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Research Report

Frequency-dependent changes in synaptic plasticity and brain-derived neurotrophic factor (BDNF) expression in the CA1 to perirhinal cortex projection

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ABSTRACT

The ability of a synapse to be modulated both positively and negatively may be considered as a plausible model for the formation of learning and memory. The CA1 to perirhinal cortex projection is one of the multiple hippocampal–neocortical projections considered to be crucially involved in memory consolidation. We and others have previously demonstrated the ability of this projection to undergo long-term potentiation (LTP), however it is currently unknown whether the CA1-perirhinal projection can also be modified negatively (i.e. demonstrate long-term depression (LTD)). Here we investigate whether the CA1 to perirhinal projection *in vivo* in the anaesthetised animal shows a frequency-dependent pattern of synaptic plasticity that is coupled with brain-derived neurotrophic factor (BDNF) expression. Five groups of animals were used and each group underwent one of five different stimulation protocols (1 Hz, 5 Hz, 10 Hz, 50 Hz or 100 Hz) followed by post-stimulation recordings at baseline stimulation intensity (0.05 Hz) for 1 h. Paired-pulse facilitation (PPF) recordings were taken both during baseline and 1 h post-stimulation across six inter-pulse intervals (IPIs). Following all experiments, tissue samples were taken from area CA1 and perirhinal cortex from both the unstimulated and stimulated hemispheres of each brain and analysed for BDNF. Results indicated that LTP was observed following 50 Hz and 100 Hz HFS but LTD was not observed following any low-frequency stimulation. Pre- and post-stimulation PPF recordings revealed no difference for any of the stimulation frequencies, suggesting that the plasticity observed may involve a post- rather than a presynaptic mechanism. Finally, changes in BDNF were positively correlated with stimulation frequency in the area CA1 but the same pattern was not observed in the perirhinal cortex. These findings suggest that the CA1 to perirhinal cortex projection is electrophysiologically excitatory in nature and that changes in BDNF levels in this projection may not be predictive of changes in synaptic plasticity.

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1. Introduction

The hippocampal formation (HF) is an important structure for learning and memory (Scoville and Milner, 1957; O'Keefe and Nadel, 1978; Squire, 1992). The HF is thought to play a particular role in associating different forms of sensory information (Rolls, 1996) required to form long-term memories. Although it is not the site of storage for memories, the HF acts in an integrative role to output sensory information to the neocortex for long-term storage (Squire et al., 1984; Squire, 1992; McClelland et al., 1995; Squire and Alvarez, 1995). Among the possible physiological mechanisms for memory formation and consolidation are changes in synaptic plasticity (Martin et al., 2000).

Long-term potentiation (LTP) is just one aspect of synaptic plasticity, representing a long-lasting increase in synaptic strength (Bliss and Lømo, 1973). Long-term depression (LTD) considered the converse process, is a long-lasting reduction in synaptic strength usually induced following low-frequency stimulation (LFS; Bramham and Srebro, 1987). This phenomenon has also been described in the literature. The ability of a synapse to be modulated both positively and negatively by different frequencies supports the case for changes in synaptic strength as a candidate for the physiological basis of learning and memory (Bear et al., 1987; Thiels et al., 1996). In particular, this modifiable ability of the synapse supports recent suggestions that memories are dynamic rather than static in nature, they can be updated, erased or impaired by subsequent experiences and therefore, there is a need for synapses to reflect this by also having the ability to change strength, raise or lower synaptic thresholds (Abraham and Williams, 2008) and to shift the synaptic modification range (Rioult-Pedotti et al., 2007) rather than simply being unmodifiable and locked at a certain strength.

Previously, we have described both short- and long-term synaptic plasticity in the CA1-perirhinal cortex projection. We have demonstrated that stimulation of area CA1 using a 250 Hz high-frequency stimulation (HFS) protocol results in paired-pulse facilitation (PPF) and LTP in the perirhinal cortex (Kealy and Commins, 2009). These findings agree with previous research which has demonstrated that this projection is indeed capable of sustaining long-term changes in synaptic plasticity (Cousens and Otto, 1998; Ivanco and Racine, 2000). We now wish to extend our previous findings and examine whether different stimulation frequencies have differential effects on synaptic plasticity in this pathway and whether the CA1 to perirhinal cortex projection is also capable of sustaining LTD, thus conforming to the Bienenstock–Cooper–Munro (BCM) model of biphasic synaptic modification (Bienenstock et al., 1982).

In hippocampal area CA1, a number of studies have shown that LTD can be induced by LFS (Thiels et al., 1994; Doyère et al., 1996; Citri et al., 2009; Hosseinmardi et al., 2009). NMDA-dependent homosynaptic LTD in area CA1 can be induced with LFS (1–3 Hz) of the Schaffer collateral (Dudek and Bear, 1992). Dudek and Bear (1993) later showed that this synaptic plasticity was bidirectional, LTP and LTD could be induced in the same synapses following a series of HFS and LFS protocols and these findings were later reproduced *in vivo* (Heynen et al., 1996). Further, our laboratory has demonstrated that the hippocampal output projections are also capable of being modified in an activity-dependent fashion. For example, the CA1-subiculm projection is capable of sustaining LTP (Commins et al., 1998b), while the CA1 to entorhinal cortex projection has been shown to sustain LTP following 50 Hz, 100 Hz and 250 Hz HFS protocols (Craig and Commins, 2005, 2007) and LTD following 1 Hz, 5 Hz and 10 Hz LFS protocols (Craig and Commins, 2007). In the perirhinal cortex, activity-dependent LTD has been described following 1 Hz LFS that seems to be reliant on metabotropic glutamate (mGlu) receptors (Cho et al., 2000b, 2002). Recently, kainate glutamate receptor-dependent LTD has also been identified in the perirhinal cortex and this seems to be induced via a different level of activity compared to AMPA-dependent LTD (Park et al., 2006). Interestingly, a role for perirhinal LTD in object recognition memory has been suggested as antagonism of L-type voltage-dependent calcium channels (VLDCCs) blocks object recognition memory and the induction of LTD but not the induction of LTP (Seoane et al., 2009). Furthermore, viral blockade of mGlu and AMPA receptors block perirhinal LTD *in vitro* and also recognition memory (Griffiths et al., 2008). These experiments suggest that LTD and LTP may play differential roles in perirhinal-dependent recognition memory, with an LTD-like mechanism being suggested as the process underlying this process (Warburton et al., 2003; Barker et al., 2006).

There is increasing molecular evidence to suggest that LTP and LTD are different extremes of the same process (Bienenstock et al., 1982; Bear, 2003; Yu et al., 2008). There are a number of molecular processes found to be important in LTP that are also implicated in LTD including Ca^{2+} (Mulkey and Malenka, 1992; Cummings et al., 1996), protein phosphatases (Mulkey et al., 1993, 1994; Dickinson et al., 2009), BDNF (Aicardi et al., 2004), extracellular signal-regulated kinase (ERK; Norman et al., 2000; Thiels et al., 2002; Gallagher et al., 2004), NMDA glutamate receptors (Dudek and Bear, 1992; Kirkwood et al., 1993) and AMPA glutamate receptors (Lüscher et al., 1999; Wang and Linden, 2000). The most studied model of the LTP/LTD dichotomy is the cycling of AMPA glutamate receptors to and from the postsynaptic membrane. The insertion of AMPA receptors into the postsynaptic membrane has been implicated in the induction of LTP (Shi et al., 1999, 2001; Barry and Ziff, 2002) and conversely, the endocytosis of AMPA receptors has been suggested to be the mechanism underlying LTD (Lüscher et al., 1999; Wang and Linden, 2000; Holman et al., 2007). This AMPA receptor endocytosis has been shown to be Ca^{2+}-dependent (Beattie et al., 2000) mGlu receptor-dependent (Snyder et al., 2001; Xiao et al., 2001), protein kinase C-dependent (Czarnecki et al., 2007) and Arc-dependent (Bramham et al., 2010).

The presence of BDNF can also alter the effect observed at different stimulation frequencies, suggesting that neurotrophins may play a role in modulating metaplasticity (prior synaptic activity resulting in changes in the potential for synaptic plasticity; Abraham and Bear, 1996). It has been suggested that BDNF may shift the synaptic modulation threshold, preventing the induction of LTD *in vivo* (Jiang et al., 2003). For example, at lower frequencies where LTP is normally not observed, LTP can be induced in the presence of BDNF (Figurov et al., 1996; Huber et al., 1998). Huber et al. (1998) also demonstrated that at frequencies that would normally induce strong LTD; there is an attenuation of depression in the presence of BDNF. Other studies have shown that application of BDNF in

visual cortex slices can completely block LTD (Akaneya et al., 1996; Kumura et al., 2000) and that this attenuation of LTD by BDNF is phospholipase C-dependent (Ikegaya et al., 2002). Furthermore, in the hippocampus there is an activity-dependent effect for BDNF expression. LFS shows little or no changes in BDNF levels whereas the use of HFS results in significant increases in BDNF levels (Springer et al., 1994; Hartmann et al., 2001; Balkowiec and Katz, 2002; Gärtner and Staiger, 2002). In the perirhinal cortex, levels of HFS sufficient to induce LTP lead to significant increases in BDNF levels lasting 5–12 min and conversely levels of LFS sufficient to induce LTD lead to a significant but transient decrease in BDNF levels (Aicardi et al., 2004). Similar to LTP, surface expression of the TrkB receptor also has also been shown to be activity-dependent with LFS resulting in no increase in TrkB surface expression but there is a significant increase in TrkB surface expression following HFS (Du et al., 2000).

In this study, we will examine the plastic properties of the CA1 to perirhinal cortex projection by using five different stimulation frequency protocols (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz). We will investigate the effect of each stimulation frequency on synaptic strength; we expect HFS protocols to induce LTP and LFS protocols to induce LTD. Therefore we expect to determine the BCM threshold for this projection, i.e. the frequency at which LTD becomes LTP. In addition, we will determine whether these changes in stimulation frequencies affect short-term plasticity in this projection by analysing paired-pulse facilitation (PPF). Furthermore, we will determine whether the locus of change in synaptic strength is pre- or postsynaptic by comparing PPF levels before and after stimulation. Finally, we will analyse BDNF levels in the area CA1 and perirhinal cortex using ELISA. We hypothesise that following a HFS protocol, there will be significantly higher levels of BDNF in the stimulated hemisphere compared to the unstimulated hemisphere and that following a LFS protocol, there will be significantly lower levels of BDNF in the stimulated hemisphere compared to the unstimulated hemisphere.

2. Results

2.1. *Effect of different stimulation frequencies on synaptic strength*

We initially recorded fEPSPs in all groups using a 0.05 Hz stimulation protocol for 10 min (−10–0 min) before applying one of five different stimulation protocols (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz). Following this, recordings were again conducted at 0.05 Hz for a further 60 min. To examine the effects of the different stimulation frequencies on synaptic strength, a 5×4 mixed factorial ANOVA was used with time analysed on 4 levels (−10–0 min, 0–10 min, 20–30 min and 50–60 min) as a within-groups measure. Stimulation frequency was analysed on 5 levels (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz) as a between-groups measure. Overall, there was a significant effect of time ($F=126.536$; df=3, 135; $p<0.001$). Stimulation frequency was also shown to have a significant effect ($F=5689.724$; df=4, 45; $p<0.001$). In addition, an interaction effect between stimulation frequency and time was shown ($F=13.076$; df=12, 135; $p<0.001$).

Each stimulation frequency group was analysed separately in order to determine the effect of the stimulation frequency on synaptic plasticity. Repeated-measures ANOVAs were ran for each group with Bonferroni correction to examine the specific differences at four different times (−10–0 min, 0–10 min, 20–30 min and 50–60 min) within each group. There was a significant effect for time in the 1 Hz group ($n=6$, $F=5.922$; df=3, 27; $p<0.01$, Fig. 1a). *Post-hoc* analysis showed that 1 Hz stimulation failed to induce post-tetanic potentiation (PTP) as there was no significant difference in fEPSP slope size between baseline and the 0–10 min interval (103.005%±1.606; $p>0.05$) or the 20–30 min interval (103.487%±2.622; $p>0.05$). However, fEPSP slopes during the 50–60 min interval (113.17%±5.75) were significantly higher compared to baseline levels ($p<0.05$).

In the 5 Hz group ($n=6$, Fig. 1b), there was a significant effect found for time ($F=90.090$; df=3, 27; $p<0.001$). The 5 Hz stimulation protocol induced potentiation lasting approximately 25 min before dropping to below 120% of baseline. The fEPSPs recorded in the 0–10 min interval (135.614%±1.237) were significantly higher than baseline levels ($p<0.001$) and they were also significantly higher than fEPSP averages at the 20–30 min (119.173%±1.867; $p<0.001$) and 50–60 min intervals (110.494%±1.750; $p<0.001$). However, even though fEPSPs in the 0–10 min interval were significantly higher than those in the 20–30 min ($p<0.001$) and the 50–60 min intervals ($p<0.001$), this was not classified as PTP as the potentiation seen in the first 10 min remains at approximately the same level throughout that time, as opposed to PTP's characteristic large increase in fEPSP slope over the first 2–3 min post-HFS followed by a sharp decline in fEPSP slope size.

A significant effect for time was also found in the 10 Hz group ($n=6$, $F=26.725$; df=3, 27; $p<0.001$, Fig. 1c). There was a significant increase in fEPSP slope size compared to baseline levels at the 0–10 min (123.392%±2.261; $p<0.001$) and 20–30 min intervals (115.477%±2.090; $p<0.05$) but there was no significant difference between baseline fEPSP slope values and those in the 50–60 min interval (102.857%±1.008; $p>0.05$). In addition, there was no significant difference between the 0–10 min interval and the 20–30 min ($p>0.05$) which indicates that there was no PTP following a 10 Hz stimulation.

As with the three previous groups, there was a significant effect for time in the 50 Hz group ($n=6$, $F=40.712$; df=3, 27; $p<0.001$; Fig. 1d). Unlike the other groups, a 50 Hz stimulation induced PTP and LTP. PTP was observed in the first 3 min of recording before fEPSP slopes decreased in size. However, fEPSP slopes in the 0–10 min interval (156.365%±4.549) remained significantly higher compared to baseline ($p<0.001$). fEPSP slopes remained significantly higher compared to baseline levels in both the 20–30 min (138.416%±2.862; $p<0.001$) and the 50–60 min intervals (130.550%±2.069; $p<0.001$). The fEPSP slope values in the 0–10 min interval were significantly higher compared to the 50–60 min interval ($p<0.01$) which indicates that PTP had been induced.

Finally, there was also a significant effect for time in the 100 Hz group ($n=6$, $F=35.836$; df=3, 27; $p<0.001$; Fig. 1e). Like the 50 Hz group, the 100 Hz group also exhibited PTP and LTP. Again PTP was observed in the first 3 min of recording before fEPSP slopes decreased in size. Overall, fEPSP slopes in the 0–10 min interval (156.742%±6.381) remained significantly potentiated compared to baseline levels ($p<0.001$). fEPSP slopes also remained significantly higher compared to baseline levels in the 20–30 min (140.941%±3.271; $p<0.001$) and the

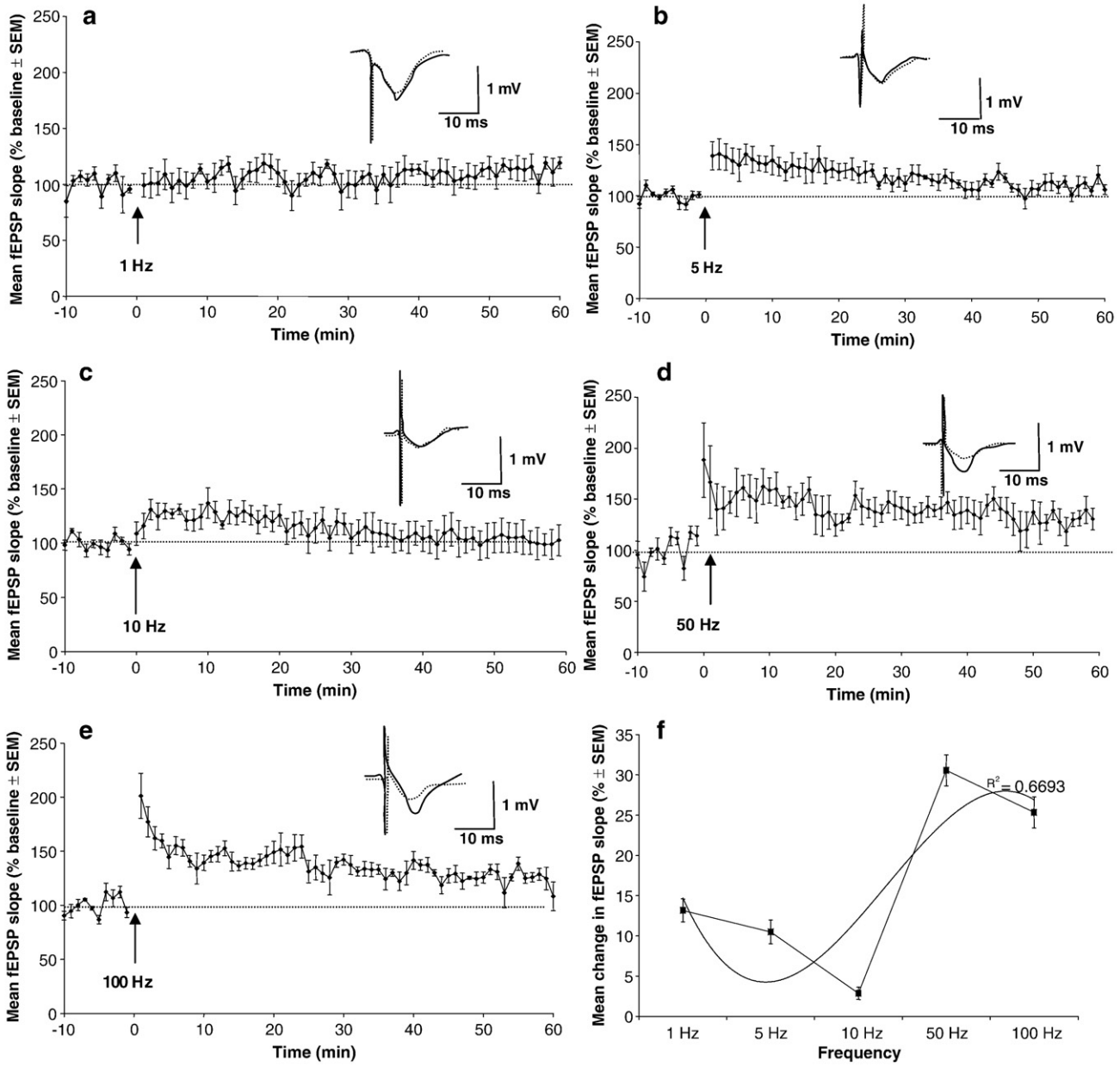

Fig. 1 – Plot of fEPSP slopes before and after (a) 1 Hz, (b) 5 Hz, (c) 10 Hz, (d) 50 Hz and (e) 100 Hz stimulation protocols in the CA1 to perirhinal cortex projection ($n = 6$ in each group). Each point represents an average of three fEPSP slopes recorded over 1 min and data is expressed as a percentage of baseline fEPSP slopes where baseline is approximately 100%. Insets are representative fEPSP traces from each group showing typical fEPSPs at baseline (dashed line) and 1 h post-HFS (solid line). (f) Comparison of potentiation levels for the five stimulation frequencies averaged over the final 10 min of recording expressed as a percentage of baseline fEPSP slopes.

50–60 min intervals (125.336%±2.895; $p<0.001$). Finally, the fEPSP slope values in the 0–10 min interval were significantly higher compared to the 50–60 min interval ($p<0.01$) indicating that PTP had been induced.

Finally we compared the differences between each group at the four specified time points (−10–0 min, 0–10 min, 20–30 min and 50–60 min). Baseline levels (−10–0 min) showed no significant differences between the responses of the five different stimulation frequencies ($F<0.001$; df=4, 45; $p>0.05$) as would be expected. However, there were significant differences between the five stimulating frequencies immediately after HFS (0 to 10 min post-HFS; $F=36.953$; df=4, 45; $p<0.001$). Tukey *post-hoc* analysis revealed that the 50 Hz and 100 Hz groups had significantly higher responses compared to the other three groups (all $p<0.01$), while the 5 Hz and 10 Hz groups had significantly higher responses than 1 Hz only (both $p<0.01$).

Looking at the middle time period after HFS (20 to 30 min post-HFS) again showed a significant effect for stimulation frequency ($F=37.558$; df=4, 45; $p<0.001$). Tukey *post-hoc* analysis revealing a similar pattern: the 50 Hz and 100 Hz groups displayed significantly higher responses compared to

the other stimulation groups (all $p<0.01$) and, the 5 and 10 Hz groups showing higher responses than the 1 Hz group (both $p<0.01$).

A final one-way ANOVA analysing the 50 to 60 min post-HFS recording period revealed further significant differences between the groups ($F=31.720$; df=4, 45; $p<0.001$) that are summarised in Fig. 1f. At this stage, Tukey *post-hoc* analysis showed that both the 50 Hz and 100 Hz groups had higher levels of potentiation compared to all other groups (all $p<0.01$), while the 10 Hz group had significantly lower responses compared to all groups (all $p<0.01$) except 1 Hz group ($p>0.05$). These results would suggest that higher stimulation frequencies are required to induce LTP in the CA1 to perirhinal cortex pathway but that we were unable to induce LTD with lower frequencies.

2.2. *Effect of different stimulation frequencies on pre- and post-stimulation paired-pulse facilitation*

Baseline PPF values were initially compared across groups to ensure consistency of response. A main effect of interval was found ($F=27.25$, df=5, 125, $p<0.01$) but neither a group ($F=1.633$, df=4, 25, $p>0.05$) nor a Group X interval interaction effect was noted ($F=1.32$, df=20, 125, $p>0.05$). Significant facilitation effects were demonstrated at the 20 ms, 40 ms, 60 ms, 120 ms IPIs (all $p<0.01$), with facilitation peaking at the 40 ms IPI. These baseline effects were very similar to those described by us previously in this pathway (Kealy and Commins, 2009).

We then compared the baseline PPF values to those recorded 1 h post-HFS in order to determine whether any changes in synaptic strength could be localised pre- or postsynaptically. Baseline versus post-HFS was analysed using a 2×6×5 mixed factorial ANOVA with time (baseline and post-HFS) and interpulse interval (IPI) (20 ms, 40 ms, 60 ms, 120 ms, 240 ms and 480 ms) as within-group measures and stimulation frequency (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz) as a between-groups measure (Fig. 2). There was no significant effect found for time ($F=3.896$; df=1, 25; $p>0.05$) or for stimulation frequency ($F=1.344$; df=4, 25; $p>0.05$) but there was a significant effect found for IPI ($F=43.096$; df=5, 125; $p<0.001$). Finally, no significant interaction effects were found between time and stimulation frequency ($F=0.416$; df=4, 25; $p>0.05$), time and IPI ($F=2.217$; df=5, 125; $p>0.05$) or for IPI and stimulation frequency ($F=1.549$, df=20, 125; $p>0.05$).

2.3. *Effect of different stimulation frequencies on BDNF levels*

We first compared BDNF levels in the area CA1 of the hippocampus using a 2×5 mixed factorial ANOVA, with hemisphere (stimulated and unstimulated hemispheres) as the within-group measure and stimulation frequency (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz) as the between-groups measure. There was no significant effect for hemisphere ($F=3.534$; df=1, 25; $p>0.05$). However, there was an overall effect for stimulation frequency ($F=5.319$; df=4, 25; $p<0.01$) but there was no interaction effect found between hemisphere and stimulation frequency ($F=1.350$; df=4, 25; $p>0.05$). Fig. 3a compares the mean percentage increase/decrease of BDNF concentration in the stimulated hemisphere compared to the unstimulated side for each group. Although no significant differences between the groups were observed ($F=1.101$, df=4, 25, $p>0.05$), a positive correlation between the percentage change and stimulus frequency was noted ($p<0.05$).

BDNF levels in the perirhinal cortex were also compared using a 2×5 mixed factorial ANOVA with hemisphere (stimulated and unstimulated hemispheres) again as the within-group measure and stimulation frequency (1 Hz, 5 Hz, 10 Hz, 50 Hz and 100 Hz) as the between-groups measure. There was no significant effect found for hemisphere ($F=0.723$; df=1, 25; $p>0.05$) but there was a significant effect found for stimulation frequency ($F=5.111$; df=4, 25; $p<0.01$) and there was also a significant interaction effect found between hemisphere and stimulation frequency ($F=5.901$; df=4, 25; $p<0.01$). Dependent *t*-tests demonstrated that in the 1 Hz group, stimulation lead to a significant decrease in BDNF levels ($t=3.567$; df=5; $p<0.05$). Additionally, stimulation lead to a significant increase in BDNF levels in the 10 Hz group ($t=-10.563$; df=5; $p<0.001$). Again, Fig. 3b summarises these results demonstrating the mean percentage change in BDNF concentration in the stimulated compared to the hemisphere side and revealing an overall significant difference between the groups ($F=2.770$, df=4, 25, $p<0.05$) with *post-hoc* tests demonstrating that the percentage change in the 10 Hz group was significantly different to the 50 Hz group.

3. Discussion

As shown previously, using a HFS protocol, LTP can be induced along the CA1 to perirhinal cortex pathway (Kealy and Commins, 2009) and here we have demonstrated that LTP can be induced at a number of different stimulation frequencies in an activity-dependent manner. Higher frequencies (50 Hz and 100 Hz) induced robust LTP of a similar level to LTP observed following 250 Hz HFS. Short-term plasticity in the form of PTP was also observed in these groups. LFS either failed to induce LTP (10 Hz) or low levels of potentiation were seen at the end of the 1 h recording period (1 Hz and 5 Hz). In all three LFS groups, there was no PTP observed which suggests that PTP requires a rigorous stimulation protocol in order to be induced in this projection. We also suggest that because there was no change in post-stimulation PPF compared to baseline PPF in any stimulation group, any long-term plastic changes observed in these groups are predominantly postsynaptic in nature.

The most striking finding of this study was the absence of LTD induction following LFS. This is contrary to what we had hypothesised as LTD has been demonstrated in other areas of the neocortex. For example, in the entorhinal cortex both LFS and pairing of presynaptic LFS and postsynaptic depolarisation can induce LTD (Deng and Lei, 2007) and in the perirhinal cortex there have been multiple reports of LTD being induced (Cho et al., 2000b, 2002). In addition, LFS of the area CA1 results in the induction of LTD in the CA1-entorhinal cortex projection (Craig and Commins, 2007). Although LTD has not been described in the CA1 to perirhinal cortex projection previously, theta-pulse stimulation (TPS) has been shown to transiently depotentiate EPSPs that were previously exhibiting LTP (Cousens and Otto, 1998).

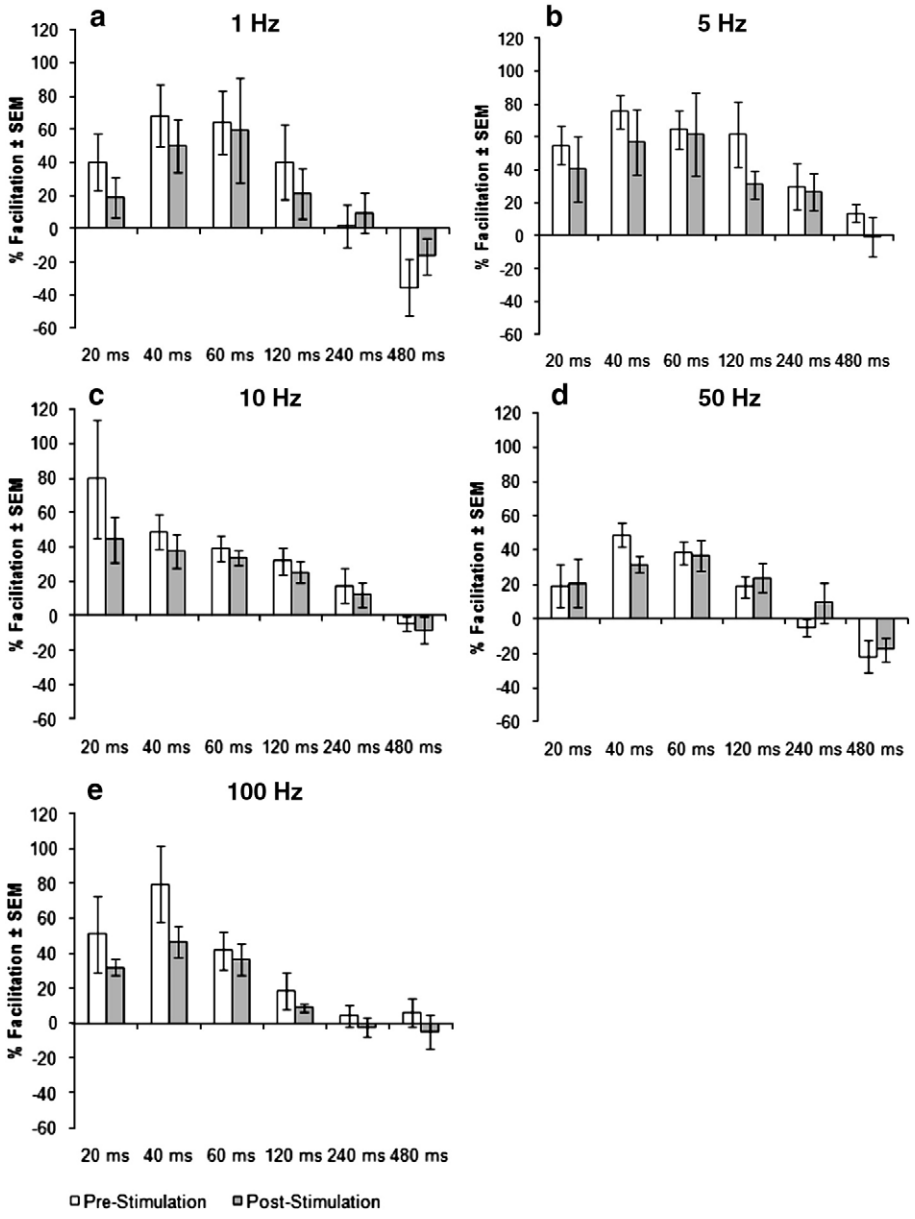

Fig. 2 – Comparison of pre-stimulation paired-pulse facilitation (PPF) values to post-stimulation PPF values in the CA1 to perirhinal cortex projection in the five different stimulation frequency groups: (a) 1 Hz; (b) 5 Hz; (c) 10 Hz; (d) 50 Hz; and (e) 100 Hz. There were no significant effects found for time in any group, indicating that the locus of change for synaptic plasticity was largely postsynaptic in nature. There were no significant effects for stimulation frequency, indicating that the locus of change for synaptic plasticity did not alter with different stimulation frequencies.

However, the induction of LTD has a track record of being difficult with other studies showing that it is not always possible to induce *in vivo*; LFS in area CA1 and the dentate gyrus failed to result in LTD in the adult rat (Errington et al., 1995) and LFS and two-pulse stimulation of the area CA1 fails to induce LTD in the CA1 to subiculum projection (Anderson et al., 2000). The findings of Anderson et al. (2000) are pertinent to our findings presented here as they found that 1 Hz LFS led to a late-developing potentiation similar to the potentiation seen in the final 10 min recording period in our 1 Hz group. In the perirhinal cortex, it has been shown that LTD is dependent on the size of intracellular Ca^{2+} increases (Cho et al., 2000a) which suggests that that a certain threshold of Ca^{2+} release must be reached in order for a given stimulation protocol to induce either LTD or LTP. In addition, Cho et al. (2000a) found that perirhinal LTD and LTP were induced via separate mechanisms and as such LTD and LTP in the perirhinal cortex may not represent two ends of the same activity-dependent process. In addition, perirhinal LTD can be blocked by previous exposure to learning (Massey et al., 2008) and is dependent on previous visual experience (Jo et al., 2006). These examples show how sensitive the BCM threshold is to shifting following experience and this sensitivity may explain why LFS in this projection failed to induce LTD. Changes in methodology might overcome this, such as, using two trains of LFS to induce LTD (one train to alter the metaplasticity of the projection,

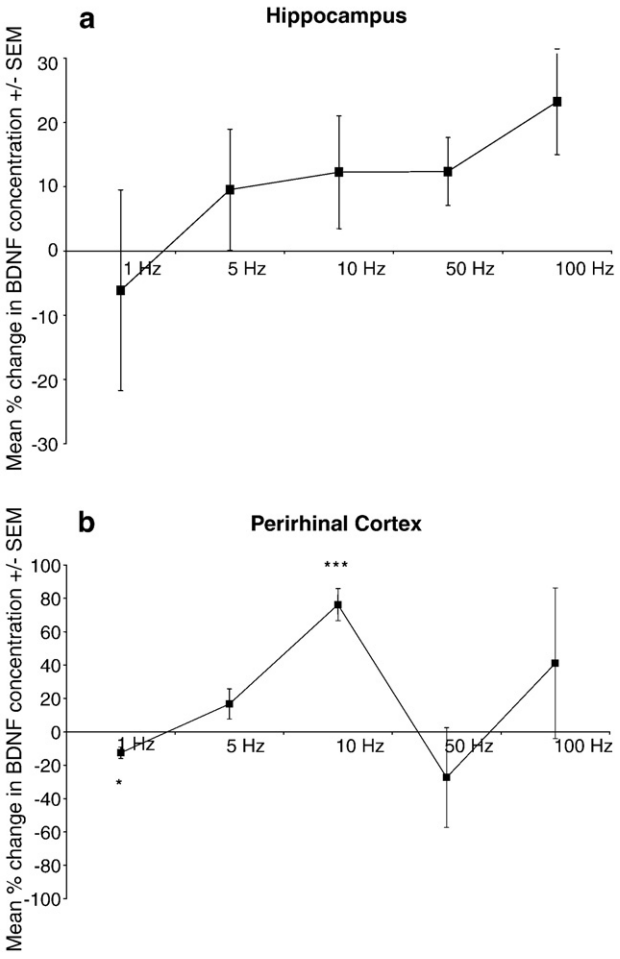

Fig. 3 – Mean percentage increase or decrease in BDNF concentration in the stimulated hemisphere of the hippocampus (a) and perirhinal cortex (b) compared to the unstimulated contralateral hemisphere. $^{*}p<0.05$; $^{***}p<0.001$.

perhaps by reducing available BDNF and altering glutamate receptor distribution and another to induce LTD (see Craig and Commins, 2007) or indeed by using younger animals (Errington et al., 1995).

BDNF has been shown to regulate hippocampal LTP by enhancing synaptic responses to HFS (Figurov et al., 1996) and alter the threshold for synaptic plasticity (Ikegaya et al., 2002). Although early reports had suggested that the presence of BDNF alone was enough to induce potentiation (Kang and Schuman, 1995a,b), this finding has not been replicated in other laboratories (see Patterson et al., 1996; Figurov et al., 1996, see Minichiello, 2009 for a comprehensive review). The lack of LTD observed at lower frequencies in our study may be explained by the presence of BDNF, as it has been demonstrated that application of BDNF *in vitro* can prevent the induction of LTD (Akaneya et al., 1996; Huber et al., 1998; Kinoshita et al., 1999). Furthermore, LTD induction has been associated with a concurrent reduction of BDNF in the perirhinal cortex (Aicardi et al., 2004). Taken together, these studies suggest that BDNF signalling must drop below a certain level in order for LTD to be induced, either by reductions in BDNF levels or by attenuating BDNF signalling downstream (e.g. inactivation of TrkB or MAPK signalling. Unfortunately, with the technique used in our study (i.e. ELISA analysis), we are unable to state definitely how BDNF and plasticity in the CA1-perirhinal pathway are related. Combined with the fact that BDNF effects are both local and time dependent (Bramham et al., 1996), makes interpretation of the exact role of BDNF in this projection difficult.

In this study, although there was no difference in BDNF concentration in the stimulated compared to the unstimulated hemisphere (though it is known that unilateral LTP can trigger bilateral increases in BDNF, Bramham et al., 1996) there was a correlation between stimulation frequency and the magnitude of the stimulation-induced changes in BDNF levels in the area CA1. This correlation hints at a molecular biphasic effect with a modifiable threshold level (something akin to the BCM model for synaptic plasticity), whereby low levels of frequency stimulation leads to decreased BDNF concretion and whereas higher levels of frequency stimulation leads to increased BDNF (significant increases were observed in area CA1 following 250 Hz stimulation protocol, see Kealy and Commins, 2009). This suggestion should be explored with other biochemical markers and along other projections. Furthermore, we suggest that any plastic changes that occur in the CA1-perirhinal cortex may be a result of post rather than presynaptic changes. This suggestion is highlighted by the fact that we found no significant differences in PPF pre and post-stimulation. However, we should be cautious in this interpretation because in addition to changes in presynaptic release probability, paired-pulse responses can be affected by many other factors including, for example, the recruitment of polysynaptic circuits (Shyu and Vogt, 2009). Interestingly we find significant changes in BDNF concentration in the perirhinal cortex of the stimulated compared to the unstimulated hemisphere in a number of frequency groups (1 Hz and 10 Hz). These changes, however, did not follow a predicted pattern, for example, a large significant increase in BDNF levels in the perirhinal cortex following 10 Hz LFS was not accompanied by LTP. To explain these disparate findings, we posit that these changes in BDNF levels may underlie metaplasticity in this projection and that BDNF levels may not actually be directly predictive of LTP/LTD.

This metaplastic BDNF hypothesis is supported by the finding in the visual cortex where BDNF-induced blockade of LTD is prevented by tyrosine kinase (including TrkB) antagonism (Kumura et al., 2000) and inhibition of TrkB signalling *in vitro* subsequently lead to the induction of LTD (Jiang et al., 2003) showing that regulation of LTD may occur downstream of BDNF itself. Endocannabinoid-induced LTD can be impaired with BDNF application and it was confirmed that LTD could be induced by blocking the TrkB receptor (Huang et al., 2008). In the developing visual cortex in the rat, blockade of the TrkB receptor prevents the induction of LTP but the strength and form of LTD in the same tissue were unaffected (Sermasi et al., 2000). This suggests that the BDNF and its TrkB receptor are required for LTP and their absence allows for LTD induction to occur more readily.

Complementing these findings, deletion of the gene for the p75 neurotrophin receptor (the universal neurotrophin receptor) in mice results in an impairment of LTD in the area CA1 (Woo et al., 2005) suggesting that neurotrophins, although perhaps not BDNF but other members of the protein family which have been suggested to play different roles in synaptic plasticity (Castrén

et al., 1993), are involved in the induction of LTD through the p75 receptor. As blockade of tyrosine kinase receptors in general still allowed for LTD induction (Kumura et al., 2000), the case for p75 playing a greater role in LTD is made stronger. Further to this, different forms of BDNF may also play distinct roles in plasticity. BDNF is initially secreted as a precursor proBDNF before mature BDNF is generated. Mature BDNF binds the receptor TrkB, whereas proBDNF binds p75 (Lu, 2003). Through these two receptors pro- and mature BDNF elicit different cellular responses with proBDNF-p75 binding, for example, facilitating hippocampal LTD (Woo et al., 2005). Future research in this projection could look at the roles played by different forms of BDNF and its receptors in modulating synaptic plasticity.

Lastly, it could be that this projection is electrophysiologically excitatory in nature and that LTD is just difficult to induce. Evidence for this comes from the projection's readiness to induce LTP (Cousens and Otto, 1998; Kealy and Commins, 2009) and the lack of LTD using LFS protocols shown previously to induce LTD. In the projections going from the hippocampus to the entorhinal cortex, the projections originating in the distal CA1 and proximal subiculum, and terminating in the lateral entorhinal cortex show similar 'excitability' (ability to sustain LTP readily and with limited LTD) whereas those originating in the proximal CA1 and distal subiculum, and terminating in the medial entorhinal cortex showed a greater tendency for electrophysiologically 'inhibitory' activity (greater tendency to show LTD, see Craig and Commins, 2007). As the lateral entorhinal cortex *anatomically* shows strong interconnectivity with the perirhinal cortex and the medial entorhinal cortex receives input from the postrhinal cortex (Insausti et al., 1997; Burwell and Amaral, 1998) and there seems to be a segregation of projections connecting the hippocampus and the entorhinal cortex (Witter et al., 2000), we suggest that the CA1 to perirhinal cortex projection forms part of the CA1/subiculum to lateral entorhinal cortex circuit. Therefore a tendency towards potentiation over depression may be expected. We predict that the postrhinal cortex is most likely associated with the hippocampus to medial entorhinal cortex circuit and we hypothesise projections from the hippocampus to the postrhinal cortex to exhibit depression more readily. While it seems clear that, in general, hippocampal–parahippocampal projections can be segregated along two parallel pathways anatomically (Witter et al., 2000) and perhaps, as suggested above, electrophysiologically, it is difficult to know at present whether this segregation is also reflected at a functional level. It is known that there is a functional difference along the longitudinal axis of the hippocampus, with the dorsal hippocampus involved more in information processing and the ventral hippocampus involved in emotion and stress (Fanselow and Dong, 2010), more research is needed to examine functional differences along the hippocampal–parahippocampal parallel projections.

4. Experimental procedures

4.1. Surgery

Adult male Wistar rats ($n=30$; approximately 3 months old; weight: 300–400 g; Biomedical Unit; University College Dublin) were anaesthetised using urethane (ethyl carbamate; 1.5 mg/kg; i.p.; Sigma) and mounted on a stereotaxic frame. An incision was made to expose the skull and burr holes were made to allow the electrodes to be inserted into the correct coordinates (Paxinos and Watson, 2005).

A stainless bipolar stimulating electrodes (50 μm diameter), insulated apart from the tip, were aimed at the area CA1. Stainless wire recording electrodes (50 μm diameter) were aimed at the perirhinal cortex. Coordinates for both electrodes were based on previous studies on this projection (Cousens and Otto, 1998; Kealy and Commins, 2009); the stimulating electrode (CA1) was inserted 6.3 mm posterior to Bregma, 5.5 mm lateral to the midline and lowered to a depth of 2.2 mm measured from the surface of the brain. The recording electrode (perirhinal cortex) was inserted 5.2 mm posterior to Bregma, 4.3 mm lateral to the midline and lowered to a depth of 5.0 mm measured from the surface of the brain. The recording electrode was inserted at an angle of 17° to increase the chances of hitting the correct population of cells that are part of the monosynaptic CA1 to perirhinal projection described previously (Cousens and Otto, 1998; Kealy and Commins, 2009).

4.2. Stimulation and data acquisition

Signals were filtered between 1 Hz and 1 kHz and then amplified (DAM-50 differential amplifier, World Precision Instruments, Hertfordshire, UK). Recordings were digitised using a PC running Spike2 (version 5.02, CED, Cambridge, UK) connected to a CED-1401 interface (CED, Cambridge, UK). In analysing the field excitatory postsynaptic potentials (fEPSPs), the slope of the response was measured (Gooney and Lynch, 2001). The slope was calculated from the middle two-thirds of the downward-deflecting component of the response.

Field EPSPs were evoked by stimulating with a square-wave (constant current pulse of 0.1 ms duration at a frequency of 0.05 Hz). Although both Population Spike and fEPSPs were monitored, the incidences of the occurrence of population spike remained low (less than 5% of cases). By means of input/output curve determination the maximum fEPSP was found for each individual animal. The intensity of stimulus was then set at a level that evoked a fEPSP slope of 50–60% of the maximum. This level is similar to that we have used before (Craig and Commins, 2005, 2006) on the CA1 and subicular to EC pathway, Cousens and Otto (1998) on the CA1–perirhinal pathway and to that used by other authors in area CA1 (Wöhrl et al., 2007).

Baseline paired-pulse facilitation (PPF) effects were measured after the electrodes were allowed to settle for 10 min. Pairs of stimuli were then delivered with various interpulse intervals (IPIs) of 20, 40, 60, 120, 240 and 480 ms. The PPF value was calculated by taking the value of six slopes values from the first stimuli out of the pairs (fEPSP1) for a given IPI and then normalising the average of six slope values from the second stimuli from the pairs (fEPSP2) with the resulting value expressed as a percentage (Commins et al., 1998a). Following this, baseline measurements were induced at a rate of 0.05 Hz for another 10 min.

Following baseline recording baseline responses to single stimuli (0.05 Hz) over 10 min, each group ($n=6$ in each) was treated using one of five possible stimulation protocols (1 Hz, 5 Hz, 10 Hz, 50 Hz or 100 Hz). Each stimulation protocol contained a constant number of stimuli (900) and varied only

in the frequency by which the pulses were delivered. Following these stimulation protocols, recordings were made at 0.05 Hz for 1 h. Following this hour of recording, post-HFS PPF recordings were made using the same protocol as the pre-HFS PPF recordings. The stimulus intensity for all experimental interventions (PPF and the five stimulation frequencies listed above) was set at baseline intensity. Changes in fEPSP slope were assessed by measuring the slope of the response post-HFS compared to baseline response.

4.3. *Brain-derived neurotrophic factor enzyme-linked immunosorbent assay (ELISA)*

After each experiment, all animals were sacrificed by decapitation and their brains were immediately removed. The brains were then dissected on ice. An area of approximately 3 mm^3 was removed from both area CA1 and perirhinal cortex that contained the final resting place of both the stimulating and recording electrode respectively. Equivalent sized areas in the same animal's unstimulated hemisphere were also removed for subsequent analysis. These samples were frozen and stored in Krebs-CaCl2/dimethyl sulfoxide (DMSO; Krebs solution was made using pre-prepared formula; all from Sigma, Ireland). All samples were later washed in Krebs-CaCl2 and homogenised. 10 μl aliquots of each sample were analysed using a Bradford protein assay in order to determine total protein concentration. Utilising these results, the sample solutions were normalised to be equal in concentration and an enzyme-linked immunosorbent assay (ELISA) for BDNF was performed using a BDNF Emax ImmunoAssay System kit (Promega Corporation), following the manufacturer's protocol.

4.4. *Statistical analysis*

A series of dependent *t*-tests and repeated measures analyses of variance (ANOVAs) with the appropriate post-hoc test (Tukey at the 5% level of significance) were performed using SPSS 15.0 for Windows (SPSS Software, Seattle, WA, USA). A star-rated system was used where appropriate ($^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$).

4.5. *Ethical considerations*

Laboratory procedures for the maintenance and experimentation of animals conformed to the Department of Health (Ireland) guidelines and the European directive 86/609/EC. Every effort was made to minimise the suffering and the number of animals used in this study.

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