Ihre Ergebnisse zurückfordern bis zu dem Zeitpunkt der Veröffentlichung der Untersuchung.

Im unwahrscheinlichen Fall, dass Sie im Verlaufe der Untersuchung negative, schmerzhafte und/oder diskriminierende Erfahrungen machen, sollten Sie den/ die Betreuer/-in des Experiments (Name, E-mail, Telefon) kontaktieren und die Situation schildern.

Sollte **mindestens eine** der folgenden Ausschlusskriterien auf Sie zutreffen, so sind Sie unter Umständen nicht geeignet an der Untersuchung teilzunehmen:

- Jegliche Sehbehinderungen (außer bei korrigierter Sehhilfe);
- Vorgeschichte psychologischer (z.B. Depression) und/oder neurologischer (z.B. Epilepsie) Erkrankungen;
- schwere Kopfverletzungen bis hin zur Bewusstlosigkeit;
- derzeitige Einnahme von psychoaktiven Substanzen/Medikamenten;
- andere relevante medizinische Faktoren;
- hoher Blutdruck/Herzrate;
- Vorgeschichte von Drogen- und/oder Alkoholproblemen;
- Klaustrophobie.

……

Ich habe den oben beschriebenen Ablauf und die Bedingungen des Experiments gelesen und verstanden und stimme meiner Teilnahme zu. Ich habe zudem verstanden, dass ich das Recht habe meine **Teilnahme am Experiment zu verweigern** und ich das Experiment **jederzeit und ohne Angabe von Gründen abbrechen kann.**

Unterschrift der Versuchsperson	Ort, Datum

Falls Sie das Gefühl haben, dass die oben genannten Informationen oder Bedingungen vernachlässigt oder missachtet wurden, können Sie sich jederzeit an den Betreuer/-in der Untersuchung wenden (**Markus Hofmann; mhofmann@uni-wuppertal.de**) oder an die Ethikkommission der Bergischen Universität Wuppertal.