Visual human long-term potentiation

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Abstract

Long-term potentiation (LTP) is the synaptic mechanism that underlies learning and memory formation. LTP has been extensively explored by studies that was conducted on animals. Furthermore, LTP has been studied in human cortical tissue obtained from patients prior to going into surgery. However, due to the invasiveness of this method, the study of LTP in humans has not been explored in as much depth as it has in animals.

Recently however, an increasing number of studies have shown that LTP-like effects can be induced using high-frequency sensory stimulation in humans. Thus, there is considerable potential for sensory stimulation to be used as a non-invasive alternative to induce and measure LTP in humans (hLTP). The effect reported from the studies that utilized this method so far has strongly implied this effect is analogous to the LTP as found in animals and human cortical tissue. Comparatively, this method of examination is still relatively new. This calls for further experiments to be conducted to extend the understanding of this paradigm and the effect documented using these protocols. The non-invasive hLTP paradigm has the potential, not only to explore LTP in healthy human participants, but to further the understanding of learning and memory formation.

While the literature at present suggest this effect to be localised to the cortical region, this has yet to be clearly determined. Therefore, one of the two key aims of this thesis was to examine where visual hLTP is occurring in the brain using the non-invasive paradigm. Results from this set of experiments strongly indicated hLTP to be occurring in the visual cortical region.

Furthermore, while the study of stress hormones in relation to memory performance has received substantial amount of attention, adrenal steroids influence on LTP has been less explored in healthy human participants. The non-invasive technique appears to be highly promising as a method to examine LTP in healthy human participants. Therefore, the second

key aim of this thesis was to investigate the influence of cortisol on hLTP. The results gave some indication that less stress is correlated with better learning and memory formation.

The potential of the rapid sensory stimulation paradigm is just being uncovered. Furthermore, this paradigm could be highly useful if applied to neurocognitive disorders in the clinical settings. A discussion of this is presented at the end of this thesis.

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Chapter 1: General Introduction

1.1 Long-Term Potentiation

While Aristotle suggested that memories left physical traces or imprints, it was Santiago Ramon y Cajal, a Spanish neuroanatomist who was the first to propose that memory consolidation must be achieved by enhancing the communication efficiency of existing neurons (Bliss & Collingridge, 1993; Sorabji, 2004). Essentially, the storage of new memories becomes more difficult as we age due to the fact that the formation of new neurons in the human brain declines as one gets older.

In 1949, Donald Hebb did further studies to extend the work of Cajal (Bliss & Collingridge, 1993; Spatz, 1996). Hebb proposed that among the existing neuronal connections, when two cells are activated simultaneously, the communication between these cells can be strengthened. The Hebbian model is commonly described as “cells that fire together are wired together”.

In 1996, Lomo initially aimed to examine the synaptic connections between the perforant pathways to the dentate gyrus in the rabbit hippocampal formation during in vitro experimentation. He unexpectedly discovered that when he presented a short high-frequency burst of electrical stimulation to presynaptic fibers it resulted in the enhanced transmission in post-synaptic cells. The enhancement in the transmission between the pre and post synaptic cells lasted for hours.

Following on from Lomo (1996), in 1973, Bliss and Gardener-Medwin, and Bliss and Lomo demonstrated long-lasting synaptic communication efficiency in granule cells of the dentate gyrus following high-frequency repetitive electrical stimulation to the rabbits’ hippocampal formation. The enhancement was estimated to last up to 10 hours in anesthetized rabbits (Bliss & Lomo, 1973), and up to 16 weeks in unanesthetized rabbits (Bliss & Gardner-Medwin, 1973). This phenomenon, whereby repeated stimulation can result in synaptic

strengthening leading to more efficient communication between two neurons was originally known as “long-lasting potentiation”. However, this process is now referred to as “long-term potentiation” (LTP) (Cooke & Bliss, 2006; Bliss & Collinridge, 1993; Bliss & Lomo, 1973; Malenka, 2003; Spatz, 1996).

LTP is thought to reflect the manifestation Hebb’s concept concerning the increased strength in communication between cells when the cells are activated simultaneously. Consequently, LTP became increasingly popular as a candidate to study learning and memory formation. LTP was initially, and predominately, studied in the hippocampus (e.g. Bliss & Collingridge, 1993). Examination of LTP at both the cellular and molecular level in animals repeatedly showed that the hippocampus is involved in learning. Hence, it is suggested that LTP plays a significant role in the consolidation of memory (Abraham et al., 2002; Malenka & Nicoll, 1999; Malenka 2003). In other words, LTP is thought to underlie learning and memory formation (Cooke & Bliss, 2006; Bliss & Collinridge, 1993; Bliss & Lomo, 1973; Malenka, 2003; Spatz, 1996).

The following is a review of the properties of LTP. The review includes a coverage of the molecular basis, different phases, and the three main properties (co-operativity, input-specificity, and associativity) of LTP.

1.2 Molecular Basis of Long-Term Potentiation

The underlying biochemical process behind LTP is still being researched, although a widely accepted model has emerged (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999). At the start of the biochemical path of LTP, post-synaptic N-methyl-D-aspartate (NMDA) receptors, one of the two glutamatergic receptors present in the post-synaptic cell membranes are activated. The other glutamate receptor present in post-synaptic cell membranes is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropinate (AMPA) receptor.

At the resting membrane potential, magnesium ions bind to NMDA receptors and inhibit ion movements through the channels (Malenka & Nicoll, 1999; Nowak, Bregestovski, Ascher, Herbet, & Prochiantz, 1984). When a cell fires, glutamate neurotransmitters get released from the pre-synaptic cell and travel across the synapse to bind onto glutamate receptors (NMDA and AMPA). Once AMPA receptors are activated, the influx of sodium ions will open the ion channel to allow for the depolarization of the post-synaptic membrane. When there is only weak stimulation, only AMPA receptors get activated, this will lead to the postsynaptic neuron being slightly depolarized. While being only slightly depolarized, even when glutamate neurotransmitters binds to NMDA receptors few sodium ions can flow freely through the channel. During this situation, AMPA receptor will mediate the excitatory postsynaptic potential.

If the depolarization current is strong enough, AMPA receptors can depolarize the membrane which will result in magnesium ions leaving via the NMDA receptor channels. The binding of glutamate to NMDA receptors will allow the influx of calcium and sodium ions. It is the influx and the rise of calcium ions that results in LTP (Lynch, Larson, Kelso, Barrionuevo, & Schottler, 1983; Malenka & Nicoll, 1999; Malenka, Kauer, Zucker, & Nicoll, 1988).

There is increasing support for this molecular mechanism that underlies LTP. Such as the administration of an NMDA receptor antagonist can prevent the occurrence of LTP (Bliss & Collingridge, 1993; Collingridge, Kehl, & McLennan, 1983; Gustafsson & Wigstrom, 1988; Larkman & Jack, 1995; Madison, Malenka, & Nicoll, 1991; Nicoll & Malenka, 1995; Nicoll, Kauer, & Malenka, 1988; Teyler & DiScenna, 1987). Along the same vein, calcium chelators can prevent the occurrence of LTP by inhibiting the increase in the level of intracellular calcium (Lynch *et. al.*, 1983; Malenka *et al*., 1988; Malenka, Lancaster, & Zucker, 1992; Yang, Tang, & Zucker, 1999). Conversely, increasing postsynaptic calcium

results in LTP (Lynch *et. al.*, 1983; Malenka *et al*., 1988; Malenka, Lancaster, & Zucker, 1992; Yang, Tang, & Zucker, 1999).

Although the literature strongly suggests LTP is NMDA receptor dependent (e.g. Artola & Singer, 1987; Heynen & Bear, 2001), Grover and Teyler (1990) reported that LTP could still be achieved even when NMDA channels were blocked using 2-amino-5-phosphonovaleric acid (APV). After further examination, Grover and Teyler (1990) showed that this type of LTP could be prevented with an L-type voltage-dependent calcium channel (VDCC) antagonist (i.e. Nifedipine). This implied that LTP could be achieved with either NMDA receptor or VDCC. While LTP can be prevented from occurring via either pathways with calcium chelators (Morgan & Teyler, 1999), LTP achieved through NMDA or VDCC are distinguished based on the rate of stimulation. NMDA receptor dependent LTP requires a lower induction rate to occur (~25Hz) than VDCC LTP, which requires a much higher rate of stimulation (200Hz) (Grover & Teyler, 1990). Due to the induction rates that are employed in the experiments conducted as part of this thesis, this thesis focused on LTP that is NMDA dependent.

1.3 Phases of Long-Term Potentiation

LTP is segregated into three phases. Each phase is distinguished based upon the cellular processes that occur. Specifically, phases are divided based on whether or not new proteins are produced (Anwyl, Mulkeen, & Rowan, 1989; Bliss & Collingridge, 1993; Frey, Huang, & Kandel, 1993; Kelleher, Govindarajan, & Tonegawa, 2004; Malenka, 1991; Reymann & Frey, 2007; Soderling & Derkach, 2000).

The first phase of LTP is short-term potentiation (Malenka, 1991). Short-term potentiation is characterized by the involvement only of existing proteins (Malenka, 1991). In other words, short-term potentiation does not result in the production of new proteins (Anwyl,

Mulkeen, & Rowan, 1989; Soderling & Derkach, 2000). Short-term potentiation occurs when the necessary influx of intracellular calcium does not quite reach the threshold to induce more lasting LTP, (Frey, Krug, Reymann, & Matthies, 1988; Frey et al., 1993; Kauer, Malenka, & Nicoll, 1988; Kelleher et al., 2004; Krug, Lossner, & Ott, 1984; Malenka, & Nicoll, 1999; Nguyen, Abel, & Kandel, 1994; Reymann & Frey, 2007; Vickers, Dickson, & Wyllie, 2005). This short-lasting effect decays over 15-30mins following induction (Anwyl, Mulkeen, & Rowan, 1989; Malenka, 1991; Soderling & Derkach, 2000).

The second phase of LTP is referred to as early-LTP (Malenka, 1991). Early-LTP lasts for 1-3 hours on average (Bliss & Collingridge, 1993; Kelleher et al., 2004; Reymann & Frey, 2007; Soderling & Derkach, 2000). Early-LTP is usually induced by a short one-off burst of rapid stimulation (Kelleher et al., 2004). Protein kinase can alter the level of intracellular calcium achieved that determines the occurrence of LTP. For early-LTP to occur, phosphorylation of protein kinases are necessary (Frey et al., 1988; Frey et al., 1993; Kauer et al., 1988; Kelleher et al., 2004; Krug et al., 1984; Nguyen et al., 1994; Reymann & Frey, 2007; Vickers et al., 2005). Consequently, when protein kinase activity is prevented, short-term potentiation occurs (Lovinger, Wong, Murakami, & Routtenberg, 1987; Malenka, Kauer, Perkel, Mauk, Kelly, Nicoll, & Waxham, 1989; Malinow, Madison, & Tsien, 1988; Reymann, Davies, Matthies, Kase, & Coilingridge, 1990).

Finally there is phase three of LTP or late-LTP (Malenka, 1991). Late-LTP lasts from approximately several hours to weeks (Bliss & Collingridge, 1993; Kelleher et al., 2004; Reymann & Frey, 2007; Soderling & Derkach, 2000). There has been LTP reported to last up to a year following successful induction (Abraham et al., 2002). Other than the time period that early-LTP can last which distinguishes it with late-LTP, late-LTP is typically shown to have larger amplitudes. Furthermore, while both early-LTP and late-LTP is NMDA-receptor dependent, they are also differentiated by the stimulation rate they require for it to occur.

Early-LTP require a single burst of high-frequency stimulation. On the other hand, late-LTP typically requires a longer train of rapid stimulation (Kelleher et al., 2004). The more extended phase of stimulation is required for the protein synthesis that is necessary for late-LTP to occur (Frey et al., 1988; Frey et al., 1993; Kauer et al., 1988; Kelleher et al., 2004; Krug et al., 1984; Malenka, 1991; Nguyen et al., 1994; Reymann & Frey, 2007; Vickers et al., 2005). Support for this biochemical process come from studies that administered protein synthesis inhibitors soon after rapid stimulation. These studies did not report the occurrence of late-LTP (Frey & Morris, 1997; Huang & Kandel, 1994; Kelleher, Govindarajan, Jung, Kang, & Tonegawa, 2004; Scharf, Woo, Lattal, Young, Nguyen, & Abel, 2002). Additionally, when protein synthesis inhibitors were applied prior to induction, only early-LTP was evident (Frey & Morris, 1997; Huang & Kandel, 1994; Kelleher et al., 2004).

1.4 Properties of Long-Term Potentiation

In general, there are three key properties of LTP. First being co-operativity, second is input-specificity, and last is associativity. This section will present the details in regards to what each property is. Furthermore, there will be a description of the neurophysiology that occurs at the molecular level for each property of LTP.

The first key property of LTP is co-operativity (Bliss & Collingridge, 1993; Malenka, 2003). LTP cannot be induced when there is only a weak activation of a small number of presynaptic fibers. In other words, a threshold of stimulation must be crossed to successfully elicit LTP. In order to reach the required threshold, an adequate number of presynaptic fibers must be simultaneously activated (i.e. co-operate) to elicit LTP at specific synapses. The requirement of the activation of multiple fibers to achieve potentiation is known as co-operativity (Bliss & Collingridge, 1993; Malenka, 2003). At the molecular level, co-operativity requires a strong depolarizing current to drive magnesium ions out of NMDA

receptor channels and for the intracellular calcium level to rise in-order to induce LTP (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999).

The second key property of LTP is input-specificity. Potentiation will only be evident in the synapses that are active during the processing of a stimulus (Bliss & Collingridge, 1993; Malenka, 2003). The synapses that were not active during the processing of a stimulus will not get potentiated. Input-specificity describes the fact that LTP reflects local synaptic modifications (Bliss & Collingridge, 1993; Malenka, 2003; Malenka & Nicoll, 1999). It is the localized rise of the calcium ions in the dendritic spine that is the biochemical process that underlies input-specificity (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999).

The third and final key property of LTP is associativity. Even when synapses are stimulated below the threshold for LTP to occur, LTP can still be induced provided that there is simultaneous activation of another set of synapses on the same cell receiving rapid stimulation (Bliss & Collingridge, 1993; Malenka, 2003). At the molecular level, associativity occurs when a strong depolarizing current activates a set of synapses leading to the influx of calcium ions in the adjacent areas of the cell membrane resulting in LTP (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999). Associativity may be the underlying explanation as to how connections between memories are made (Bliss & Collingridge, 1993; Malenka, 2003). In summary, the three main properties of LTP are co-operativity, input-specificity and associativity.

1.5 Long-Term Depression

While rapid stimulation elicits LTP, repetitive stimulation at a lower frequency induces long-term depression (Bear, 1996; Dudek & Bear, 1992; Kemp, McQueen, Faulkes, & Bashir, 2000; Mulkey & Malenka, 1992; Raymond, 2007). Similar to LTP, long-term depression also requires the activation of NMDA receptors and a change in the level of post-

synaptic calcium ions. However, compared to LTP, long-term depression results from a much smaller influx of calcium (Bear, 1995; Bear & Malenka, 1994; Kirkwood & Bear, 1994; Mulkey & Malenka, 1992).

Long-term depression is likely involved with the process of preserving neuroplasticity through inhibiting the brain from being overly saturated by LTP (Stevens, 1990). Long-term depression is linked to the reduction in branching, dendritic length and spine density (Monfils & Teskey, 2004).

Long-term depression is also an important process in learning and memory formation (Braunewell & Manahan-Vaughan, 2001; Cook & Bliss, 2006; Malenka & Bear, 2004). While it is worthy to note that both long-term depression and LTP plays a significant role in human learning and memory consolidation (Braunewell & Manahan-Vaughan, 2001; Cook & Bliss, 2006; Malenka & Bear, 2004), this thesis focused on LTP.

1.6 Prior Study of Long-Term Potentiation

Following on from the initial demonstration and establishment by Bliss and Gardener-Medwin, and Bliss and Lomo in 1973, animals have been the most common option in which to explore LTP. LTP has been extensively studied at both the cellular and molecular levels over the years in a range of organisms (e.g. Abraham et al., 2002; Malenka & Nicoll, 1999; Malenka 2003). The early study of LTP utilizing animals has been rather invasive, commonly involving local field and intracellular potential recording methods. Because these methods are intrusive, research on humans has been difficult and over time researchers have tried to come up with techniques to examine LTP that are less invasive.

Employing electrical stimulation was the initial attempts to non-invasively induce LTP and were successful at eliciting LTP (Korn, Oda, & Faber, 1992; Oda, Charpier, Murayama, Suma, & Korn, 1995). Oda, Kawasaki, Morita, Korn, and Matsui (1998) presented auditory

tones and examined the response of goldfish Mauthner cell synapses before and after induction. Oda et al. (1998) found a significant increase in the post-synaptic response following induction (Oda et al., 1998). Oda et al. (1998) was one of the first to document successful non-invasive LTP induction by sensory stimulation. More importantly, Oda et al. (1998) managed to demonstrate that it is possible to non-invasively induce plasticity with high-frequency sensory stimulation. This LTP achieved through sensory induction is analogous to LTP reported following direct electrical stimulation.

In 2000, Zhang, Tao, and Poo conducted an experiment on developing tadpoles. Using intracellular recording, Zhang et al. (2000) monitored the neurons in the tadpoles' tectum. Zhang et al. (2000) removed the eye that is ipsilateral to the tectum then repeatedly stimulated the contralateral eye with a visual stimulus at varying luminance (i.e. a dimming light). They reported the activation of NMDA receptors and a raised post-synaptic response in the tectum cells. Zhang et al. (2000) argued the activity observed is similar to LTP. Zhang et al. (2000) documented the increase in response following stimulation to have lasted for approximately 1.5 hours. The most important implication from Zhang et al.'s (2000) experiment is that they have demonstrated that synaptic modification is possible following repetitive visual stimulation.

Later in 2002, Eyding, Schweigart, and Eysel examined area 17 and 18 of the cat's visual cortex. Eyding et al. (2002) began by mapping the receptive fields of the cells in the relevant areas of the visual cortex. Eyding et al. (2002) then performed co-stimulation by applying high-frequency visual stimulation to neurons in the primary regions and to the surrounding synapses. This was intended to achieve associative synaptic plasticity. Following induction, Eyding et al. (2002) remapped the receptive fields in the primary areas and adjacent regions. Findings from Eyding et al. (2002) showed an increase in size, modifications to the subfield structures, and a change in the response of the receptive fields.

Eyding et al. (2002) documented that these changes remained evident for approximately 1 hour and 40 minutes following rapid visual stimulation. Eyding et al. (2002) provided evidence to suggest that high-frequency visual stimulation was still capable of inducing synaptic modifications in the developed visual cortex.

Clapp, Eckert, Teyler and Abraham (2006) also reported that high-frequency visual stimulation can induce LTP-like effects in anesthetized rats. Clapp et al. (2006) recorded the intracortical field responses before and following rapid visual stimulation. Clapp and colleagues (2006) reported an increased in the response one hour following induction. Moreover, when followed up five hours following rapid sensory stimulation, the change in response remained evident. Additionally, an increase in the response was not found when Clapp et al. (2006) administered an NMDA antagonist 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid. This demonstrated that neuroplasticity achieved by rapid sensory stimulation is NMDA receptor dependent. This will be covered in more detail in a slightly later section.

Over the years, LTP has not only been documented in the visual cortex (e.g. Aroniadou & Teyler, 1991; Artola & Singer, 1987; Heynen & Bear, 2001; Hirsch & Gilbert, 1993; Kirkwood & Bear, 1994; Kirkwood, Dudek, Gold, Aizenman, & Bear, 1993; Kirkwood, Rioult, & Bear, 1996; Komatsu, Fujii, Maeda, Sakaguchi, & Toyama, 1998; Komatsu, Toyama, Maeda, & Sakaguchi, 1981; Tsumoto & Suda, 1979) but an increasing number of studies have shown LTP in other areas of the cortex as well. For example, LTP has been shown in the motor cortical region (e.g. Aroniadou & Keller, 1995; Baranyi & Szente, 1987; Froc, Chapman, Trepel, & Racine, 2000), the auditory cortex (e.g. Gerren & Weinberger, 1983; Kudoh & Shibuki, 1994; Kudoh & Shibuki, 1997), and the somatosensory region (e.g. Crair & Malenka, 1995; Kitagawa, Nishimura, Yoshioka, Lin & Yamamoto, 1997). LTP has also been documented in the amygdala (e.g. Huang & Kandel, 1998; Huang,

Martin, & Kandel, 2000; Racine, Milgram, & Hafner, 1983) and the medial geniculate nucleus (e.g. Gerren & Weinberger, 1983).

1.7 Adrenal Glands

Cortical functioning is influenced by activity in other bodily organs, for example the adrenal glands. The adrenal glands are two triangular-shaped organs found within the human body (Alderson & Novack, 2010; Het, Ramlow, & Wolf, 2005; Kuhlmann, Kirschbaum, & Wolf, 2005; Lupien & McEwen, 1997; McKay & Cidlowski, 2003; Sauro, Jorgensen, & Pedlow, 2003). The adrenal glands are positioned above the kidneys. When an organism is faced with stressors, the adrenal glands are activated. The adrenal glands also play a part in other functions of the body. Both glands consist of two unique structures – the adrenal cortex and the adrenal medulla. These structures differ in their locations and functions (Alderson & Novack, 2010; Lupien & McEwen, 1997; McKay & Cidlowski, 2003; Sauro et al., 2003).

The outer layer of the adrenal glands is the adrenal cortex (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003). The adrenal cortex is responsible for synthesising the hormones that are crucial for day to day functioning. Two key groups of corticosteroid hormones are produced by the adrenal cortex – glucocorticoids and mineralcorticoids (Alderson & Novack, 2010; Lupien & McEwen, 1997; McKay & Cidlowski, 2003; Sauro et al., 2003; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000).

Glucocorticoid are the hormones triggered by the pituitary gland and the hypothalamus (Alderson & Novack, 2010; Lupien & McEwen, 1997; McKay & Cidlowski, 2003; Sauro et al., 2003). There are two key types of glucocorticoids, first being hydrocortisone which is also commonly known as cortisol (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003; Vedhara et al., 2000). Hydrocortisone is

responsible for regulating the body's metabolic rate. In other words, how the system converts carbohydrate, fat, and protein to energy that the body can use. Hydrocortisone also plays a part in regulating blood pressure and the functioning of the cardiovascular system. The other type of glucocorticoids synthesised by the adrenal cortex is corticosterone (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003; Vedhara et al., 2000). Corticosterone functions together with hydrocortisone to fulfil its role in regulating the body's immune system and inhibiting inflammatory responses.

The other corticosteroid hormone synthesised by the adrenal cortex is mineralcorticoid. Aldoesterone is the key mineralcorticoid hormone. Aldosterone is responsible for regulating blood pressure (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003). It also plays a part in balancing and controlling the body's salt to water ratio. The adrenal cortex also synthesises a small amount of sex steroids, but the influence of these hormones are normally overridden by other sex hormones (i.e. estrogen and testosterone) (Alderson & Novack, 2010; Lupien & McEwen, 1997; Rohleder, Wolf, & Kirschbaum, 2003; Sauro et al., 2003).

The other structure of the adrenal glands are the adrenal medulla, it is the inner part of the adrenal glands (Alderson & Novack, 2010; Lupien & McEwen, 1997; McKay & Cidlowski, 2003; Sauro et al., 2003). The adrenal medulla synthesis hormones when the sympathetic nervous system is triggered by stressors (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003). The hormones produced by the adrenal medulla plays a role in regulating the response to physical and emotional stress. The adrenal medulla produce hormones in the more commonly known as "fight or flight" situation. It releases two key hormones – epinephrine and norepinephrine (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003).

Epinephrine is more commonly known as adrenaline (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003). Epinephrine is triggered when stressors are present. Adrenaline reacts to the stressor by raising the organism's heart rate and increasing the blood flow to the brain and muscles. Furthermore, epinephrine can convert glycogen to glucose in the liver to elevate the sugar level in the blood.

The second key hormone secreted by the adrenal medulla is norepinephrine, which is more commonly known as noradrenaline (Alderson & Novack, 2010; Lupien & McEwen, 1997; Sauro et al., 2003). Noradrenaline functions with adrenaline in reaction to stress. Noradrenaline is also involved in raising the blood pressure by constricting the blood vessels.

1.8 Corticosterone and Memory Performance

The adrenal steroids (cortisol in humans; corticosterone in animals) are involved in a range of roles within the endocrine system (Lupien & McEwen, 1997; Sauro et al., 2003). For example, adrenal steroids participate in regulating the body's metabolic rate (Lupien & McEwen, 1997; Sauro et al., 2003). And more importantly, when an organism is under stress the adrenal steroids prepares the body to react most appropriately according to the situational factors (Lupien & McEwen, 1997; Sauro et al., 2003). Over the years, there has been a rising interest in furthering our understanding of the relationship between stress hormones and memory. This line of research, which used animals as key subjects (in-particular rats), has reported a range of results in regards to the influence of stress hormones on memory performance. The variation in conclusions drawn from animal studies regarding the effect that corticosterone has on memory performance has motivated further investigation in order to bring more clarity to this relationship.

Starting at one end of the relationship, extremely low levels of corticosterone has been associated with impaired memory performance. Conrad, Lupien, Thanasoullis, and McEwen

(1997) wanted to explore the relationship between spatial memory performance and the level of corticosterone in rats. To do so, Conrad et al., (1997) compared Y-maze performance of a group of healthy control rats to a group of rats with their adrenal glands surgically removed. Conrad et al. (1997) reported that in comparison to the control rats, rats with their adrenal glands removed showed impaired performance. Furthermore, when corticosterone was administered to the rats that had their adrenal glands removed, performance improved drastically. Conrad et al.'s (1997) study suggest that low levels of corticosterone can negatively impact memory performance. Similar findings have been reported by other studies that prevented the production of corticosterone by removing the adrenal glands in rats (e.g. Oitzl & de Kloet, 1992; Roozendaal, Portillo-Marquez, & McGaugh, 1996). Moreover, reports of impaired spatial navigation have also been found in studies that have left the adrenal glands intact but administered drugs to prevent the synthesis of adrenal steroids (e.g. Oitzl & de Kloet, 1992; Roozendaal et al., 1996). Furthermore, this effect was reversed when corticosterone was administered (Roozendaal et al., 1996). These studies have provided further support for the influence of costicosterone on memory performance. Hence, the general conclusion is the lack of corticosterone can largely prevent learning and memory formation in animals.

While extremely low concentration of corticosterone can impair memory formation, elevated adrenal steroids can also negatively impact learning in animals. In 1996, Endo, Nishimura, and Kimura used the radial eight arm maze to examine the relationship between the corticosterone level and spatial learning memory in rodents. The experimental group of rats had corticosterone pellets implanted into their brain, which elevates the hormone level above normal. As a control, Endo et al. (1996) implanted cholesterol pellets into the brain of another group of rats. Endo et al. (1996) found that the rats that had the corticosterone pellets implanted into their brain required significantly more number of trials to perform at the same

level as the control group. This implied that a substantially raised level of adrenal steroids also negatively influences learning and memory performance in rodents.

Furthermore, other animal studies have raised cortisol levels by placing rodents under temporary physical discomfort in order to examine the relationship between adrenal steroids and learning. These studies have shown that an acute rise in corticosterone can result in either an impaired or enhanced memory performance (e.g. De Kloet, Oitzl, & Joels, 1999; Lupien & McEwen, 1997; Roozendaal, 2002; Wolf, 2003). De Quervain, Roozendaal and McGaugh (1998) examined rats learning in a water maze. A day following the initial training De Quervain et al. (1998) applied electric shocks to the rodents' feet prior to retention testing. As expected, the control rats demonstrated focused platform searching. However, compared to the control rats, the rats that received the foot shock prior to the memory retrieval test displayed a pattern of disorganized platform searching. In addition, when De Quervain et al. (1998) blocked the production of corticosterone by administering metyrapone to rats, these rats did not show the same pattern of disorganized performance during retention testing following the foot shock. Moreover, prior to retention testing, when De Quervain et al. (1998) administered corticosterone to control rats they displayed a searching pattern comparable to rats that received the electric foot shock. De Quervain et al. (1998) results suggest that temporary physiological stressors applied prior to memory retrieval can negatively influence memory performance.

On the contrary, when McCormick, McNamara, Mukhopadhyay, and Kelsey (1997) examined the temporary rise of adrenal steroids in rats with adrenal glands removed, McCormick et al. (1997) reported different results. In comparison to the control rats, McCormick et al. (1997) reported that an acute administration of corticosterone can reverse the spatial memory impairment evident due to lack of corticosterone in the rodents' system.

This finding demonstrates that it is not the rise in corticosterone levels that results in memory impairments but rather suggests that it is a rise past an optimal level that impairs memory.

Additionally, studies that placed animals under an extended period of stress have typically found impairments correlated with the level of corticosterone present (e.g. Belanoff, Gross, Yager, & Schatzberg, 2001; Dachir, Kadar, Robinzon, and Levy, 1993; Gold, Drevets, & Charney, 2002; Lupien & McEwen, 1997; McEwen & Sapolsky, 1995; Wolf, 2003). Luine, Villegas, Martinez and McEwen (1994) restrained rats for 6 hours per day for a time period of 21 days prior to rats learning the eight arm radial maze. Luine et al. (1994) reported that these rats showed significant impairment in performance as compared to the control rats.

It may seem a bit confusing when trying to understand the abundance of animal literature that examined the relationship between memory performance and adrenal steroids. Collectively, both the chronic elevation and reduction of adrenal steroids appears to negatively impact memory formation (e.g. Het, Ramlow, & Wolf, 2005; Lupien & McEwen, 1997; Roozendaal, 2002; Sauro et al., 2003). Therefore the relationship between temporary alterations of corticosterone with the pattern of memory performance is best represented as an inverted U shaped function (e.g. Het et al., 2005; Roozendaal, 2002; Sauro et al., 2003) where extremely high or low levels of adrenal steroids can impair memory performance in animals.

There have been early demonstrations of this inverted U shaped relationship between learning and memory performance with corticosterone. Flood et al. (1978) examined avoidance training while systematically increasing the dose of adrenal steroids in rodents. Flood et al. (1978) found that while a moderate level of adrenal steroids is correlated with optimum performance, extremely high or low levels were associated with impaired performance. This was also reported by other studies that administered a moderate dose of corticosterone and demonstrated improved avoidance training (e.g. Kovacs, Telegdy, & Lissak, 1976; Kovacs, Telegdy, & Lissak, 1977; Roozendaal & McGaugh, 1996; Roozendaal,

Williams, & McGaugh, 1999). Behavioural and electrophysiological animal studies have provided further support for this inverted U shaped function between corticosterone and memory performance (Diamond, Bennett, Fleshner, & Rose, 1992; Vaher, Luine, Gould, & McEwen, 1994a; Vaher, Luine, Gould, & McEwen, 1994b).

1.9 Corticosterone and Long-Term Potentiation

The previous studies show a link between animal learning and memory performance with adrenal steroids. LTP is supposedly the cellular mechanism for learning and memory consolidation. Therefore, as LTP is thought to underlie learning and memory formation, this would suggest an influence of corticosteroids on LTP as well. Moreover, the relationship between adrenal steroids with animal LTP should be an inverted U shaped relationship, consistent with animal memory performance and corticosteroids (Diamond, Bennett, Fleshner, & Rose, 1992).

In 1987, Dubrovsky, Liquornik, Noble and Gijsbers examined the effects that adrenal steroids might have on LTP in animals. Dubrovsky et al. (1987) showed that when corticosterone was administered to anaesthetised rats, LTP was not evident in the hippocampal region. Therefore, this showed that elevated levels of corticosterone inhibited animal LTP. Filipini, Gijsbers, Birmingham, and Dubrovsky (1991) provided additional support for adrenal steroids preventing successful potentiation. Utilizing rodents, Filipini et al. (1991) removed the adrenal glands two days prior to testing to allow for recovery from the surgery. Immediately following stimulation, Filipini et al. (1991) administered corticosterone to the rats and followed the rats' response one hour post stimulation. As compared to the control group of rats, Filipini et al. (1991) found that corticosterone significantly reduced the magnitude of LTP that can be achieved.

Furthermore, this pattern was also found in studies that examined the relationship between acute administration of corticosterone and animal LTP. Under urethane anaesthesia, Pavlides, Watanabe, and McEwen (1993) monitored the response of the rats' dentate gyrus granule cell layer of the hippocampus. Compared to the control rats, the rats that received a temporary raise in corticosterone showed a significantly smaller magnitude of potentiation. Filipini et al. (1991) reported similar findings when they administered a dose of corticosterone to rats.

Consistent with the prior literature, prolonged elevation of corticosterone is also linked to a decline in the degree of LTP achieved. Apart from examining acute administration of corticosterone, Pavlides et al. (1993) monitored the effect of corticosterone when administered for an extended period of time. As expected, compared to the control rats there was a significant reduction in the potentiation observed.

So far, it appears that the relationship between the level of corticosterone with LTP achieved is negative (Bennett, Diamond, Fleshner, & Rose, 1991). That the increase in corticosterone is correlated with a decline in the magnitude of LTP successfully induced. However, later studies provided evidence to suggest that this relationship is more accurately captured in a slightly different manner. Diamond et al. (1992) surgically removed the adrenal glands of rats then implanted corticosterone pellets in order to examine the relationship between adrenal steroids and LTP. At a moderate level of corticosterone, Diamond et al. (1992) observed the magnitude of potentiation to reach its peak. This was in comparison to low and high levels of corticosterone where the level of potentiation elicited were reported to be much lower. Diamond et al. (1992) findings provided support for the inverted U shaped function between adrenal steroids and LTP.

In 1994, Pavlides, Kimura, Magarinos, and McEwen also examined the systematic changes in adrenal steroids with LTP. Pavlides et al. (1994) also removed the rodents' adrenal

glands then implanted corticosterone pellets in the rodents' brain. Pavlides et al. (1994) reported that adrenal steroids enhanced and prolonged LTP. This was compared to the control rats with their adrenal glands intact, these rats showed a decline in potentiation over the 24 hour time period following stimulation.

The pattern of results found for the relationship between adrenal steroids and animal memory performance has also been reported for the association between adrenal steroids with animal LTP (Diamond, Bennett, Fleshner, & Rose, 1992). The relationship between adrenal steroids and animal LTP further support the suggestion that LTP is the underlying mechanism for learning and memory formation (e.g. Bremner & Narayan, 1998; McEwen & Sapolsky, 1995). Furthermore, the association between adrenal steroids with animal LTP appears to be best represented by an inverted U shaped relationship, consistent with animal memory performance and adrenal steroids (Diamond, Bennett, Fleshner, & Rose, 1992).

1.10 New Non-Invasive Induction and Measurement of Long-Term Potentiation

It is often unethical to examine some research questions directly on humans until practical, and non-invasive, techniques are developed. In the meanwhile animals can act as a good research subject for more novel scientific ideas. Regarding LTP, animal studies have established that rapid sensory stimulation can successfully induced LTP. While that is the case, these animal studies have commonly employed intracellular potential and local field recording techniques to measure and quantify LTP. This meant the application of these techniques to examine the same phenomenon in humans has been hindered as they still involve invasive techniques even though LTP is induced non-invasively.

Early studies that tried to develop a human model for LTP have conducted their examination on isolated human cortical tissue that was obtained from patients prior to them going into surgery. In 1996, Chen et al. obtained tissue from the inferior and middle temporal

cortex to examine neuroplasticity with high-frequency stimulation. At the rapid stimulation rate of either 100 Hz or 40 Hz, successful potentiation was achieved. Furthermore, when NMDA receptors were blocked, LTP was also prevented. This is important as it implied that the effect shown in human cortical tissue is NMDA receptor dependent, which is consistent with the animal literature. This will be reviewed in more detail in a slightly later section. Chen et al. (1996) also documented long-term depression when the stimulation rate was reduced to 1Hz for an extended period of time (15mins). Chen et al. (1996) provided evidence that is consistent with the prior animal studies, suggesting that LTP can be induced with rapid sensory stimulation.

Further progression towards a human model came from Beck, Goussakov, Lie, Helmstaedter and Elger (2000). Beck et al. (2000) took hippocampal slices acquired from patients with epilepsy who underwent surgery to examine whether or not high frequency sensory stimulation can induce potentiation. As expected, similar to Chen et al. (1996) and consistent with the prior animal LTP studies, Beck et al. (2000) reported that rapid sensory stimulation can induced LTP in human hippocampal tissue.

While rapid sensory stimulation has been shown to be successful at eliciting LTP in *in vitro* tissue preparation, given obvious methodological limitations the extension of animal findings onto humans have not been so straight-forward. However, not long ago a substantial step forward was made by Teyler et al. (2005). Teyler et al. (2005) first documented that LTP can be non-invasively induced and measured in healthy intact human participants. As opposed to implanted electrodes, the non-invasive measurement of LTP was achieved by using surface scalp electrode (i.e. high density electroencephalography (EEG)) that recorded the brain's electrical activity. The visual evoked potential (VEP) was measured in response to a semi-circular checkerboard stimulus presented to participants at a rate of 1Hz. For half of the presentations, the stimulus was presented to the participants' left visual field with the

remaining presented to the right visual field. After measuring the VEP, induction was achieved by presenting the same stimulus at a rate of 9Hz for 120 seconds to either the left or the right visual field. Following rapid stimulation, VEP was recorded again while participants were presented with the stimulus presented at 1Hz. The VEPs taken before and after induction were compared to see if any changes occurred that might be consistent with LTP.

Teyler et al. (2005) used independent component analysis and identified five components of the VEP - P100, N1a, N1b, P2, and P3. Not all components showed an increase in amplitude following rapid visual stimulation. However, the falling phase of the N1 component, which is also referred to as the N1b, was the only component that showed a significant rise in the amplitude following induction. The N1b occurred approximately between 170-190ms.

The increase in the amplitude of the N1b component that Teyler et al. (2005) found unexpectedly decayed over the recording of the VEP during the presentation of baseline blocks that followed the rapid visual stimulation. While the post-induction blocks were required to monitor participants' response following stimulation, Teyler et al. (2005) hypothesized that these post-induction blocks were the explanation for the reduction in the amplitude of the N1b component observed. In other words, it could have been due to the presentation of stimuli at a low-frequency following high-frequency presentation that resulted in the reduction of the N1b amplitude. To clarify this, Teyler et al. (2005) conducted follow up experiments with exactly the same experimental procedures but various post-induction baseline blocks were removed. This was to investigate whether this effect was due to a natural decline in the amplitude of N1b over time or due to low frequency stimulation given immediately after rapid stimulation. After omitting various post-induction blocks, Teyler et al. (2005) showed that the decay in the amplitude of N1b was reduced. This meant that low-

frequency stimulation given immediately following induction is the most probable explanation behind why there was a decay in the amplitude of the N1b component observed.

Furthermore, this “LTP-like” effect was documented to last up to approximately an hour. It was also speculated that if post-induction blocks were withdrawn, this effect could be evident for even longer. Source estimation analysis indicated the activity was bilaterally localized to the striate and extrastriate areas. From here on, sensory induced LTP and human LTP (hLTP) refers to the significant increase in evoked potentials following non-invasive rapid sensory stimulation and measurement of LTP conducted on healthy human participants.

The studies employed here, which involve a single burst of stimulation over a relatively short period of time (approximately 2 minutes), produce an effect that has been shown to last for at least one hour. Therefore it is most likely the effect under current investigation is a form of early-LTP.

Additionally, Smallwood et al. (in press) recently utilized the visual hLTP paradigm and documented an interesting finding. Smallwood et al. (in press) found that in comparison to a group of participants with less physical activity, increased physical activity can result in the level of potentiation achieved to be maintained beyond a 30 minute delay.

It should be noted that successful non-invasive induction and measurement of LTP is not limited to the visual domain. Auditory hLTP has been reported (e.g. Clapp et al., 2005a; Zaehle et al., 2007) in studies employing a similar paradigm as to Teyler et al. (2005). Furthermore, hLTP has been demonstrated in the motor cortex using transcranial magnetic stimulation rather than high-frequency sensory induction (e.g. Huang et al., 2005; Stefan, Kunesch, Cohen, Benecke, & Classen, 2000).

1.11 NMDA Receptor Dependence of Long-Term Potentiation

One property of cellular LTP is that it is NMDA receptor dependent, and this property is commonly demonstrated in non-human preparations (Artola & Singer, 1987; Harris et al., 1984). To further examine if sensory induced LTP is analogous to cellular LTP, it is important to determine if hLTP demonstrate properties that are consistent with the properties seen in cellular LTP.

Using rats as subjects, Clapp, Eckert, Teyler, and Abraham (2006) employed the non-invasive paradigm as Teyler et al. (2005) did to induce LTP. Although, it is worthy to note Clapp et al. (2006) did not measure LTP non-invasively. The rats were first anesthetized then two electrodes were screwed into their skull. The electrodes were used to record the VEP during the experiment. Following rapid sensory stimulation, a significant increase in VEP was reported. Furthermore, Clapp et al. (2006) showed that this response remained evident for 5 hours following stimulation.

As the key interest was to investigate whether or not sensory induced LTP is also NMDA receptor dependent, Clapp et al. (2006) injected rats with NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid to block NMDA receptors. Rats that had their NMDA receptors blocked did not show a significant change in intracortical field response following high-frequency stimulation. Hence, Clapp et al. (2006) provided strong evidence that hLTP is indeed NMDA receptor dependent as demonstrated in cellular LTP.

However, in 2013, Eckert, Guevremont, Williams, and Abraham tried to replicate this finding by Clapp et al. (2006) in anesthetized adult rats. Unfortunately, Eckert et al. (2013) failed to replicate the findings shown in Clapp et al. (2006). Although, in a more recent study, Han, Huang, Sun, Duan, and Yu (2014) have since again reported that sensory induced LTP is indeed dependent on NMDA receptors.

While findings from rat studies have been a little inconsistent, this is human sensory induced LTP, a model established in hope to extend animal findings to humans. Therefore, investigation of NMDA dependency property on humans is essential. Furthermore, examining NMDA dependency property on humans may help clarify the findings as seen in animal studies that utilized the non-invasive technique.

Chen et al. (1996) investigated synaptic plasticity via high frequency stimulation on cortical slices removed from patients for therapeutic reasons. The tissue used in the study was from the inferior and middle temporal cortex. Chen et al. (1996) showed that when NMDA receptors were blocked, the magnitude of potentiation initially observed following high-frequency stimulation was no longer evident. Chen et al.'s (1996) findings suggest that LTP induced by rapid stimulation is NMDA receptor dependent. Furthermore, this corresponds with the literature so far that suggest that sensory induced LTP do show properties consistent with the properties as seen in cellular LTP.

However, Chen et al. (1996) used tissue resected from the brain which means it is clearly an invasive technique. Therefore, the applicability of this phenomenon to humans is still limited without demonstration of NMDA receptor dependency in healthy human participants through less invasive techniques. This has been attended to when Cavus et al. (2009) administered NMDA receptor antagonist (ketamine) to participants following rapid sensory stimulation. As expected, Cavus et al. (2009) found that hLTP did not occur when ketamine was used to block NMDA receptor activity.

Combining the evidence so far, sensory induced LTP appears to demonstrate the property of NMDA receptor dependency. Hence, hLTP is analogous to cellular LTP as this is a property commonly shown in animal studies utilizing a range of techniques to induce LTP (Artola & Singer, 1987; Harris et al., 1984).

1.12 Input-Specificity of Long-Term Potentiation

To further ascertain that sensory induced LTP is analogous to cellular LTP, it is crucial that hLTP demonstrates the property of input-specificity. Input-specificity is another key property of cellular LTP (Bliss & Collingridge, 1993; Malenka, 2003). This property is characterized by the fact that only synapses that are active during the processing of the stimulus will get potentiated (Bliss & Collingridge, 1993; Malenka, 2003). In other words, this meant that potentiation will be absent at synapses that were not recruited during the processing of the stimulus (Bliss & Collingridge, 1993; Malenka, 2003).

McNair et al. (2006) utilized the non-invasive paradigm to investigate whether or not hLTP also demonstrates the property of input specificity. However, as opposed to having one stimulus, McNair et al (2006) had two stimuli that were visually similar yet possessed unique spatial frequencies - one cycle-per-degree sine grating vs five cycle-per-degree sine grating. During the pre-induction and post-induction blocks, participants were presented with both stimuli while VEP recordings were made. During the induction phase, participants only received one of the two stimuli shown during the pre-induction phase. As the two stimuli are visually very similar, if potentiation is only achieved with the stimulus used during high-frequency stimulation, it would suggest that hLTP is input specific. McNair et al. (2006) reported a significant rise in the amplitude specific to the stimulus utilized to induce LTP. Hence, the stimulus that was not shown during the induction phase revealed no change in the amplitude measured. McNair et al. (2006) study offers evidence to suggest that sensory induced LTP is spatial frequency specific.

In 2008, Ross et al. provided further evidence to suggest that hLTP demonstrates the property of being input-specific. Ross et al. (2008) also had two similar yet unique stimuli that differed in their orientation – vertical vs horizontal. Like McNair et al. (2006), during the pre-induction and post-induction blocks, participants were presented with both stimuli while

VEP recordings were taken. However, during the induction phase, only one of the stimuli was utilized to induce LTP. Ross et al. (2008) reported that only the stimulus used during the induction phase showed successful potentiation. The stimulus not used for rapid sensory stimulation did not reveal a significant change in response following the induction block. Ross et al.'s (2008) findings also suggested that sensory induced LTP is orientation specific.

The combination of findings from both McNair et al. (2006) and Ross et al. (2008) have provided evidence to suggest that sensory induced LTP does appear to demonstrate the property of input-specificity. A property commonly reported in studies conducted on animal (Bliss & Collingridge, 1993; Cooke & Bliss, 2006; Malenka, 2003).

Furthermore, the selective increase of the two closely related but unique stimuli found in both McNair et al. (2006) and Ross et al.'s (2008) studies suggest that hLTP reported so far is not due to general cortical excitability or an altered state of attention. If sensory induced LTP were in fact just due to general arousal, a similar pattern of response should be observed in both stimuli (i.e. both show or do not show potentiation). However, both McNair et al. (2006) and Ross et al. (2008) showed that sensory induced LTP can be reliably found using high frequency stimulation.

1.13 Locus of Visual Human Long-Term Potentiation

To further examine if sensory induced LTP is analogous to cellular LTP, another issue to consider is where this phenomenon occurs in the human brain. To date, it has been consistently found that only the amplitude of the N1b component significantly increases following rapid sensory stimulation (i.e. Teyler et al., 2005). The N1b component does not receive input directly from the ascending visual pathways. This is because the generators for the N1b component are located to region outside of the primary visual cortex (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2001; Jeffreys & Axford, 1972a; Jeffreys & Axford,

1972b). Therefore, the selective increase in the N1b component following sensory induction suggests the location of visual hLTP is most likely localized to the secondary or extrastriate visual cortex.

Furthermore, the original non-invasive study by Teyler et al. (2005) induced LTP by presenting their stimulus to either the left or right visual field. However, Teyler et al. (2005) reported a bilateral increase in the VEP recordings following rapid stimulation. This suggest that the generators of the N1b component are bilaterally localized.

Teyler et al. (2005) employed low resolution brain electromagnetic tomography source estimation (LORETA) (Pascual-Marqui, Michel, & Lehmann, 1994) to determine where the generators of the components are localized in the brain. The LORETA analysis indicated that the generators of the N1b component are located in the bilateral striate and extrastriate areas.

A limitation of source estimation techniques is that they cannot guarantee the analysis of where component generators are localized to in the human brain to be correct. Therefore, further studies were conducted to provide more information about where hLTP is occurring in the brain. The neuroimaging technique, functional magnetic resonance imaging (fMRI) provides excellent spatial resolution. Hence, fMRI is useful when trying to investigate where sensory induced LTP is occurring in the human brain.

In 2005b, Clapp et al. conducted an experiment that applied the original non-invasive paradigm by Teyler et al. (2005) and incorporated fMRI. Clapp et al. (2005b) presented semi-circular checkerboards to either the left or right visual field at a rate of 9Hz. As predicted, there was a significant and selective increase in the N1b component following induction. Furthermore, Clapp et al. (2005b) documented a significant rise in the hemodynamic (BOLD) responses over the bilateral secondary visual cortex.

The lateral geniculate nucleus cells are not spatial frequency specific (Kremers, 1999; Levitt, Schumer, Sherman, Spear, & Mavshon, 2001; Shapley & Lennie, 1985). The lateral

geniculate nucleus cells respond to a wide range of spatial frequencies (Kremers, 1999; Levitt et al., 2001; Shapley & Lennie, 1985). On the other hand, the visual cortex contains cells that are spatial frequency specific. Therefore, examination of specificity of spatial frequency can help determine where the effect is occurring in the brain. If potentiation was occurring along the ascending visual pathways, low spatial frequency sine gratings should potentiate low spatial frequency stimulus. Additionally, high spatial frequency sine gratings should potentiate both high and low spatial frequency stimuli. However, if the effect was occurring in the visual cortical regions then induction should be specific to the sine grating used during rapid sensory stimulation. As discussed in the previous section, McNair et al. (2006) found a selective increase in the amplitude of the N1b component specific to the sine grating of the stimulus used for induction. Consequently, McNair et al. (2006) reported that sensory induced LTP is spatial frequency specific. McNair et al.'s (2006) findings suggest that visual hTLP is localized to the cortical regions.

Furthermore, the ascending visual pathways do not contain neurons that process specific orientations (e.g. Hubel & Wiesel, 1962; Hubel & Wiesel, 1968). On the other hand, the visual cortex does contain neurons that respond to specific orientations (e.g. De Valois, Yund, & Helper, 1982; Hubel & Wiesel, 1962; Hubel & Wiesel, 1968). Hence, examination of orientation specificity can also help to determine where sensory induced LTP is localized to in the human brain. If the effect is taking place in the cortical region, then potentiation should be specific to the orientation of the stimulus utilized during induction. As presented in the previous section, Ross et al. (2008) found a significant increase in the amplitude of the N1b component specific to the orientation of the visual stimulus used during the induction phase. Therefore, Ross et al.'s (2008) study provided an another piece of evidence that suggest that sensory induced LTP is taking place in the neocortical regions due to visual hLTP being orientation specific.

So far, the literature reviewed indicated a few important things. Firstly, visual hLTP is long-lasting, as shown by the effect lasting well over an hour (Clapp et al., 2006; Teyler et al., 2005). Furthermore, sensory induced LTP can remain evident for even longer if the post-induction blocks were withdrawn (Teyler et al., 2005). Secondly, sensory induced LTP is input specific as supported by McNair et al. (2006) (spatial frequency specific) and Ross et al. (2008) (orientation specific) findings. Lastly, visual hLTP is most likely occurring in the neocortical regions as opposed to the ascending visual pathways as gathered from the review above. Therefore, cellular LTP as documented in prior animal studies is the most credible molecular mechanism responsible for the selective increase in the N1b component reported using the non-invasive technique to induce and measure this effect. In other words, sensory induced LTP is analogous to cellular LTP.

1.14 Inter-Ocular Transfer

While the review just covered appear to suggest that sensory induced LTP is occurring in the neocortical regions of the brain, the non-invasive paradigm and the knowledge regarding hLTP is still relatively new. Therefore, studies should be conducted to further examine where sensory induced LTP is occurring in the brain to extend what is currently known regarding this phenomenon.

Each eye has its own visual pathways that remain separate until the visual information is combined in the cortex (e.g. Baccus & Meister, 2004; Hubel, Wiesel, & Stryker, 1977). As mentioned, while the evidence tends to suggest a cortical locus of hLTP, it has not yet been determined if presentation of rapid sensory stimulation to one eye will increase the response to the stimulus presented to the other eye – a phenomenon known as inter-ocular transfer.

Even though inter-ocular transfer is common in perceptual learning (Lu, Chu, Dosher, & Lee, 2005), it does not occur for all human perceptual learning tasks. For example,

luminance contrast detection (Sowden, Rose, & Davies, 2002) and simple texture discrimination (Karni & Sagi, 1991) do not show inter-ocular transfer. Other studies have shown transfer of learning from the trained to the untrained eye. For example, Ahissar and Hochstein (1996) examined pop-out detection, Schoups, Vogels, and Orban (1995) studied orientation discrimination, and Lu et al. (2005) investigated Gabor orientation identification in the visual periphery, and they all showed transfer of learning to the untrained eye. Generally, inter-ocular transfer indicates learning is occurring at the cortical level, while lack of it suggests the change is in the ascending pathways (Gilbert, Sigman, & Crist, 2001; Lu et al., 2005).

The original non-invasive hLTP paradigm induced LTP to either one or both visual fields while both eyes were viewing the stimuli. Therefore, this meant that potentiation could have occurred at any point between the ascending visual pathways to the visual neocortex. A limitation of the original paradigm is that it cannot objectively determine where visual hLTP occurs in the brain. Therefore, combining the methodology of the inter-ocular transfer technique with the original non-invasive paradigm can provide more information regarding the locus of visual hLTP.

Rather than rapidly stimulating both eyes with a visual stimulus, participants can be evenly allocated into conditions where only their left or right eye receives the LTP-inducing stimulus while the other eye is covered with an eye patch. During the pre-induction and post-induction blocks, the eye that will receive the induction is covered with an eye patch while participants can be presented with the same stimulus to the other eye that does not receive the induction with VEP recorded for comparison. If visual hLTP is occurring in the visual cortical area, an increase in VEP after induction should be observed even though recordings will be taken while viewing with the non-induced eye. Based upon the previous literature it is thought that the induction should influence cortical cells that receive input from both eyes. This

method should provide indicative results as to where visual hLTP is occurring, whether it is in the ascending visual pathways or in the circuits of the visual cortex. The first set of experiments was conducted to examine where visual hLTP is occurring using the methodology of inter-ocular transfer. Details provided in a slightly later section.

1.15 Cortisol and Memory

Now turning the focus to adrenal steroids influence on learning and memory formation in humans, there is also a range of findings currently available. The common perception is that a lack of or at least minimal stress is related to better cognitive performance. However, based on the review of the literature regarding the relationship of corticosterone with learning and memory performance in animals, this relationship may not be as straight-forward as one might hope it should be.

Animal studies commonly implanted pellets in the brain or placed the animal under physical stress to manipulate the corticosterone level. Furthermore, animal studies predominately tested learning and memory formation with spatial memory tasks. On the other hand, oral administration of corticosteroids to examine the relationship between corticosteroids and memory in humans has become an increasingly popular choice due to the control the researchers can have over the level of cortisol being raised.

Beckwith, Petros, Scaglione, and Nelson (1986) were one of the first researchers that began to utilize oral administration of cortisol to examine how varying the dosage might relate to changes in cognitive performance. While having a double-blind paradigm in place to minimize potential biases, Beckwith et al. (1986) administered various dosages of hydrocortisone to participants and also administered glucose to another group of participants as control. One hour after receiving an oral dosage of either hydrocortisone or glucose, participants were presented with short lists of words that they were asked to listen to and later

recall. Beckwith et al. (1986) demonstrated that memory performance was dependant on the dose of hydrocortisone received and the amount of practice allocated to the task. Participants showed an enhanced memory performance for all dosages of hydrocortisone received. Therefore, Beckwith et al. (1986) findings implied that a temporary rise in cortisol facilitates learning and memory formation.

However, the literature is not universally supportive of the suggestion that an increase in cortisol leads to improved memory formation. A decade later, Kirschbaum, Wolf, May, Wippich, and Hellhammer (1996) also examined the influence of acute elevation in adrenal steroids on memory performance but reported findings that conflicted with Beckwith et al. (1986). Kirschbaum et al. (1996) gave participants either an oral dose of cortisol or placebo then one hour later they assessed participants' performance in tasks involving spatial thinking or declarative memory. Kirschbaum et al. (1996) reported a significant negative relationship between stress hormones and memory performance. This led Kischbaum et al. (1996) to argue that an acute elevation in cortisol is related to a decline in memory performance. Newcomer, Craft, Hershey, Askin, and Bardgett (1994) also examined the acute rise in cortisol. As compared to the control group, Newcomer et al. (1994) found a significant impairment in both attention and memory performance when the cortisol level was raised. Therefore, Newcomer et al. (1994) study provided evidence to support Kirschbaum et al. (1996).

Aside from the studies that examined the acute elevation in cortisol, there have also been studies conducted that examined a more prolonged rise in the level of cortisol with human memory performance. Wolkowitz et al. (1990) administered an oral dose of cortisol to one group of participants for five consecutive days. Unsurprisingly, as compared to the control group that received a placebo for that period of time, Wolkowitz et al. (1990) reported that the participants with their cortisol level elevated showed a significantly lowered level of performance in verbal memory tasks. In addition, consistent to Kirschbaum et al.'s (1996)

study, Wolkowitz et al. (1990) also found a negative relationship between the level of cortisol with memory performance. Wolkowitz et al. (1990) findings suggest that both acute and prolonged elevation in cortisol are correlated with impaired memory performance. In 1993, another study also examined the acute elevation of cortisol over an extended period of time (Wolkowitz et al., 1993). Consistent with Wolkowitz et al. (1990), Wolkowitz et al. (1993) also reported impaired memory performance for both the temporary and prolonged rise in the level of cortisol. Wolkowitz et al. (1990) and Wolkowitz et al. (1993) findings were further supported by Newcomer et al. (1999). Newcomer et al. (1999) administered either a placebo or a dose of cortisol to their participants over a four day period. Newcomer et al. (1999) showed that as compared to the group of participants that received a placebo, an elevated level of cortisol over a four day period is correlated with an impaired level of performance on the declarative memory test they employed.

While the change in the level of cortisol, whether it be an acute or a prolonged increase, appears to have detrimental effects on memory performance, there is literature that suggest that this relationship is more complicated (Lupien & McEwen, 1997). Yerkes and Dodson (1908) provided evidence to suggest that a different function describes the relationship between cortisol with memory performance more accurately. Yerkes and Dodson (1908) suggested that cognitive performance and attentional state can be seen as an inverted-U shaped relationship. This means that moderate levels of arousal, as compared to under or hyper arousal, is linked to optimum cognitive performance. Applying this idea to cortisol and memory performance, extremely low or high level of stress hormones should be correlated with a decline in the level of memory performance.

Fehm-Wolfsdorf, Reutter, Zenz, Born, and Lorenz-Fehm (1993) provided evidence to support the suggestion that an inverted-U shaped function better captures the relationship between cortisol and memory performance. Fehm-Wolfsdorf et al. (1993) monitored

participants' performance in a free recall task. There were two groups of participants, one group of participants received a dose of hydrocortisone while the other group of participants received a placebo. Fehm-Wolfsdorf et al. (1993) findings revealed an inverted-U shaped relationship between the level of cortisol and memory performance. Therefore, as compared to low and high levels of cortisol, memory performance peaked when there was a moderate level of stress hormone present. Fehm-Wolfsdorf et al. (1993) study is support for Yerkes and Dodson's (1908) hypothesis. In 1994, Newcomer, Craft, Hershey, Askins, and Bargett also found evidence to support the inverted-U shaped function between cortisol level and memory performance. Furthermore, an inverted U shaped function is consistent with the animal literature that also examine adrenal steroids' effects on memory performance and found that the relationship is also best described as an inverted-U-shaped function (i.e. Diamond et al., 1992).

Taking a slight shift in focus, the relationship between cortisol with memory has also been extended to clinical populations. While there is a range of studies conducted on a variety of disorders, most have reported a disturbance in memory performance associated with the abnormal level of cortisol in the patient's body (e.g. Nassman et al., 1998; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Starkman, Gebaski, Berent, & Schteingart, 1992; Starkman et al., 1999; Starkman, Schteingart, & Schork, 1981).

Patients that suffer from Cushing's syndrome have a chronic elevation of cortisol level circulating in their plasma. Several studies have shown a clear relationship between memory impairment and the level of cortisol in patients diagnosed with Cushing's syndrome (e.g. Mauri et al., 1993; Starkman et al., 1992; Starkman et al., 1999; Starkman et al., 1981). Additionally, the relationship between the level of cortisol with memory performance as reported in patients with Cushing's syndrome is also consistent with the literature that suggest

prolonged elevation in the level of cortisol is correlated with a decline in memory performance (i.e. Kirschbaum et al., 1996; Newcomer et al., 1999; Wolkowitz et al., 1990).

In neurodegenerative disorders such as Alzheimer's disease, a decline in cognitive performance normally results and progressively gets worse over time. Furthermore, the level of cortisol becomes less and less regulated due to a generalized degeneration of neurons within the patient's brain (e.g. Nassman et al., 1998).

Consistent with neurodegenerative disorders like Cushing's syndrome and Alzheimer's disease, depression is a neurocognitive disorder that has also been found to show a similar pattern of memory performance in relation with the cortisol level (e.g. Sheline et al., 1996). People that suffer from depression are normally exposed to stressors over an extended period of time. Therefore, it is normal for patients diagnosed with depression to have an unregulated level of cortisol. A large number of studies that examined the influence of the level of cortisol with memory performance in patients diagnosed with depression commonly reported a negative relationship (e.g. Rubinow, Post, Savard, & Gold, 1984; Sheline et al., 1996; Van Londen et al., 1998).

1.16 Cortisol and Long-Term Potentiation

In humans, it is obvious that cortisol not only has an important role with regards to memory performance in healthy participants but also in relation to a variety of neurocognitive disorders (e.g. Nassman et al., 1998; Sheline et al., 1996; Starkman et al., 1992; Starkman et al., 1999; Starkman et al., 1981). Therefore, understanding the relationship between the level of cortisol and memory performance is not only interesting to the scientific world but it can potentially provide beneficial knowledge that can be applied in the clinical setting.

LTP is the underlying mechanism to learning and memory formation (Cooke & Bliss, 2006; Bliss & Collinridge, 1993; Bliss & Lomo, 1973; Malenka, 2003; Spatz, 1996). While

there have been some animal studies conducted that examined the relationship between adrenal steroids and the magnitude of potentiation achieved, the same has not occurred using human participants. This is largely due to methodological limitations of prior techniques available to examine the relationship of cortisol with learning and memory formation in humans. Until recently, non-invasive techniques to examine potentiation in humans were not readily available. However, Teyler et al.'s (2005) study showcased the potential of using rapid sensory stimulation to examine LTP in healthy humans.

While using oral administration of cortisol has been a common choice to alter adrenal steroids (Fehm-Wolfsdorf et al., 1993; Kirschbaum et al., 1996; Newcomer et al., 1999; Wolkowitz et al., 1990), other slightly more natural stressors have also been explored (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975). For example, the cold-pressor technique has been used in some studies to alter the level of cortisol in participants (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975). The cold-pressor technique is when the experimenter instruct the participants to immerse their non-dominate hand in a bucket of ice-water (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975). Studies that employed this technique have shown a rise in the level of cortisol in participants.

Therefore, one method to examine LTP and cortisol in healthy humans is to combine the rapid sensory stimulation paradigm with the cold-pressor technique. In comparison to other methods that can also elevate the level of cortisol (e.g. oral administration), while the cold-pressor technique is not going to be comfortable for the participant it is less invasive. Employing the cold-pressor technique follows the pattern of making the experimental paradigm as non-intrusive as possible, and this contrasts with more artificial and invasive methods used in earlier studies. Conducting experiments using this proposed methodology

should shed more light onto the relationship between the level of cortisol with LTP and ultimately with learning and memory formation in healthy humans.

1.17 Aims of the Current Thesis

Studies that have employed the non-invasive paradigm (e.g. Clapp et al., 2005a; Clapp et al., 2006; McNair et al., 2006; Ross et al., 2008; Zaehle et al., 2007) as originally presented by Teyler et al. (2005) have reported findings which suggest that the experimental protocols are a very promising method of examining LTP. Moreover, this non-invasive paradigm is still relatively new with much potential to uncover through further examination. This leads onto the overarching aim of this thesis – to further explore sensory induced LTP using healthy human participants.

The first key aim of this thesis was to further explore where visual hLTP is occurring in the human brain. To examine the first aim of this thesis, the non-invasive paradigm was combined with the methodology of inter-ocular transfer. Furthermore, not only is the relationship between adrenal steroids and memory very interesting, the link between stress hormones and LTP in humans is much less examined as compared to the animal studies (e.g. Bennett et al., 1991; Diamond et al., 1992; Pavlides et al., 1994). Therefore, the second key aim of this thesis was to examine the relationship between the level of cortisol as manipulated by the cold-pressor technique with sensory induced LTP.

Chapter 2: Experiment One

Prior studies that have utilized the non-invasive paradigm to induce LTP have shown the paradigm to be a highly promising method of investigating LTP in healthy human participants (e.g. Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). These studies have reported that rapid sensory stimulation can elicit an effect which is similar to cellular LTP. While this is the case, the non-invasive paradigm is still relatively new. More importantly, it is crucial that the basic protocols that all the experiments in this thesis are based upon actually achieve what they are intended to. Therefore, experiment one was conducted to demonstrate that the protocols employed could replicate visual hLTP. By establishing this, subsequent findings that are gathered from examining where visual hLTP occurs in the brain and the association with cortisol in healthy humans can be interpreted with more confidence. In other words, to ensure that the results found are unlikely to be due to issues with the protocols itself but are most likely showcasing a reliable effect.

To be most comparable to the prior non-invasive studies, experiment one utilized the basic non-invasive paradigm (i.e. Teyler et al., 2005). Firstly, to further examine the long-lasting property of visual hLTP that is commonly shown in cellular LTP (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999), experiment one also took VEP recordings up to one hour following induction.

Secondly, in order to demonstrate that the experimenter can manipulate when hLTP will (or will not) occur, experiment one had two designs. Design one had two pre-induction blocks combined with three post-induction blocks. Design two had three pre-induction blocks while combined with two post-induction blocks. Having two designs varying between two or three pre-induction blocks is a methodological improvement to the original non-invasive paradigm (Teyler et al., 2005). The two designs can potentially demonstrate that the occurrence of hLTP is tied to the presentation of the LTP inducing stimulus and not due to the

repeated stimulation that occurs during the baseline blocks over the time course of the experiment.

Furthermore, experiment one also induced visual hLTP at 9Hz. This was to be consistent with the original non-invasive paradigm. Also, Hamm et al. (2005) suggested that the induction rate of 9Hz is optimal to induce visual hLTP, that 9Hz is below the perceptual fusion rate and most effective when using checkerboards to elicit visual hLTP.

Moreover, as the later experiments planned to incorporate the methodology of inter-ocular transfer to examine where visual hLTP is occurring in the brain, monitoring eye dominance is also important. Eye dominance was determined using a straight-forward test - the Miles test (Porac & Coren, 1976), refer to Figure 1 below. Firstly, participants were instructed to extend both arms in front of their body then to position their hands to make a small triangle between the thumbs and first knuckles. Then participants were instructed to focus on a small object (e.g. door knob) through the triangle they have created while viewing with both eyes opened. Lastly, participants were instructed to close one eye at a time to determine which eye is their dominant eye. If they close their left eye and the object remains in view then they are right eye dominant. On the other hand, if participants close their left eye and their hand appears to have shifted off the object by moving to the left, then they are left eye dominant.

Figure 1. The Miles test where participants created a small triangle between their thumbs and first knuckles. Then participants were instructed to focus on a small object through the triangle to determine their dominant eye.

Additionally, experiment one (and all the following experiments in this thesis) defined P1, N1, P2, and N1b similar to the previous non-invasive studies (McNair et al., 2006; Ross et al., 2008). The P1 component was defined as the first positive peak in the amplitude of the ERP. The N1 component was defined as the first negative peak in the amplitude of the ERP. The P2 component was defined as the second positive peak in the amplitude of the ERP. Lastly, the N1b component was defined as the part of the waveform that extends from the peak of the N1 component to the midway point between the peak of the N1 component and the peak of the P2 component for each participant. Using this definition of the time window for the N1b component was to make the experiments in the current thesis most comparable to prior studies that used the non-invasive paradigm. Also, the significant increase in the amplitude of the N1b component that reflects hLTP is commonly reported to be occurring in a specific area on the scalp (e.g. Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). Therefore, this meant that the P1, N1, P2 and N1b potential could be measured with only a few selected electrodes. This will be described shortly.

Lastly, following Kadamn and Bhalerao's (2010) guideline, a statistical power analysis was performed to determine the sample size required to achieve a certain power and level of significance. Generally, most studies aim to achieve at least 80% power (Fitzner & Heckinger, 2010; Kadam & Bhalerao, 2010). Furthermore, it is also standard for experiments to test at the 5% level of significance (Fitzner & Heckinger, 2010; Kadam & Bhalerao, 2010). There was also an aim to obtain a minimum of 80% power and to test at the 5% level of significance with all experiments conducted as part of this thesis. Based on prior non-invasive studies that also examined visual hLTP (McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005) a sample size of eight per group gives a power of 0.834, implying that the proposed sample size is more than adequate for the purpose of this experiment. Furthermore, this thesis aimed to detect as opposed to determine the size of the effect. Thus, while a larger sample

size would be beneficial to determine the true estimate, because detection is the primary focus a smaller sample size is argued to be sufficient. Therefore, all the experiments conducted as part of this thesis maintained a minimum of eight participants. There was no overlapping sample, no participant participated in more than one study.

Additionally, sex hormones have been reported to have a significant influence on memory (e.g. Postma, Winkel, Tuiten, & van Honk, 1999) indicating the potential complication of examining its' relationship with LTP. Moreover, early studies have reported the effects of estrogen and progesterone on EEG (e.g. Dvorak & Bocan, 1980). Over the menstrual cycle, electrical activity has been repeatedly documented to fluctuate as the hormones vary (e.g. Gawali, Rokade, Janvale, & Mehrota, 2009; Soliz-Ortiz, Ramos, Arce, Guevara, & Corsi-Cabrera, 1994). Therefore, until more clarity is reached regarding the relationship between sex hormones with memory and EEG, only recruiting male participants was arguable more appropriate for the current thesis. This was an attempt to make the interpretation of results more straight-forward.

2.1 Methods

2.1.1 Participants

Sixteen males gave their informed consent prior to participating in the experiment. All the participants reported normal or corrected-to-normal vision. The participant's ages ranged from 18 to 28 years (M = 22.25, SD = 3.85). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 50 to 100, with an average quotient of 82.50 (SD = 18.32). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

2.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master P2270 computer monitor (dimension: 47.5cm x 27cm, resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The screen luminance was measured with a Konica Minolta LS-110 Luminance Meter before (M = 52.40cd/m^2, SD = 0.60) and after (M = 51.48cd/m^2, SD = 0.90) the experiment. All the participants maintained a viewing distance of 57cm from the monitor.

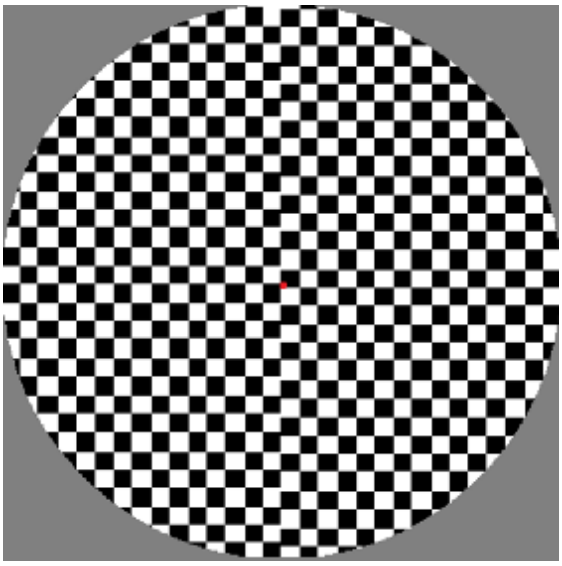

Figure 2. The experimental stimulus employed in the experiment.

2.1.3 Procedure

The experiment had two types of blocks – VEP and induction blocks. The first were the VEP blocks, in which checkerboards were presented centrally at a rate of 1 Hz. Each of VEP block consisted of 210 checkerboard stimuli. There were four VEP blocks of 7 minutes duration, starting every 15 minutes. A fifth VEP block, which started 1 hour following the induction block, completed the experimental protocol. During the VEP blocks, EEG was recorded while the stimuli were viewed with both eyes open. The second type of block was the induction block, in which the checkerboards were presented centrally at a rate of 9 Hz and viewed with both eyes open. The induction block consisted of 1000 checkerboard stimuli. The VEP blocks are classified as pre-induction or post-induction blocks depending upon when the induction block was presented, but they are otherwise identical.

As mentioned, experiment one has two designs in an attempt to demonstrate that hLTP is induced in response to the induction block and not in response to the repeated presentation of the VEP blocks. The participants were evenly allocated into the two designs (refer to Figure 3). Participants allocated to design one received two pre-induction blocks (Pre1 and Pre2), and the induction period was presented during the interval between Pre2 and Post1.

The induction block was followed by two post-induction blocks (Post1 and Post2), and then there was a delay that measured one hour timed from the end of the induction block until the beginning of the last post-induction block (Post3).

Participants allocated to design two received three pre-induction blocks (Pre1, Pre2 and Pre3), with the presentation of the induction block occurring during the waiting period between Pre3 and Post1. There was one post-induction block (Post1) followed by a delay of one hour timed from the end of the induction block to the beginning of the last post-induction block (Post2). In both design one and two, the delay period was used to re-wet the electrodes to ensure optimal recording.

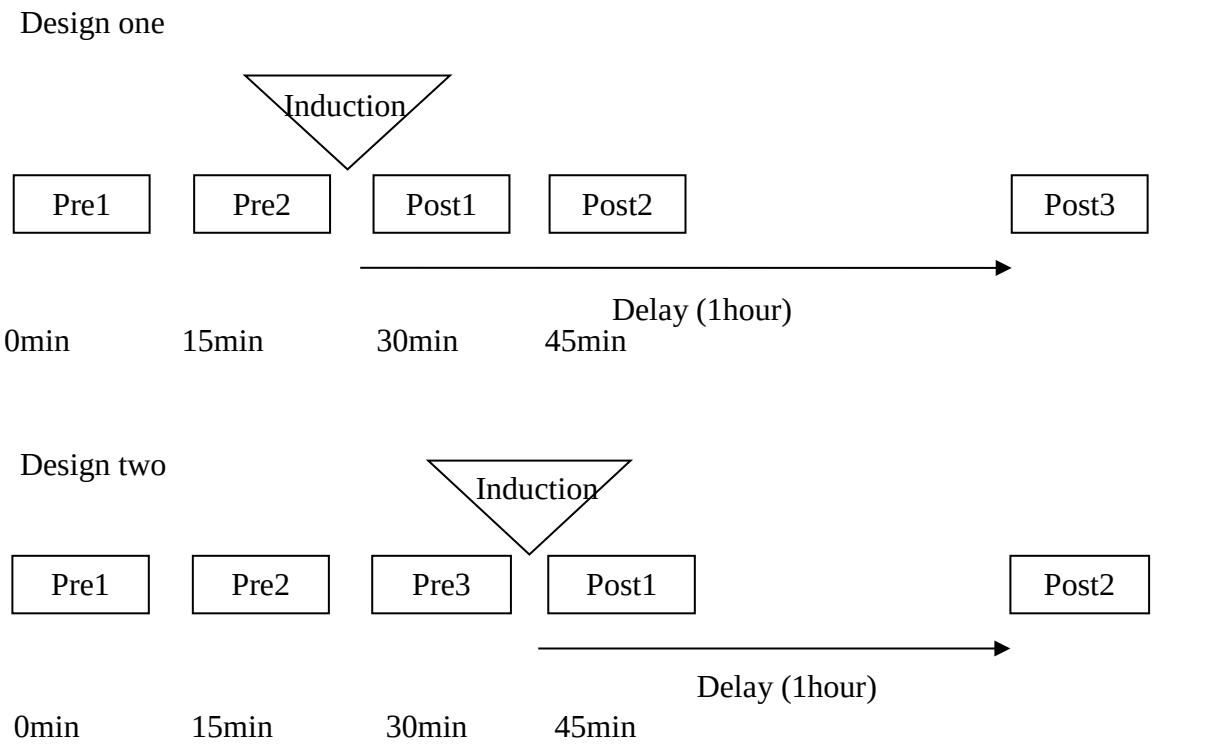

Figure 3. The order of blocks that participants received depending if they were allocated to design one or two for this experiment.

2.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). This sampling rate was determined to be better in comparison to lower sampling rates. Lower sampling rates are lower in resolution, this means they are less likely to capture potentially valuable information. Therefore, using a higher sampling rate can retain more information (e.g. gamma activity) that could be used to examine other questions of interest in the future that requires better temporal dynamics. All electrode impedances were below 40kΩ, which is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and was later re-referenced to the average reference off-line.

2.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. Epoch is discarded if either eye have “moved” or “blinked. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Jervis et al. (1985) determined the best ocular correction method is to decorrelate EEG from the electro-oculogram (EOG). Current thesis measured the EOG to achieve this, whereby a vertical over both eyes and a horizontal over both eyes were taken. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4 below.

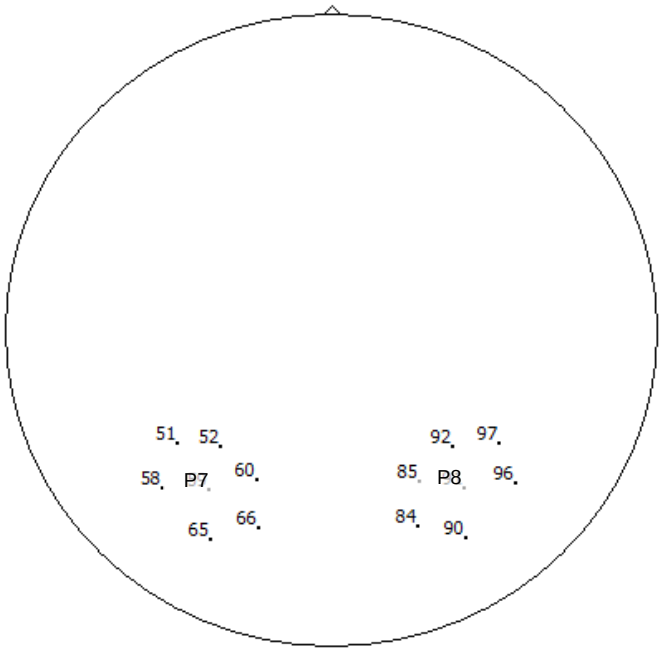

Figure 4. The approximate location of the left and right hemisphere electrodes (marked and centred on approximately P7 (left) and P8 (right) under the 10-20 system) that are used to measure the amplitude of the N1b component.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), and block (Pre1/Pre2/Post1/Post2/Post3 and Pre1/Pre2/Pre3/Post1/Post2) were involved as factors in the analysis. Dominant eye and hemisphere never reached significance as main effects or in any interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3 and Pre1/Pre2/Pre3/Post1/Post2) as a within-subject factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the stability of the post-induction blocks by examining the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing, which could potentially

reflect long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for hLTP.

For design two (refer to Table 2), the stability of the pre-induction blocks was tested by contrasts one and two, which investigated the linear and quadratic trends over the pre-induction blocks; these were expected to be non-significant. Contrast three compared the post-induction blocks for stability and was also predicted to be non-significant. The last contrast compared the pre-induction to post-induction blocks and this is the critical test for hLTP. The pre and post stability contrasts never reached significance in any of the experiments reported here and so only the critical post-pre contrast testing for hLTP will be presented.

Table 1. Contrasts used to test questions of interest for design one.

	Pre1	Pre2	Post1	Post2	Post3
Pre Stability	-1	1	0	0	0
Post Stability (Linear)	0	0	-1	0	1
Post Stability (Quadratic)	0	0	1	-2	1
Post-Pre (hLTP Test)	-3	-3	2	2	2

Table 2. Contrasts used to test questions of interest for design two.

	Pre1	Pre2	Pre3	Post1	Post2
Pre Stability (Linear)	-1	0	1	0	0
Pre Stability (Quadratic)	1	-2	1	0	0
Post Stability	0	0	0	-1	1
Post-Pre (hLTP Test)	-2	-2	-2	3	3

To investigate the odds of any change to the N1b component not due to rapid visual stimulation, the amplitudes of the P1 and P2 component were also analyzed in a similar way to the amplitude of the N1b component. If the P1 and P2 amplitudes changed as N1b did, then results obtained could just be reflecting a general cortical excitation or an altered attentional stated that is unrelated to the high-frequency stimulation given.

2.2 Results

2.2.1 Design One

The analysis of amplitude of the N1b component revealed a main effect for block ($F_{(4,28)} = 8.380$, $p < .001$, $\eta^2 = .545$). The contrast comparing the pre-induction to post-induction blocks was significant ($F_{(1,7)} = 24.278$, $p = .002$, $\eta^2 = .776$). This indicated that there was a significant increase in the amplitude of the N1b component following induction (see Figure 5 and 6 below). As noted, none of the other contrasts reached significance.

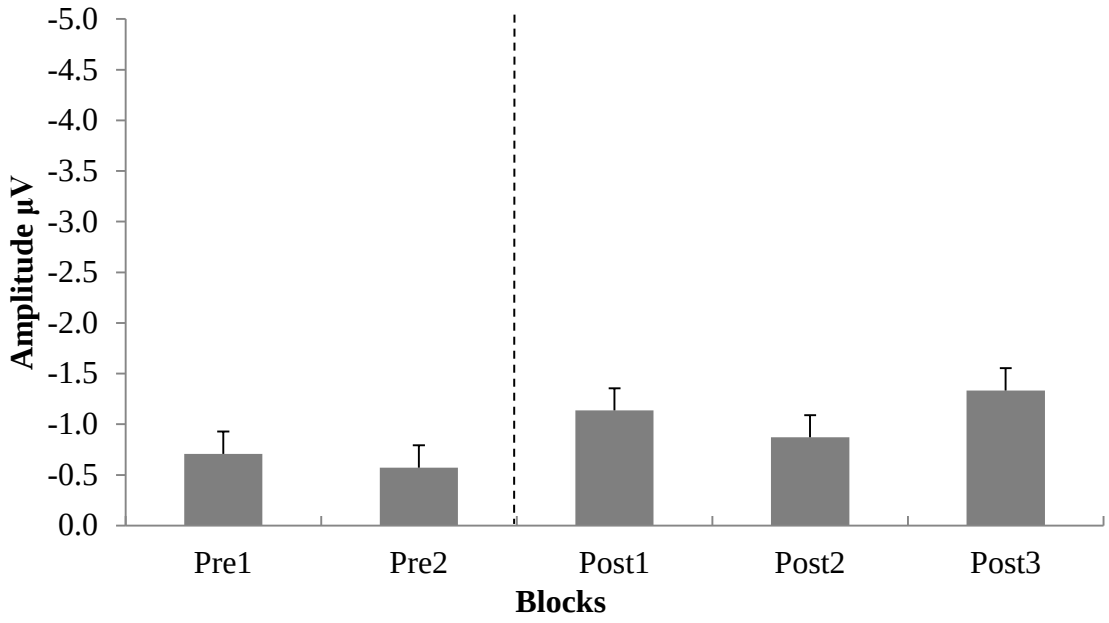

Figure 5. The pre-induction and post-induction amplitude change of the N1b component for design one. The vertical dashed line indicate when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

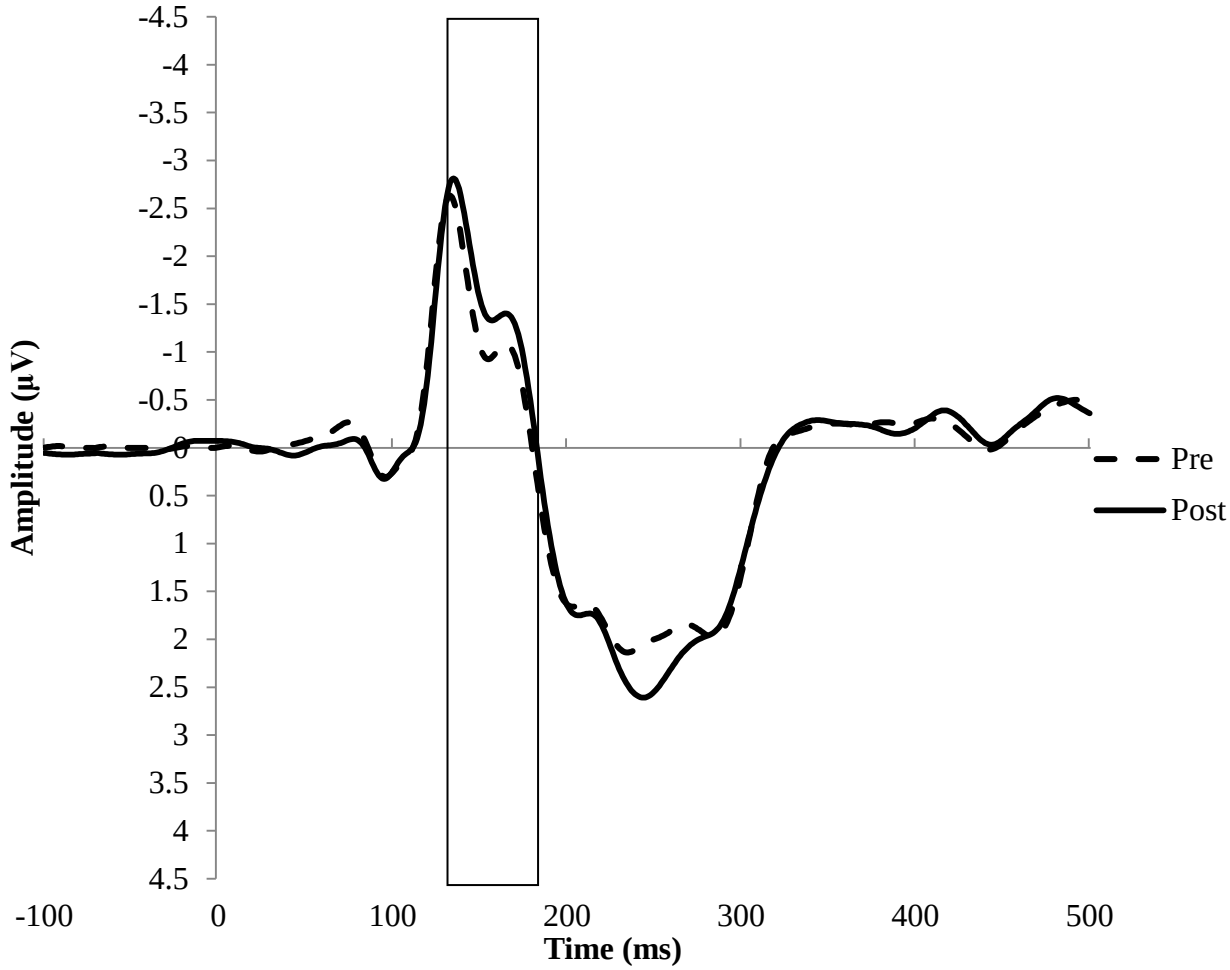

Figure 6. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes for design one. The transparent bar shows the average N1b time window (131 – 180ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = 2.183$, $p > .05$, $\eta^2 = .238$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 1.191$, $p > .05$, $\eta^2 = .145$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 2.084$, $p > .05$, $\eta^2 = .229$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 4.003$, $p > .05$, $\eta^2 = .364$). Furthermore, none of the other contrasts reached significance.

2.2.2 Design Two

The analysis of amplitude of the N1b component revealed a main effect for block ($F_{(1.573,11.009)} = 6.452$, $p = .018$, $\eta^2 = .480$). The contrast comparing the pre-induction to post-induction blocks was significant ($F_{(1,7)} = 13.942$, $p = .007$, $\eta^2 = .666$). This indicated that there was a significant increase in the amplitude of the N1b component following induction (see Figure 7 and 8 below). Furthermore, none of the other contrasts reached significance.

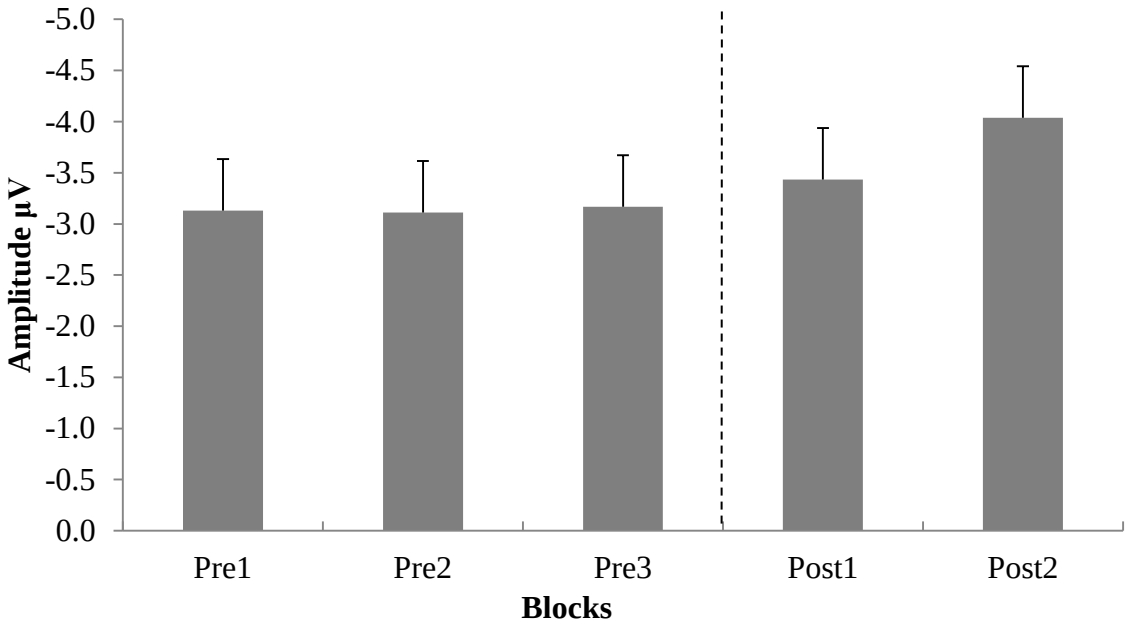

Figure 7. The pre-induction and post-induction amplitude change of the N1b component for design two. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

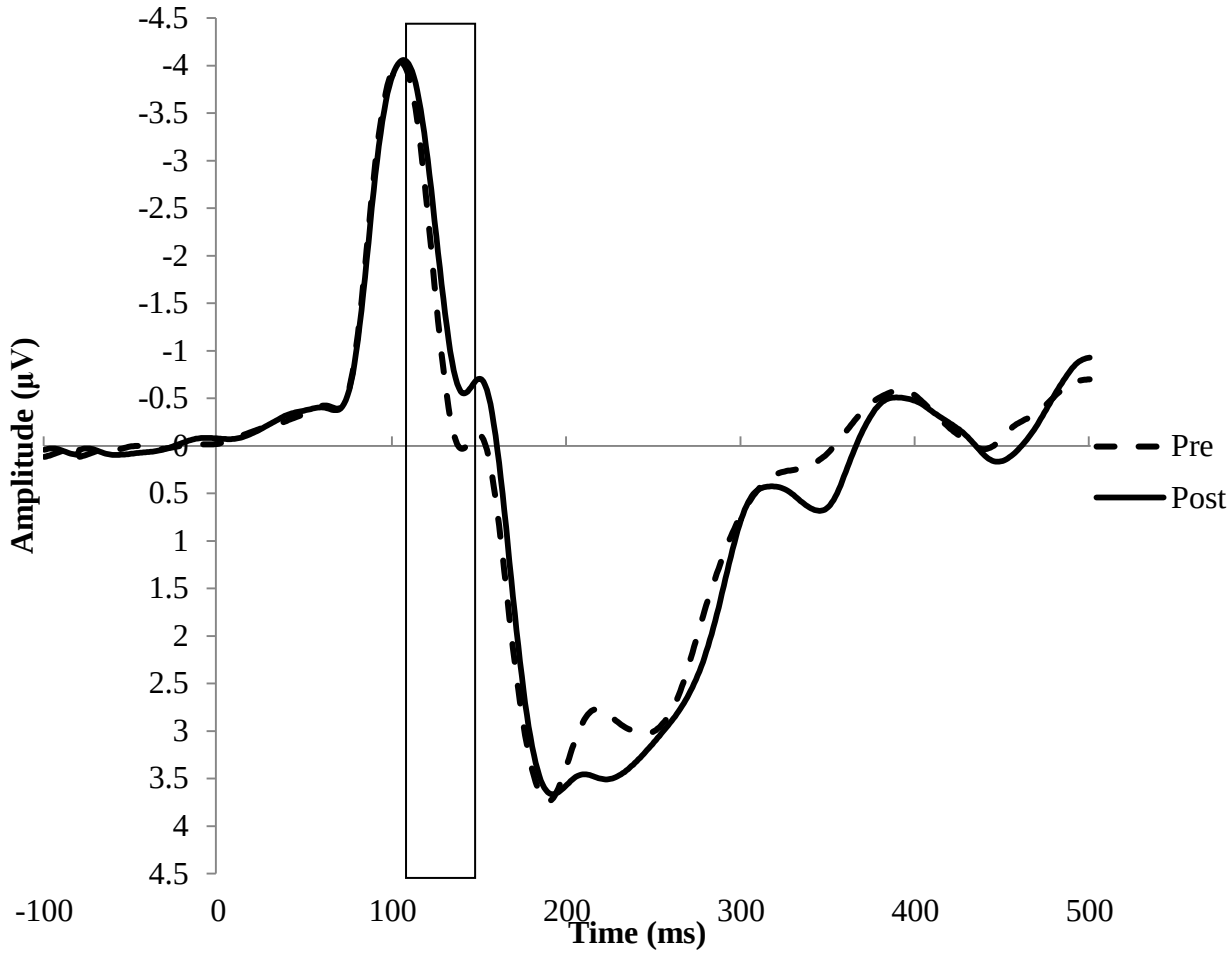

Figure 8. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes for design two. The transparent bar shows the average N1b time window (109 – 146ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = .621$, $p > .05$, $\eta^2 = .082$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .754$, $p > .05$, $\eta^2 = .097$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 2.713$, $p > .05$, $\eta^2 = .279$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .588$, $p > .05$, $\eta^2 = .078$). Furthermore, none of the other contrasts reached significance.

2.3 Discussion

Experiment employed two designs that differed by the number of pre-induction and post-induction blocks presented to participants. Design one had two pre-induction blocks with three post-induction blocks. Design two had three pre-induction blocks with two post-induction blocks. In design one and two, participants viewed the checkerboard stimuli with both eyes during the induction block. Furthermore, VEP recordings were taken while both eyes were viewing the checkerboard stimuli presented.

In both design one and two, hLTP was successfully induced. Moreover, in both designs, VEP amplitudes were stable prior to and following the presentation of the LTP-inducing stimulus. The results reported suggest that the increase in the N1b was stable over 1 hour following induction and that the increase in the amplitude of the N1b component was linked to the presentation of the LTP-inducing stimulus.

In-order to be more comparable to the prior studies that also reported a significant change to the N1b component through rapid sensory stimulation (e.g. Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008), experiment one's design was based off the original non-invasive paradigm as presented by Teyler et al. (2005). However, extra experimental protocols were added to the original non-invasive paradigm to further examine hLTP. As clearly shown in this experiment, high-frequency sensory stimulation has demonstrated it could induce hLTP which replicates the findings from the prior non-invasive studies (e.g. Clapp et al, 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005).

Furthermore, not only did this experiment successfully replicate findings from the previous non-invasive studies (e.g. Clapp et al, 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005), it also showed that visual hLTP is long lasting. With visual hLTP being long-lasting, this is consistent with the prior non-invasive studies (e.g. Clapp et al, 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005) and further supports the idea that

hLTP is similar to cellular LTP. As remaining evident for a significant period of time is a key property shown in cellular LTP (Bliss & Collingridge, 1993; Malenka & Nicoll, 1999).

Moreover, Teyler et al. (2005) demonstrated it was possible to make hLTP last for a much longer period of time. Teyler et al. (2005) achieved this by withholding the presentation of blocks at low-frequency stimulation immediately after rapid sensory induction. By doing so, this not only showed that sensory induced LTP is long lasting but to an extent demonstrated that the control the experimenter could have over the magnitude of potentiation that remains following induction. Not only had experiment one shown the non-invasive paradigm could achieve hLTP using those experimental protocols, but more importantly having both designs revealing successful potentiation indicated that the experimenter can manipulate exactly when hLTP occurs depending on when rapid stimulation is presented to the participants.

On another note, while the baseline amplitude for design one and two appear to be a bit different, it is most likely due to random sampling error. As discussed earlier, this thesis aimed to detect as opposed to determine the size of the effect. A sample size of eight was sufficient to obtain a minimum of 80% power. If future experiments increase the sample size, it is expected that the baseline for both designs should end up to be relatively similar.

Nevertheless, as experiment one has established that the basic protocols for both design one and two can successfully elicit visual hLTP, subsequent experiments took variations of these designs to examine the two key aims of this thesis. Following next was the investigation of the first key aim of this thesis, which was to determine where visual hLTP is occurring in the human brain. This was explored by adapting experiment one's protocols with the methodology of inter-ocular transfer.

Chapter 3: Binocular and Monocular Recording and Induction

Gathered from the review of the previous literature, visual hLTP appears to be occurring in the visual cortex. However, the original non-invasive paradigm has a limitation, the potentiation was induced to either one or both visual fields. Hence, this meant that visual hLTP could have occurred at any point between the ascending visual pathways and the visual cortex. Further testing was conducted to extend what is currently know in regards to where visual hLTP is occurring in the human brain.

When the left and right eyes register information, the visual content travels along the ascending visual pathways until the information is combined in the visual neocortex (e.g. Baccus & Meister, 2004; Hubel, Wiesel, & Stryker, 1977). In other words, the visual pathways remain separate until the information from each eye is combined in the neocortical region. Therefore, the effect known as inter-ocular transfer can potentially provide more information regarding where visual hLTP is occurring in the human brain (Gilbert et al., 2001; Lu et al., 2005).

If high-frequency visual stimulation is presented to only one eye but hLTP is also seen when the post-induction stimulus is presented to the non-induced eye, it will indicate visual hLTP is occurring in the cortical area. On the other hand, if sensory induced LTP is only evident in the eye that receives the LTP-inducing stimulus, it will suggest that visual hLTP is more likely taking place in the ascending visual pathways. The following experiments incorporated the methodology of inter-ocular transfer with the experimental protocols as carried out in experiment one to examine where visual hLTP is occurring in the brain.

3.1 Experiment Two

Like experiment one, experiment two also had both design one and two. In addition, experiment two also allocated participants to receiving the LTP-inducing stimulus to either their left or right eye while the other is covered with an eye patch. Furthermore, during the pre-induction and post-induction blocks, VEP recordings were only taken from the eye that did not receive rapid sensory stimulation. Recording VEP with only one eye viewing the stimuli contrasts to the original non-invasive paradigm (Teyler et al., 2005) and experiment one where both eyes viewed the stimuli during baseline recording. If significant potentiation is still reported it will suggest that hLTP is occurring in the visual cortical area. Failure to induce hLTP will suggest that the effect is likely to have occurred in the ascending visual pathways. This set of experimental protocols should provide some information regarding where visual hLTP is occurring in the brain.

3.1.1 Methods

3.1.1.1 Participants

A new group of males (16) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 28 years (M = 21.44, SD = 5.07). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 68 to 100, with an average quotient of 91.73 (SD = 10.72). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

3.1.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master P2270 computer monitor (dimension: 47.5cm x 27cm, resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The screen luminance was measured with a Konica Minolta LS-110 Luminance Meter before (M = 51.43cd/m^2, SD = 2.75) and after (M = 50.16cd/m^2, SD = 2.04) the experiment. All the participants maintained a viewing distance of 57cm from the monitor.

3.1.1.3 Procedure

The participants were evenly allocated into design one and two as described in Chapter 2 (refer to Table 3) with two changes to the procedure. Firstly, during the induction block the LTP-inducing stimulus was only presented to the left or right eye while the other eye was covered with an eye patch. Secondly, during the pre-induction and post-induction blocks VEP was recorded monocularly from the non-induced eye while the other eye was covered with an eye patch.

Table 3. The allocation of participants into design one and two for experiment two.

Participant	Eye Induced	Dominant Eye
1	Left	Right
2	Left	Right
3	Left	Left
4	Left	Left
5	Right	Right
6	Right	Right
7	Right	Left
8	Right	Left

3.1.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

3.1.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms,

DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved” or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In the preliminary analysis, dominant eye (left and right), hemisphere (left and right), induced eye (left and right), viewing eye (left and right), and block (Pre1/Pre2/Post1/Post2/Post3 and Pre1/Pre2/Pre3/Post1/Post2) were involved as factors in the analysis. Dominant eye, hemisphere, induced eye, and viewing eye never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3 and Pre1/Pre2/Pre3/Post1/Post2) as a within subject factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for LTP.

For design two (refer to Table 2), contrast one and two investigated the linear and quadratic trends over the pre-induction blocks and these were expected to be non-significant. Contrast three compared the post-induction blocks for stability and was predicted to be non-significant. The last contrast compared the pre-induction to post-induction blocks and this is the critical test for hLTP. In all the experiments, none of the pre and post stability contrasts

reached significance and so only the critical post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 and P2 component were also analyzed in a similar way to the amplitude of the N1b component.

3.1.2 Results

For design one, the analysis of the amplitude of the N1b component revealed no main effect for block ($F_{(4,28)} = 1.319$, $p > .05$, $\eta^2 = .159$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .725$, $p > .05$, $\eta^2 = .094$). Furthermore, none of the other contrasts reached significance. This indicated that the amplitude of the N1b component did not change following induction (as seen in Figure 9 and 10 below).

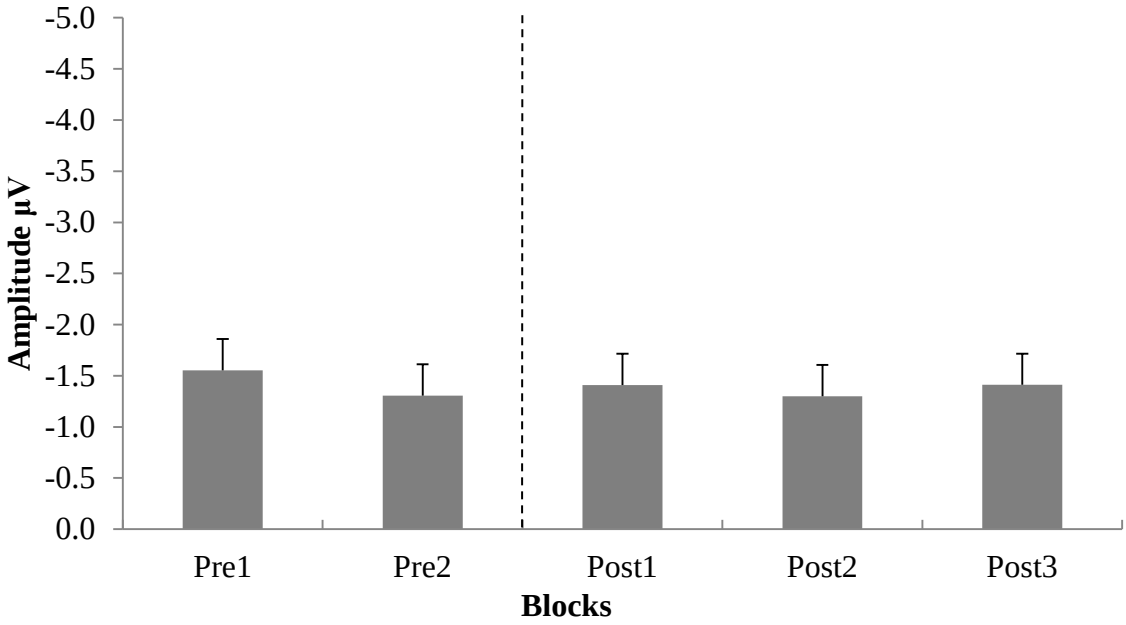

Figure 9. The pre-induction and post-induction amplitude change of the N1b component for design one. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

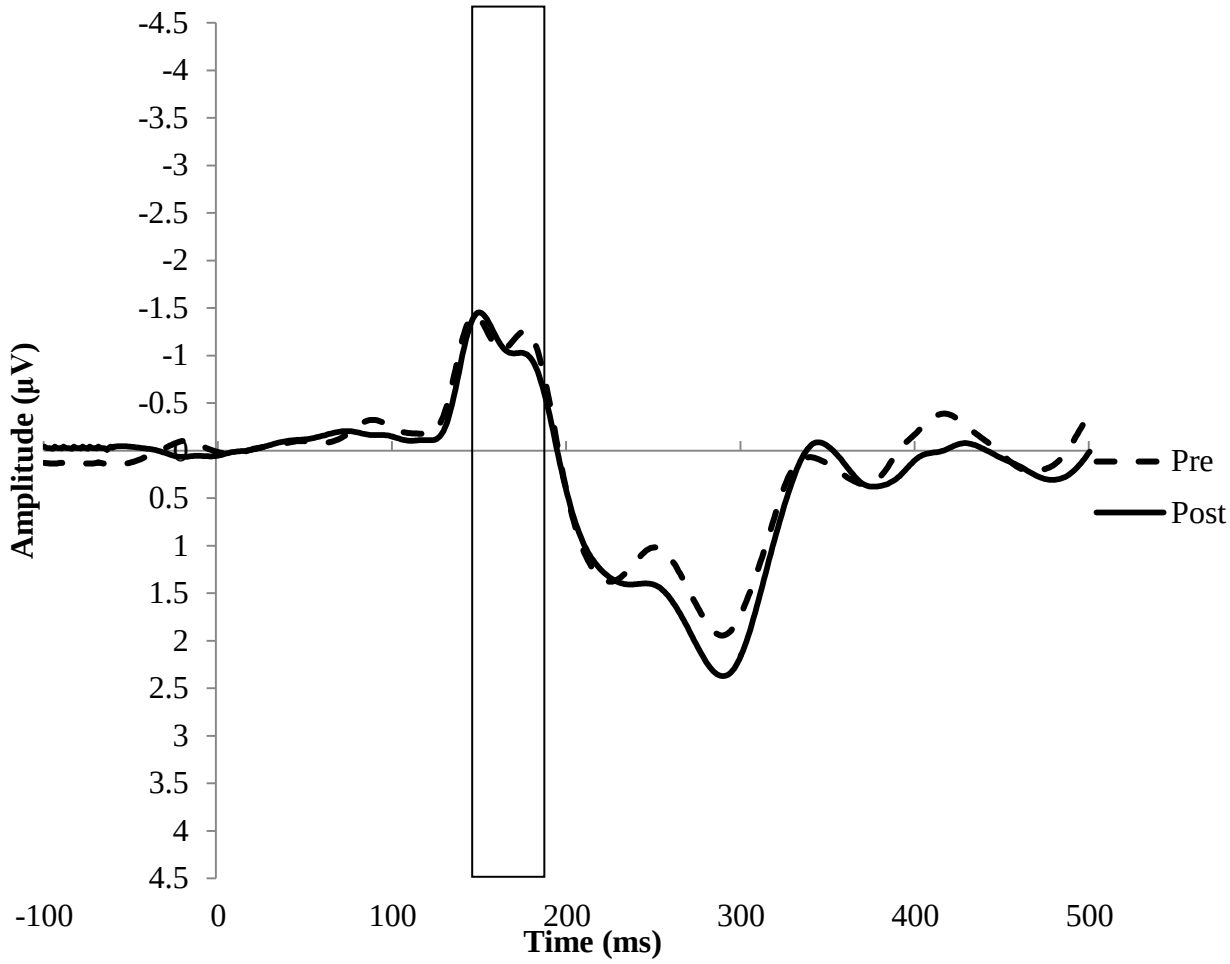

Figure 10. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes for design one. The transparent bar shows the average N1b time window (145 – 190ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = .574$, $p > .05$, $\eta^2 = .076$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .263$, $p > .05$, $\eta^2 = .036$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = .904$, $p > .05$, $\eta^2 = .114$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .176$, $p > .05$, $\eta^2 = .025$). Furthermore, none of the other contrasts reached significance.

For design two, the analysis of the amplitude of the N1b component revealed no main effect for block ($F_{(1.375,9.625)} = .623$, $p > .05$, $\eta^2 = .082$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .215$, $p > .05$, $\eta^2 = .030$). Furthermore, none of the other contrasts reached significance. This indicated that the amplitude of the N1b component did not change following induction (as seen in Figure 11 and 12 below).

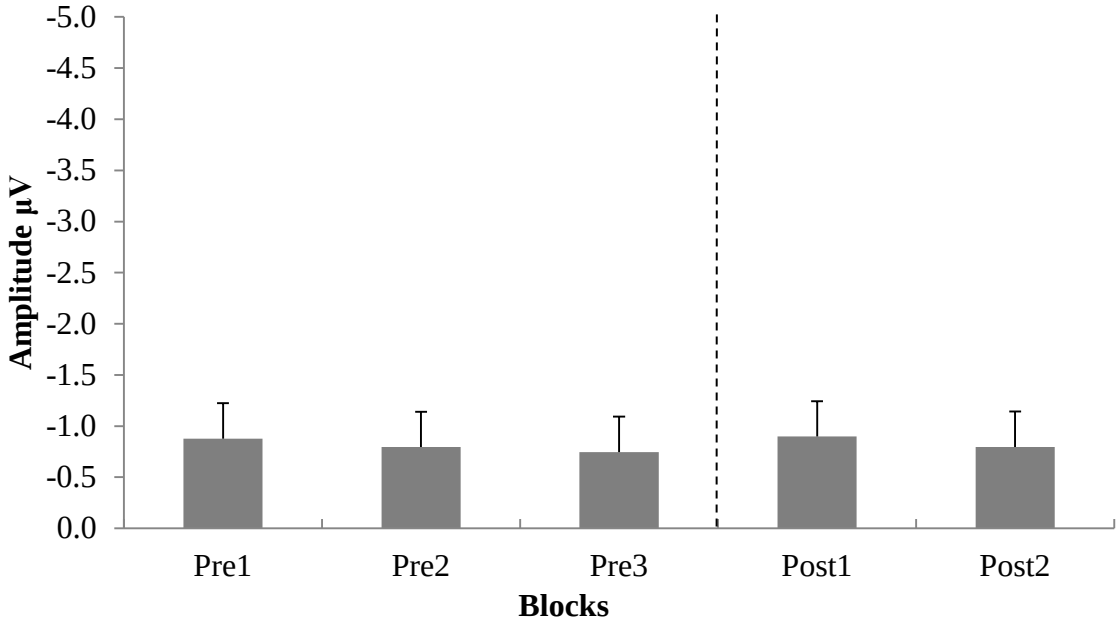

Figure 11. The pre-induction and post-induction amplitude change of the N1b component for design two. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

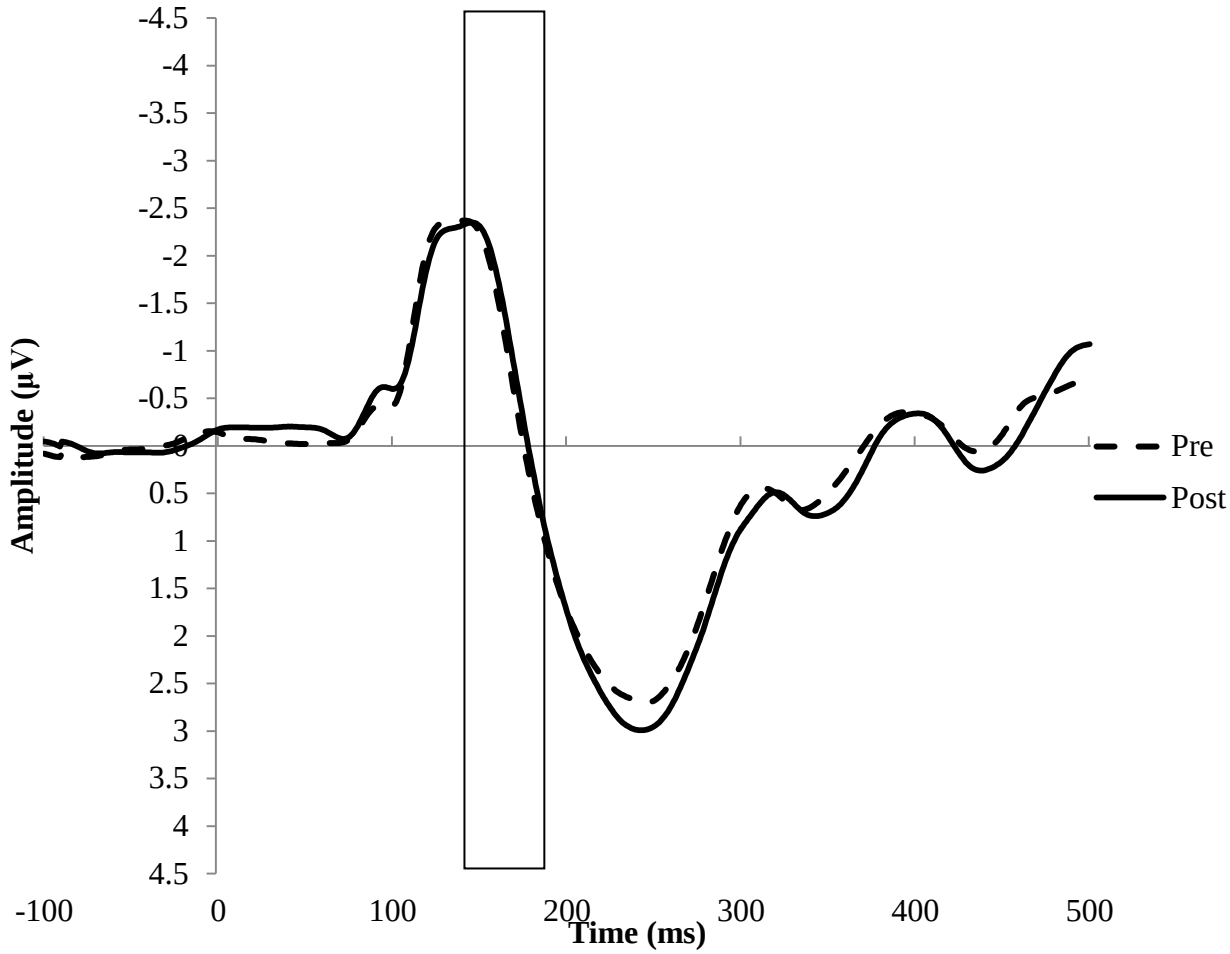

Figure 12. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes for design two. The transparent bar shows the average N1b time window (141 – 189ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = .691$, $p > .05$, $\eta^2 = .090$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 1.562$, $p > .05$, $\eta^2 = .182$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 1.926$, $p > .05$, $\eta^2 = .216$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 4.624$, $p > .05$, $\eta^2 = .398$). Furthermore, none of the other contrasts reached significance.

3.2 Experiment Three

As discussed in chapter one, the published evidence so far appears to suggest that visual hLTP has a cortical locus. Experiment two combined both the basic protocols as performed in experiment one together with the methodology of inter-ocular transfer. While both design one and two in experiment one showed successful potentiation, experiment two did not reveal similar results when examining the VEP recordings taken from the eye that did not receive induction.

At first glance, it appears to suggest that visual hLTP is taking place in the ascending visual pathways. However, previous non-invasive studies showed effects that cannot be explained pre-cortically (e.g. McNair et al., 2006; Ross et al., 2008). Furthermore, these studies stimulated and recorded binocularly (i.e. with both eyes viewing) (e.g. McNair et al., 2006; Ross et al., 2008). Therefore, before concluding that hLTP is not taking place in the neocortical regions, it was necessary to take a step back and examine whether or not monocular induction (i.e. presenting the LTP-inducing stimulus to one eye only) could actually induce visual hLTP. And whether or not hLTP could be measured from monocular viewing of the checkerboard stimulus.

This lead to experiment three, which was conducted to examine whether or not monocular induction and monocular baseline viewing was sufficient to induce and measure hLTP. Experiment three followed the same experimental procedure as experiment two, with the exception that monocular viewing during the pre-induction and post-induction blocks were taken from the eye that received the LTP-inducing stimulus as opposed to the eye that did not.

3.2.1 Methods

3.2.1.1 Participants

A new group of males (8) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 28 years (M = 20.25, SD = 1.75). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 50 to 100, with an average quotient of 73.13 (SD = 20.50). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

3.2.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master P2270 computer monitor (dimension: 47.5cm x 27cm, resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The screen luminance was measured with a Konica Minolta LS-110 Luminance Meter before (M = 51.90cd/m^2, SD = 0.54) and after (M = 51.28cd/m^2, SD = 0.89) the experiment. All the participants maintained a viewing distance of 57cm from the monitor.

3.2.1.3 Procedure

Experiment one had established that both design one and two can successfully induce visual hLTP. Experiment three was conducted to follow up on experiment two regarding whether or not monocular induction can successfully elicit visual hLTP. Therefore, only design one was utilized for efficient examination.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment two, during the induction block the LTP-inducing stimulus was only presented to the left or right eye while the other eye was covered with an eye patch. During the pre-induction and post-induction blocks VEP were recorded from the induced eye while the other eye was covered with an eye patch, this was the key variation to experiment two.

3.2.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

3.2.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved”

or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), viewing eye (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant eye, hemisphere, and viewing eye never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3) as a within subjects factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre- to post-induction blocks and this is the critical test for LTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 and P2 component were also analyzed in a similar way to the amplitude of the N1b component.

3.2.2 Results

The analysis of amplitude of the N1b component revealed no main effect for block ($F_{(4,28)} = .843$, $p > .05$, $\eta^2 = .108$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 1.404$, $p > .05$, $\eta^2 = .167$). Furthermore, none of the other contrasts reached significance. This indicated that the amplitude of the N1b component did not change following induction (as seen in Figure 13 and 14 below).

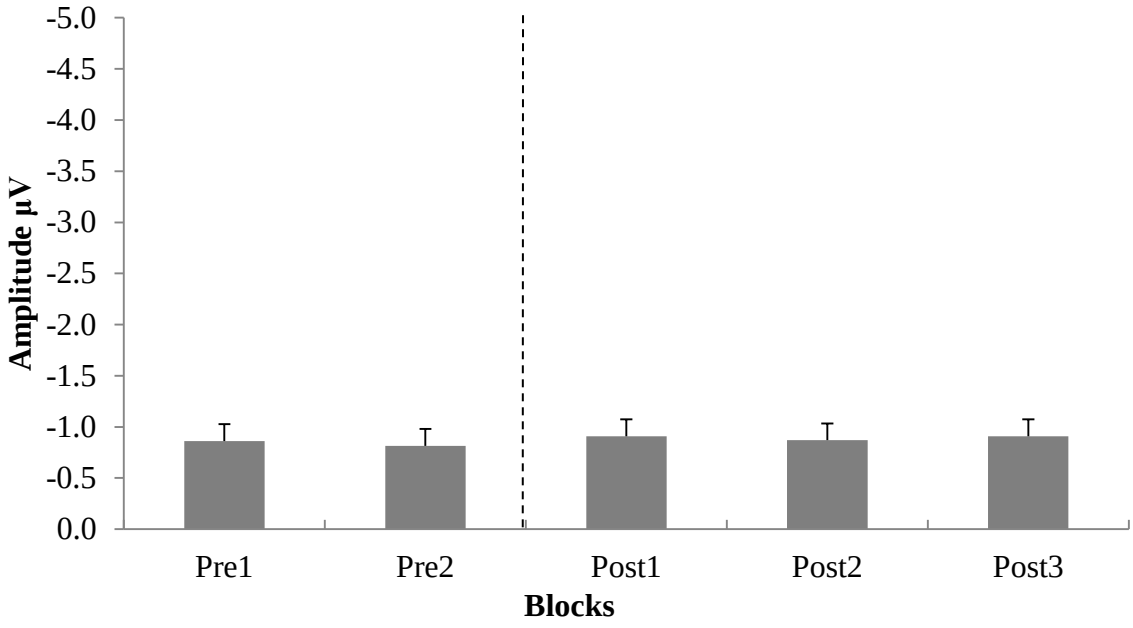

Figure 13. The pre-induction and post-induction amplitude change of the N1b component. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

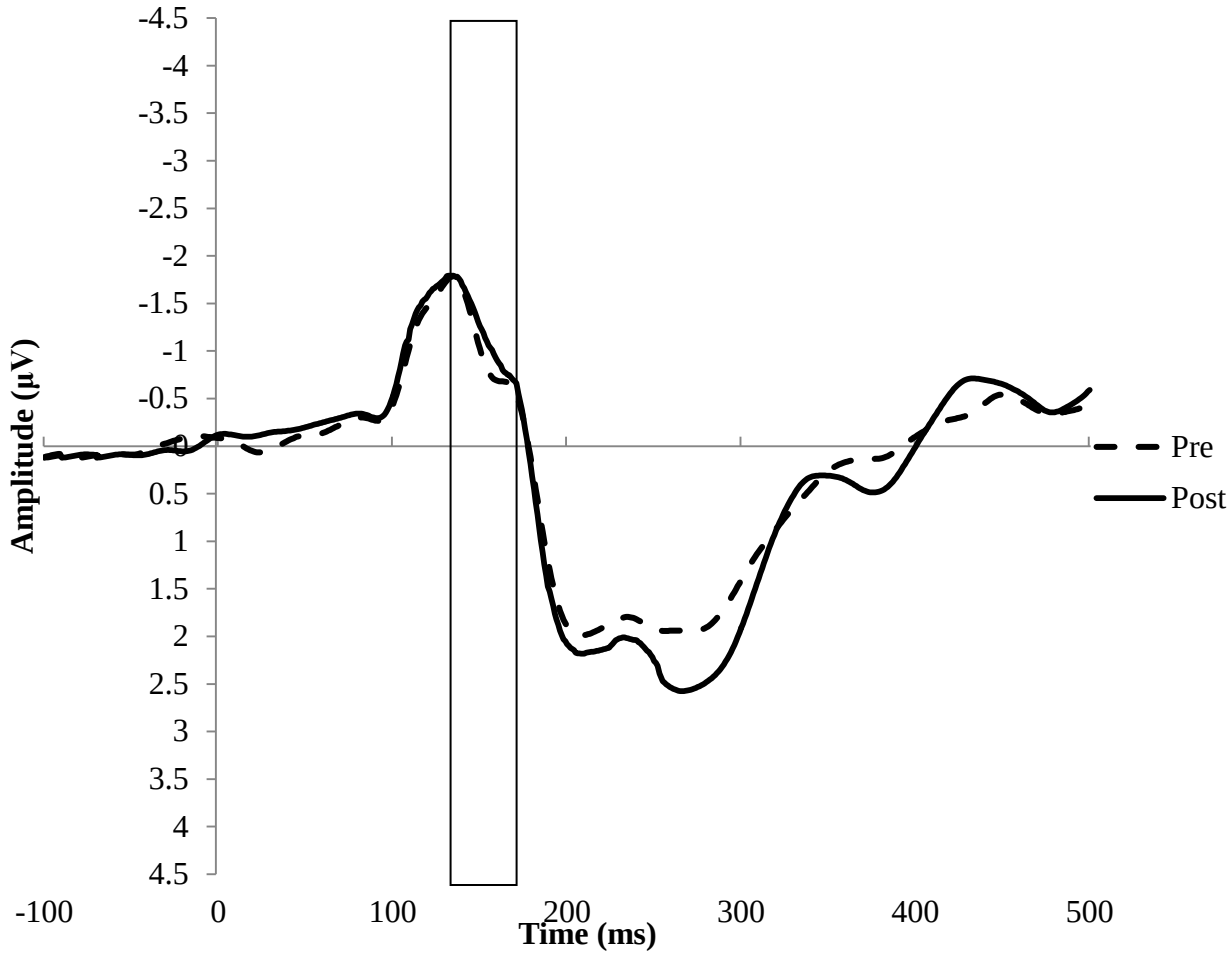

Figure 14. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the average N1b time window (133 – 170ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = 1.343$, $p > .05$, $\eta^2 = .161$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .008$, $p > .05$, $\eta^2 = .001$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 4.018$, $p > .05$, $\eta^2 = .365$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 3.697$, $p > .05$, $\eta^2 = .346$). Furthermore, none of the other contrasts reached significance.

3.3 Experiment Four

Experiment three again showed no significant potentiation following monocular induction during monocular viewing. The results so far suggest that visual hLTP was not successfully achieved in either of the experiments where the induction was carried out with only one of the eyes viewing the LTP-inducing stimulus combined with monocular recording of VEP during the baseline blocks.

Follow up experiments were conducted to examine if this failure to obtain hLTP was due to monocular recording of VEP being incapable of measuring hLTP or if monocular viewing of the LTP-inducing stimulus was incapable of eliciting hLTP. These hypotheses were tested by inducing monocularly and recording VEP binocularly in addition to inducing binocularly, a procedure known to induce hLTP as in experiment one, but recording VEP monocularly. If binocular stimulation was required to induce visual hLTP, the former variation to the paradigm should not show potentiation whereas the later variation should show a significant change in amplitude of the N1b component. Experiment four induced to one eye and took VEP recordings while both eyes were viewing the stimuli.

3.3.1 Methods

3.3.1.1 Participants

A new group of males (8) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 28 years (M = 19.13, SD = 1.36). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 60 to 100, with an average quotient of 85.71 (SD = 13.97). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

3.3.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master P2270 computer monitor (dimension: 47.5cm x 27cm, resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The screen luminance was measured with a Konica Minolta LS-110 Luminance Meter before (M = 50.30cd/m^2, SD = 0.81) and after (M = 50.56cd/m^2, SD = 0.58) the experiment. All the participants maintained a viewing distance of 57cm from the monitor.

3.3.1.3 Procedure

Experiment one had established that both design one and two could successfully induce visual hLTP. Experiment four was conducted to follow up on experiment three regarding whether or not monocular induction could successfully elicit visual hLTP. Therefore, only design one was utilized for efficient examination.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment two, during the induction block the LTP-inducing stimulus was only presented to the left or right eye while the other eye was covered with an eye patch. However, like experiment one during the pre-induction and post-induction VEP blocks were recorded while both eyes were viewing the checkerboard stimuli.

3.3.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

3.3.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved”

or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), induced eye (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant eye, hemisphere, and induced eye never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3) as a within subjects factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for hLTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 and P2 component were also analyzed in a similar way to the amplitude of the N1b component.

3.3.2 Results

The analysis of the amplitude of the N1b component revealed no main effect for block ($F_{(4,28)} = .258$, $p < .05$, $\eta^2 = .036$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .003$, $p > .05$, $\eta^2 = .044$). Furthermore, none of the other contrasts reached significance. This indicated that the amplitude of the N1b component did not change following induction, suggesting that monocular stimulation could not induce visual hLTP (as seen in Figure 15 and 16 below).

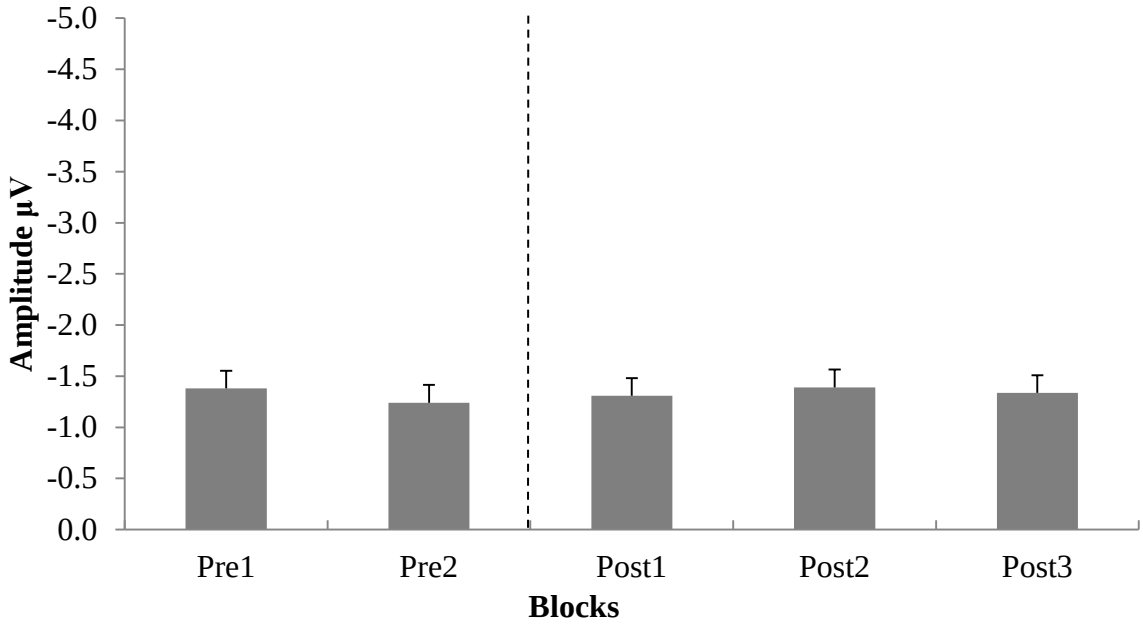

Figure 15. The pre-induction and post-induction amplitude change of the N1b component. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

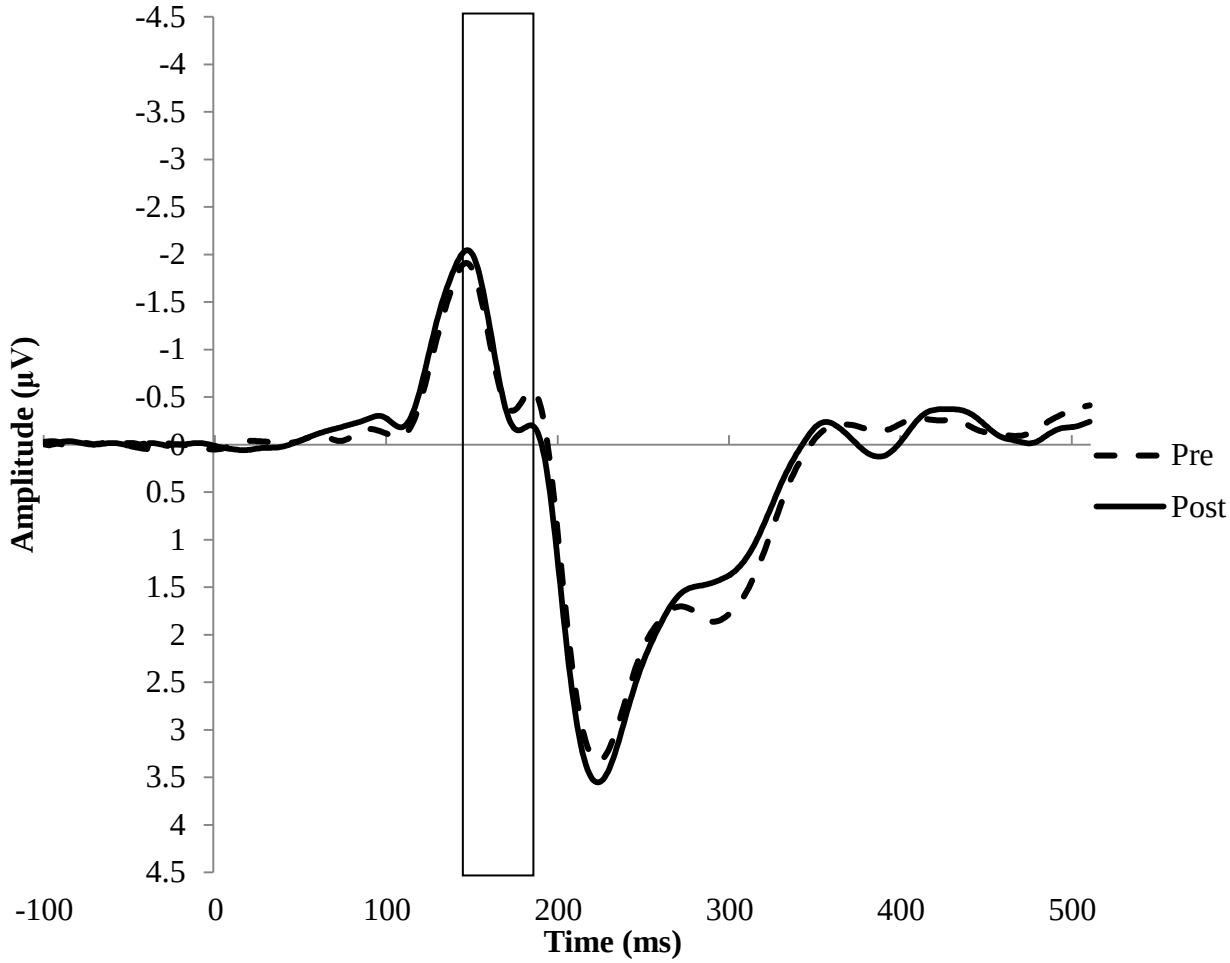

Figure 16. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the average N1b time window (143 – 188ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = .339$, $p > .05$, $\eta^2 = .046$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .300$, $p > .05$, $\eta^2 = .041$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 3.731$, $p > .05$, $\eta^2 = .348$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 1.215$, $p > .05$, $\eta^2 = .148$). Furthermore, none of the other contrasts reached significance.

3.4 Experiment Five

In experiment four participants viewed the checkerboard stimuli during the induction block with only one of their eyes but viewed the stimuli during the VEP blocks with both eyes. It is well established that hLTP can be measured during the VEP blocks when they are viewed binocularly as this is the typical paradigm (e.g. McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005; experiment one). Furthermore, participants viewed the stimuli with both eyes during the VEP recordings before and following the induction block. Experiment four also did not show a significant increase in the amplitude of the N1b component following induction. Therefore, when the results from experiment four with that of the results from experiments two and three are combined, the conclusion is that monocular induction (i.e. viewing the LTP-inducing stimulus with one eye only) does not appear to be sufficient to induce visual hLTP.

Finally, in order to determine if monocular recording is capable of measuring visual hLTP one more experiment was required. During the induction block in experiment five, participants viewed the checkerboard stimuli with both eyes. However, during the recording of the VEP blocks prior to and following the induction block, only one of the eyes viewed the checkerboard stimuli while the other eye was covered with an eye patch.

3.4.1 Methods

3.4.1.1 Participants

A new group of males (8) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 28 years (M = 24.13, SD = 6.53). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 60 to 100, with an average quotient of 82.50 (SD = 12.82). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

3.4.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master P2270 computer monitor (dimension: 47.5cm x 27cm, resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The screen luminance was measured with a Konica Minolta LS-110 Luminance Meter before (M = 51.04cd/m^2, SD = 0.55) and after (M = 50.76cd/m^2, SD = 0.32) the experiment. All the participants maintained a viewing distance of 57cm from the monitor.

3.4.1.3 Procedure

Experiment one had established that both design one and two could successfully induce visual hLTP. Experiment five was conducted as the last follow up experiment to investigate whether monocular recording of VEP was incapable of measuring hLTP or if monocular induction was not sufficient to induce hLTP. Therefore, only design one from experiment one was utilized for efficient examination.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment one, during the induction block both eyes were viewing the LTP-inducing stimuli. However, like experiment two and three during the pre-induction and post-induction blocks VEP was recorded with only either the left or the right eye viewing the checkerboard stimuli while the other eye was covered with and eye patch.

3.4.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

3.4.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis,

Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved” or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), viewing eye (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant eye, hemisphere, and viewing eye never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3) as a within subjects factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for hLTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 and P2 component were also analyzed in a similar way to the amplitude of the N1b component.

3.4.2 Results

The analysis of amplitude of the N1b component revealed a main effect for block ($F_{(2.137,14.958)} = 5.280$, $p = .017$, $\eta^2 = .430$). The contrast comparing the pre-induction to post-induction blocks was significant ($F_{(1,7)} = 8.526$, $p = .022$, $\eta^2 = .549$). The results indicated that binocular stimulation is required to elicit visual hLTP (as seen in Figure 17 and 18 below), and that monocular viewing during the pre-induction and post-induction VEP recording blocks is capable of measuring hLTP if it has been induced. Furthermore, none of the other contrasts reached significance.

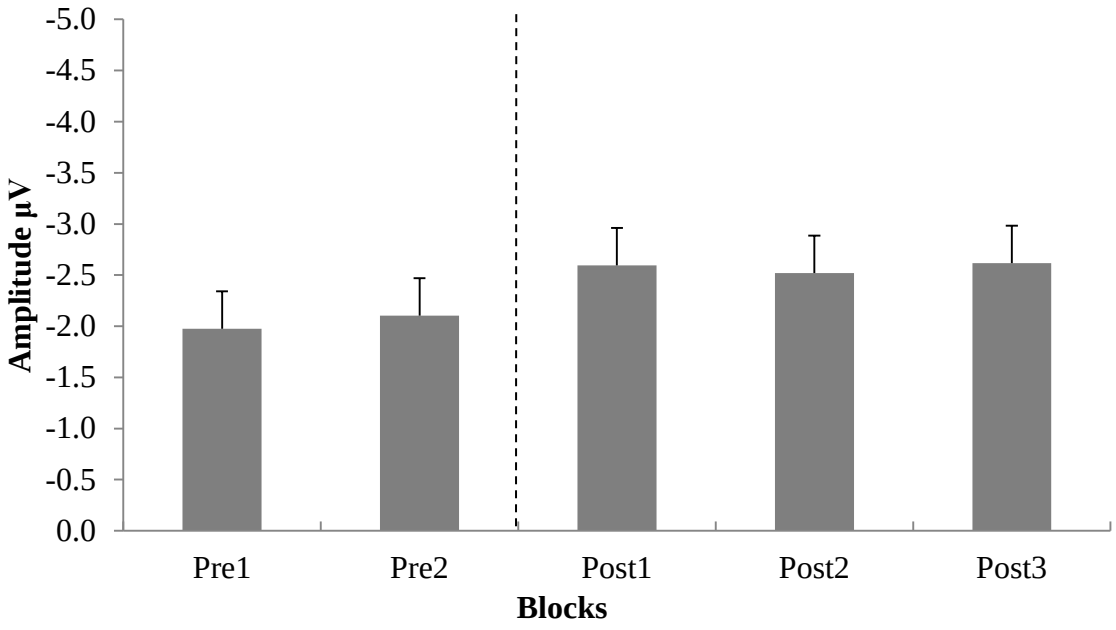

Figure 17. The pre-induction and post-induction amplitude change of the N1b component. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

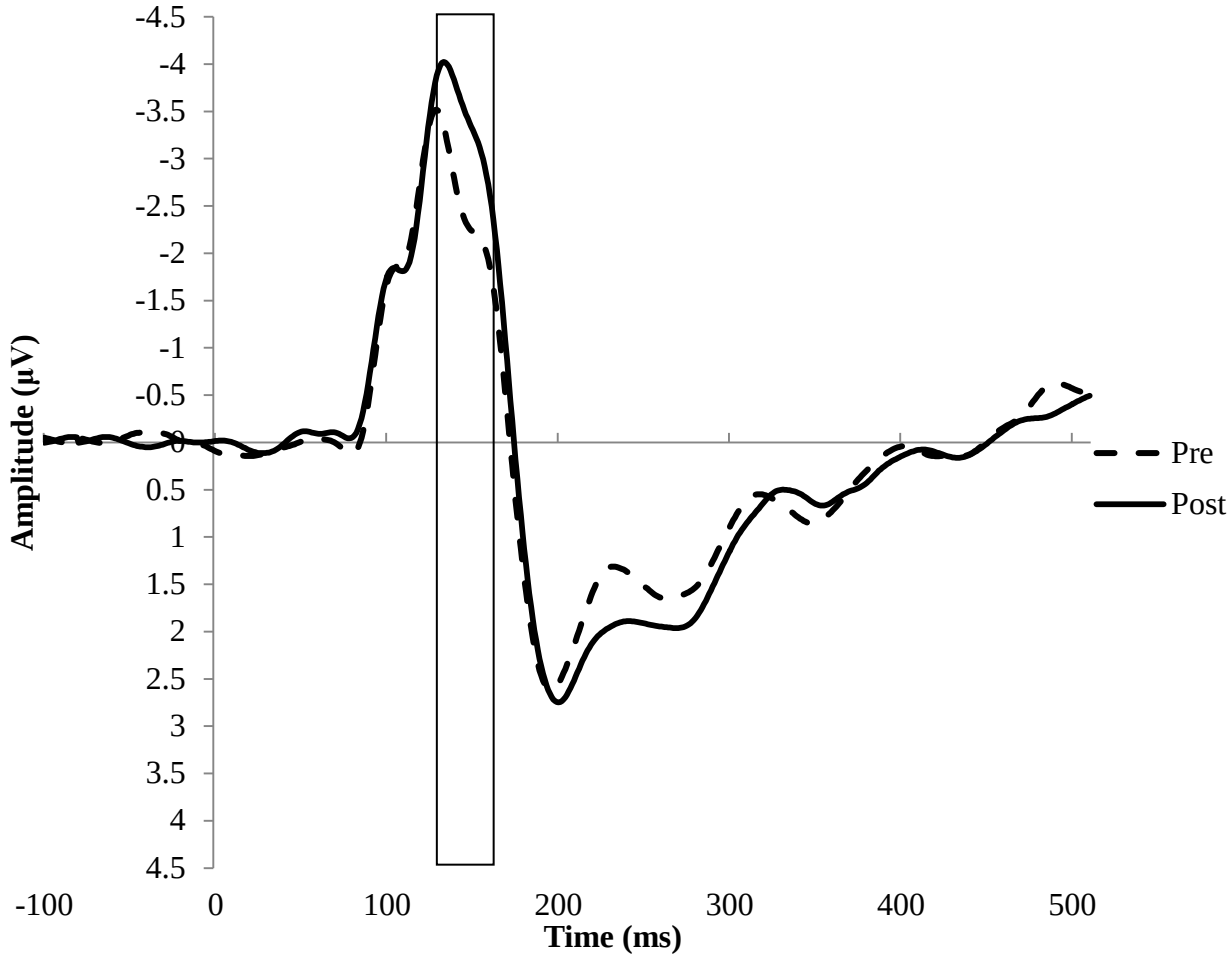

Figure 18. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the average N1b time window (129 – 162ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,28)} = 1.458$, $p > .05$, $\eta^2 = .172$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = 4.219$, $p > .05$, $\eta^2 = .376$). Furthermore, none of the other contrasts reached significance.

The analysis of the amplitude of the P2 component revealed no main effect for block ($F_{(4,28)} = 3.296$, $p > .05$, $\eta^2 = .320$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,7)} = .740$, $p > .05$, $\eta^2 = .096$). Furthermore, none of the other contrasts reached significance.

3.5 Further Analysis

Following the separate analysis of the experiments, the data were combined based on whether the participants received monocular or binocular induction. This was to demonstrate that hLTP is still evident even after combining experiments that took VEP recordings from one or both eyes. Hence, this is another piece of evidence to show that the VEP recording method was not key but it was down to whether participants received stimulation to one or both eyes. Moreover, it could be that participants that receive induction to only one eye produces a smaller effect. Therefore, combining the experiments this way can provide further demonstration that the sample size used give sufficient power.

Two paired samples t-tests were conducted on the collapsed values. The first paired samples t-test was conducted on the values obtained from the experiments where participants received binocular stimulation during the induction block (experiment one and five). The second paired samples t-test was conducted on values obtained from the experiments where participants received monocular stimulation during the induction block (experiment two, three, and four).

The results showed that the amplitude of the N1b component before (M=-1.94, SD=1.96) and after (M=-2.47, SD=1.94) binocular induction significantly differed ($t_{(23)}$ = 6.276, $p < .001$, $\eta^2 = 1.28$). In contrast, the amplitude of the N1b component before (M=-0.80, SD=1.20) and after (M=-0.84, SD=1.22) monocular induction did not significantly differ ($t_{(31)}$ = .998, $p > .05$, $\eta^2 = .18$).

3.6 Discussion

It began with one experiment (experiment two) that was set out to examine whether or not inter-ocular transfer of VEP recordings would occur. This was to investigate as to where visual hLTP is occurring in the human visual system. Whether it be along the ascending visual pathways or in the neocortical region. Experiment two used experiment one's protocol as the basis of the experimental paradigm with some additional protocols. Experiment two incorporated the methodology of inter-ocular transfer with experiment one's protocols. All the participants in experiment two received monocular induction (i.e. only one eye was viewing the LTP-inducing stimulus) with monocular VEP recording taken from the non-induced eye.

The analysis of VEP recordings obtained from the non-induced eye in experiment two showed a lack of hLTP following rapid sensory stimulation. Unsuccessful potentiation when the LTP-inducing stimulus was presented while only one eye was viewing was unexpected. At first glance the findings from experiment two appeared to suggest that visual hLTP might be occurring along the ascending visual pathways. However, the evidence gathered from the prior literature (as discussed in chapter one) had suggested a cortical locus of visual hLTP. Furthermore, there is a difference between experiment two and the prior non-invasive studies (e.g. McNair et al., 2006; Ross et al., 2008) that could potentially explain the results found. The previous non-invasive studies presented the stimulus to participants while both eyes were viewing during the baseline VEP recording and during the induction phases. Therefore, three follow up experiments were conducted. These three experiments were conducted to investigate whether or not there is a difference in hLTP achieved when comparing between monocular versus binocular viewing during the induction block. Furthermore, these three experiments wanted to examine if there was any difference between recording VEP monocularly compared to binocular viewing of the stimuli during baseline blocks.

The first follow up experiment (experiment three) replicated the experimental paradigm used in experiment two with the exception that during the pre-induction, post-induction and induction blocks the same eye was viewing the checkerboard stimuli while the other eye was covered with an eye patch (i.e. not having the transfer requirement). Like experiment two, experiment three did not reveal successful potentiation following high-frequency stimulation. To narrow down and obtain a clear indication as to whether monocular recording of VEP is incapable of measuring hLTP or monocular induction cannot successfully induce visual hLTP, two further follow up experiments were conducted.

Like experiment two and three, experiment four attempted to induce hLTP to one eye only while VEP recordings were taken with both eyes viewing the stimuli. Successful induction was not found in experiment four. Thus, one last follow up experiment was required but reversing the protocols used in experiment four. Like experiment two and three, experiment five took VEP recordings with only one of the eyes viewing the checkerboard stimuli while the other eye was covered with an eye patch. However, like experiment one, experiment five attempted to elicit hLTP by presenting the LTP-inducing stimulus with both eyes viewing. Finally, experiment five reported successful potentiation.

Combining the findings of all these experiments, it strongly suggested that the method of viewing during the pre-induction and post-induction blocks does not have an influence as to whether or not visual hLTP can be measured provided it has been induced. However, binocular induction was the key requirement to successfully induce visual hLTP. Furthermore, for the experiment that did reveal successful induction (i.e. experiment five), the change was evident for at least an hour following induction. Remaining evident for at least an hour following sensory stimulation implied that visual hLTP is long-lasting, and this was expected as evidence so far also suggest hLTP to be so.

It was unexpected that monocular viewing of the LTP-inducing stimulus would fail to successfully elicit visual hLTP (i.e. did not show inter-ocular transfer). Therefore, this highlighted the possibility that visual hLTP requires binocular viewing (i.e. viewing with both eyes) of the induction stimuli to achieve potentiation. On the contrary, monocular induction does not appear to be sufficient enough to cause any reliable changes to the amplitude of the N1b component. In other words, due to the lack of hLTP observed in the experiments that employed monocular induction regardless of VEP recording method, a binocular process should be involved in the occurrence of visual hLTP.

As a binocular process appeared to be responsible for successful potentiation, it is most likely that binocular neurons contributed to the occurrence of visual hLTP when it did occur. Studies conducted on animals were among the earliest to report the existence of binocular neurons. In 1959, Hubel and Wiesel examined the receptive fields in anaesthetized adult cats. Hubel and Wiesel (1959) was the first to document binocular neurons being located in the cat's striate cortex. Since then, binocular neurons have also been documented in other animals (e.g. Anzai, Bearse, Freeman, & Cai, 1995; Crawford et al., 1983; Cumming & Parker, 1997; Hubel & Wiesel, 1962).

In 1967, Barlow, Blakemore, and Pettigrew conducted a study on adult cats. Barlow et al., (1967) examined the neural mechanism that underlies binocular depth discrimination. They fixated the cat's head with a stereotaxic frame then tracked and recorded the action potentials of single neurons in the adult cats' primary visual cortex. Barlow et al. (1967) findings suggested that binocular neurons are primarily located in the cats' primary visual cortical region. Evidence to support that binocular neurons are localized to the primary visual cortex was also found by later studies (e.g. Barlow et al., 1967; Nikara, Bishop, & Pettigrew, 1968; Pettigrew et al., 1968).

There are clear limitations when trying to generalize animal findings directly onto humans. Therefore, later experiments were conducted on primates which are a much closer model to humans to examine where binocular neurons are located in the visual system. In 1986, Burkhalter and Van Essen conducted a study on macaque monkeys. Burkhalter and Van Essen (1986) took intracellular recording of the neurons in the monkey's visual cortex. They examined how the macaque monkey processed form, color, and disparity information. Burkhalter and Van Essen (1986) reported that binocular neurons are found in the visual neocortical area of these monkeys. Other studies have also reported findings consistent with Burkhalter and Van Essen (1986), that binocular neurons are located in the visual cortex (e.g. Maunsell & Van Essen, 1983; Poggio, 1995; Poggio & Poggio, 1984).

Studies conducted using human participants that investigated stereoscopic vision have also reported findings consistent with the animal literature (e.g. Blake & Levinson, 1977; Blake & Wilson, 2011; Grill-Spector & Malach, 2004; Neri, 2004; Parker, 2007). These studies have also found binocular neurons to be located in the human visual cortex. The binocular neurons found in the primary visual cortex (V1) are involved in the initial processing of stereoscopic vision (Parker & Cumming, 2001). Neurons in the extrastriate areas participate in the further processing of binocular depth (Parker & Cumming, 2001).

Due to basic neuroanatomay organization of the human brain, visual information from the left and right eyes remain segregated until the input is combined in the visual cortex (Anzai, Ohzawa, & Freeman, 1999). The binocular neurons found in the human visual cortex will contribute to the processing of the visual input received from both the eyes (Anzai et al., 1999). The point in the human visual system where the input from both eyes merge should provide an indication as to where visual hLTP is occurring in the brain. In other words, the primary location of where binocular neurons are found would suggest where sensory induced LTP is occurring in the human brain.

When only one of the eyes viewed the LTP-inducing stimulus (i.e. monocular induction), successful hLTP was not reported. On the other hand, in the experiments that took VEP recordings while one or both eyes were viewing the checkerboard stimuli during the pre-induction and post-induction blocks, potentiation was successful provided that the induction stimuli were view binocularly. Therefore, this suggested that in humans at least, the stereoscopic visual system contributed to the occurrence of visual hLTP and so hLTP most likely occurred in the cortical regions.

The experiments that presented the LTP-inducing stimulus to only one of the eyes failed to induce hLTP. This unsuccessful induction was found regardless of whether the stimuli was presented monocularly (i.e. viewing with one eye only) or binocularly (i.e. viewing with both eyes) while VEPs were recorded during the pre-induction and post-induction blocks. Combining this pattern of finding with the significant increase in the amplitude of the N1b component following binocular induction, the occurrence of visual hLTP must require the processing of a binocular input. Both animal (e.g. Barlow et al., 1967; Burkhalter & Van Essen, 1986; Maunsell & Van Essen, 1983; Nikara, Bishop, & Pettigrew, 1968; Pettigrew et al., 1968; Poggio, 1995; Poggio & Poggio, 1984) and human (e.g. Blake & Levinson, 1977; Blake & Wilson, 2011; Grill-Spector & Malach, 2004; Neri, 2004; Parker, 2007; Parker & Cumming, 2001) studies indicated that the binocular neurons are found in the visual neocortex. As a consequent, visual hLTP should be occurring in the visual cortical region as opposed to the ascending visual pathways. The results from this set of experiments are consistent with the current literature that also suggests visual hLTP is occurring in the visual cortical regions.

A couple of recommendations are derived from this set of experiments as future study options. Firstly, to ensure participants are engaged and attending to the visual presentation during the experiment, an additional protocol can be included to the current basic paradigm.

During the experiment, the fixation dot can change color periodically and every time it does the participant is required to make a response by pressing a button before they can continue. Secondly, these experiments provided further support for the suggestion that the current findings reflect that hLTP is occurring in the visual cortical area. When Clapp et al. (2005b) combined the non-invasive paradigm with fMRI they reported a significant increase in BOLD responses over the bilateral secondary visual cortex. As fMRI provides good spatial resolution, a future study could examine the monocular and binocular induction paradigms using fMRI to determine what areas, if any, are differentially activated by high-frequency visual stimulation.

Chapter 4: Cortisol and Human Long-Term Potentiation

The findings from the first set of experiments indicated that visual hLTP is occurring in the neocortical region of the human brain. This was established as binocular induction was required to successfully elicit visual hLTP and binocular neurons do not occur in the ascending visual pathways. The findings were consistent with earlier studies on cellular LTP and contributed to the literature regarding what is currently known about sensory induced LTP.

The second aim of this thesis was to examine the relationship between the level of cortisol with the magnitude of potentiation achieved. In comparison to the understanding of where visual hLTP is occurring in the brain, there is currently little known regarding the relationship between sensory induced LTP with cortisol.

Over the years, the studies conducted in regards to the relationship between cortisol and memory resulted in conclusions ranging from cortisol improving memory performance to cortisol impairing learning and memory formation. Some studies have reported that an extremely low level of corticosterone results in impaired memory performance (Conrad et al., 1997; Oitzl & de Kloet, 1992; Roozendaal et al., 1996). On the other hand, it has also been suggested that an extremely elevated level of adrenal steroids results in a decline in memory performance, at least in animal studies (Endo et al., 1996).

The studies that examined the acute elevation in stress hormones have been rather inconclusive (e.g. De Kloet et al., 1999; Lupien & McEwen, 1997; Roozendaal, 2002; Wolf, 2003). While some of these studies have reported that temporary elevation can enhance (e.g. McCormick et al., 1997) performance, there are others that have reported the opposite (e.g. De Quervain et al., 1998). Furthermore, a chronic elevation in stress hormone has been shown to impair learning and memory performance in animals (e.g. Belanoff et al., 2001; Dachir et

al., 1993; Gold et al., 2002; Luine et al., 1994; Lupien & McEwen, 1997; McEwen & Sapolsky, 1995; Wolf, 2003).

In spite of having a range of findings so far, an increasing number of experiments are starting to suggest that the relationship between animal stress hormones and memory performance is best captured by an inverted-U shaped function (e.g. Diamond et al., 1992; Het et al., 2005; Kovacs et al., 1976; Kovacs et al., 1977; Roozendaal, 2002; Roozendaal & McGaugh, 1996; Roozendaal et al., 1999; Sauro et al., 2003; Vaher et al., 1994a; Vaher et al., 1994b). An inverted-U shaped function means that an extremely high or low level of corticosterone results in a decline in memory performance, whereas a moderate level of stress is correlated with optimum memory performance.

Comparably, a raised level of adrenal steroids has been correlated with a decline in the magnitude of potentiation achieved (e.g. Dubrovsky et al., 1987; Filipini et al., 1991). Moreover, an acute elevation in corticosterone has also been associated with a reduction in level of LTP reported (e.g. Pavlides et al., 1993; Filipini et al., 1991). These findings corresponds to the animal studies that examined the relationship between the level of corticosterone and cellular LTP. Therefore, this reflects the relationship between cortisol (i.e. stress) with LTP, learning and memory formation.

While the relationship between corticosterone and animal LTP appears to be a negative pattern (e.g. Bennett et al., 1991), again there are studies that have suggested otherwise. Consistent with the animal literature on corticosterone and memory performance, some studies have suggested that the relationship between adrenal steroids and LTP is also best represented by an inverted U shaped function (e.g. Diamond et al., 1992; Pavlides et al., 1994). That a moderate level of adrenal steroids is associated with a bigger magnitude of potentiation achieved as compared to either extremely high or low levels of corticosterone.

While animal subjects do act as a good medium to examine stress hormones and memory formation, ultimately the application of the findings to healthy human is most desirable. However, it is also clear that generalizing the findings directly from animals to humans are limited due to biological differences between the two. Nevertheless, over the years there is also an accumulation of studies that examined stress hormones and memory using human participants.

The majority of the literature suggests that temporary (e.g. Beckwith et al., 1986; Kischbaum et al. 1996; Newcomer et al., 1994) and prolonged elevation (e.g. Newcomer et al., 1999; Wolkowitz et al. 1990) in the level of cortisol is correlated with a decline in learning and memory performance. However, similar with the animal literature (e.g. Diamond et al., 1992; Pavlides et al., 1994), results so far suggested that the relationship between cortisol and memory performance is best described as an inverted U shaped function (e.g. Fehm-Wolfsdorf et al., 1993; Lupien & McEwen, 1997; Yerkes & Dodson, 1908). Again, it is a moderate level of cortisol that is linked with optimum learning and memory formation.

Although, in comparison to the animal literature, there is far fewer studies conducted to examine cortisol and LTP in healthy humans. Firstly, as LTP is thought to be the underlying mechanism to learning and memory formation (Cooke & Bliss, 2006; Bliss & Collinridge, 1993; Bliss & Lomo, 1973; Malenka, 2003; Spatz, 1996). And secondly, sensory induced LTP appears to be analogous to cellular LTP which makes the non-invasive paradigm a very convenient methodology to examine LTP in healthy humans. Therefore, employing the non-invasive paradigm to explore how cortisol levels might influence hLTP should produce findings that can ultimately be generalized to human learning and memory formation.

The manipulation of stress hormones in human has commonly involved the oral administration of cortisol steroids (e.g. Fehm-Wolfsdorf et al., 1993; Kirschbaum et al., 1996; Newcomer et al., 1999; Wolkowitz et al., 1990). There are other studies that have chosen to

use more natural stressors to alter the level of adrenal steroids (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975). The cold-pressor technique has been used by some researchers to help investigate the relationship between cortisol and memory performance (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975). This method requires the participant to fully immerse their non-dominant hand in a bucket of ice temperature water. Experiments that have used this method have reported an elevation in the level of cortisol in participants (e.g. Andreano & Cahill, 2006; Bullinger et al., 1984; Cahill et al., 2003; Lovallo, 1975).

Therefore, the next set of experiments combined the basic experimental protocol as used in experiment one with the cold-pressor technique. This was an attempt to make this set of experiments and prior non-invasive studies as similar as possible for easier comparison of the results. Furthermore, this should also facilitate the comparability between this set of experiments and the experiments conducted earlier as part of this thesis. To keep track of changes in the level of cortisol, saliva samples were collected from each participant at various points during the experiment.

4.1 Experiment Six

To ensure the findings are most comparable with those from the previous experiments in this thesis, it is appropriate to employ a similar paradigm. The key purpose for this next set of experiments was to examine the relationship between cortisol with the level of hLTP achieved. Therefore, it is important to also establish that the method used to manipulate the cortisol level does not in and of itself cause changes to the VEP. In other words, it is important to ascertain that it is only the high-frequency stimulation that is leading to changes into the amplitude of the N1b component in order to determine if the cortisol level moderates how much potentiation can be achieved. Therefore, as one of the last three experiments conducted for this thesis, experiment six was carried out in order to determine if the ice temperature water condition (i.e. the cold-pressor technique) by itself could induce reliable changes to the amplitude of the N1b component.

Firstly, to allow for easier comparison among all experiments conducted as part of the thesis and with the prior non-invasive studies, experiment six used the basic experimental paradigm of experiment one design one. The cold-pressor technique was chosen because it was considered less intrusive compared to oral administration of corticosteroids. The key difference between experiment six and experiment one was that the induction phase was omitted and replaced with the immersion of the non-dominant hand in ice water. This was to examine the effects of the cold-pressor technique itself. Saliva samples were collected to monitor each participant's cortisol level throughout the experiment. Furthermore, because the level of cortisol has been found to be highest when people first wake up and steadily declines throughout the day (e.g. Alderson & Novack, 2010; Akil et al., 1999; Pruessner et al., 1997), data were only collected from noon onwards. Data collection beginning after 12pm should provide more stable readings of each participants' cortisol level during the experiment. This is

common practice as done by the prior studies investigating the effects of cortisol (e.g. Andreano & Cahill, 2006; Cahill et al., 2003).

4.1.1 Methods

4.1.1.1 Participants

A new group of males (14) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 20 to 28 years (M = 23.86, SD = 2.54). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 60 to 100, with an average quotient of 87.14 (SD = 15.90). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

4.1.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master computer monitor (model: S24B350) (resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The default screen resolution was set by E-Prime of 640 x 480 pixels. All the participants maintained a viewing distance of 57cm from the monitor.

4.1.1.3 Procedure

The key purpose of experiment six was to examine the effects of the cold-pressor technique itself without rapid sensory stimulation. Experiment one had established that both

design one and two could successfully induce visual hLTP. Therefore, only design one of experiment one was utilized for efficient examination.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment one, during the pre-induction and post-induction blocks VEP were recorded while both eyes were viewing the checkerboard stimulus. However, the key difference between experiment six and experiment one was the induction block was omitted. Participants were instructed to immerse their non-dominant hand in a bucket of ice temperature water for 3mins in between the Pre2 and Post1 blocks. The main question of interest was to determine if using the cold-pressor technique by itself would produce an increase in the amplitude of the N1b component.

During various points of the experiment, all the participants were instructed to chew on a cotton swab for 2mins until it is completely soaked with their saliva. This was to keep track of each participants' cortisol level throughout the experiment. Eight saliva samples were taken from each participant at the following times points: (1) before the experiment began, (2) after Pre1, (3) after Pre2 before submerging the non-dominant hand in the water, (4) after submerging the non-dominant hand in the water, (5) after Post1, (6) after Post2, (7) at the end of the delay but before Post3, and (8) after Post3.

Participants were instructed to rinse their mouth with water before the experiment began to reduce the possibility of contaminating the saliva samples with food or drinks consumed earlier in the day. Furthermore, the level of cortisol level tend to be highest when people first wake up and steadily decline throughout the day (e.g. Alderson & Novack, 2010; Akil et al., 1999; Pruessner et al., 1997). Therefore, in attempt to obtain more stable cortisol recordings all the data collection for the experiment were performed after 12pm. This is also commonly done by other studies investigating the effects of cortisol (e.g. Andreano & Cahill, 2006; Cahill et al., 2003). The cortisol level present in each saliva sample must be at least 5.0

nmol/L and above for an actual reading to be given. If the cortisol level is below 5.0 nmol/L in the saliva sample, analysis from the lab will be recorded as <5.0 nmol/L by default.

4.1.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

4.1.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved” or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant eye and hemisphere never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3) as a within subjects

factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for LTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 component was also analyzed in a similar way to the amplitude of the N1b component.

4.1.2 Results

The analysis of the amplitude of the N1b component revealed no main effect for block ($F_{(4,52)} = .975$, $p > .05$, $\eta^2 = .070$). Results showed that the N1b amplitude did not change following the ice temperature water condition (as seen in Figure 19 and 20 below).

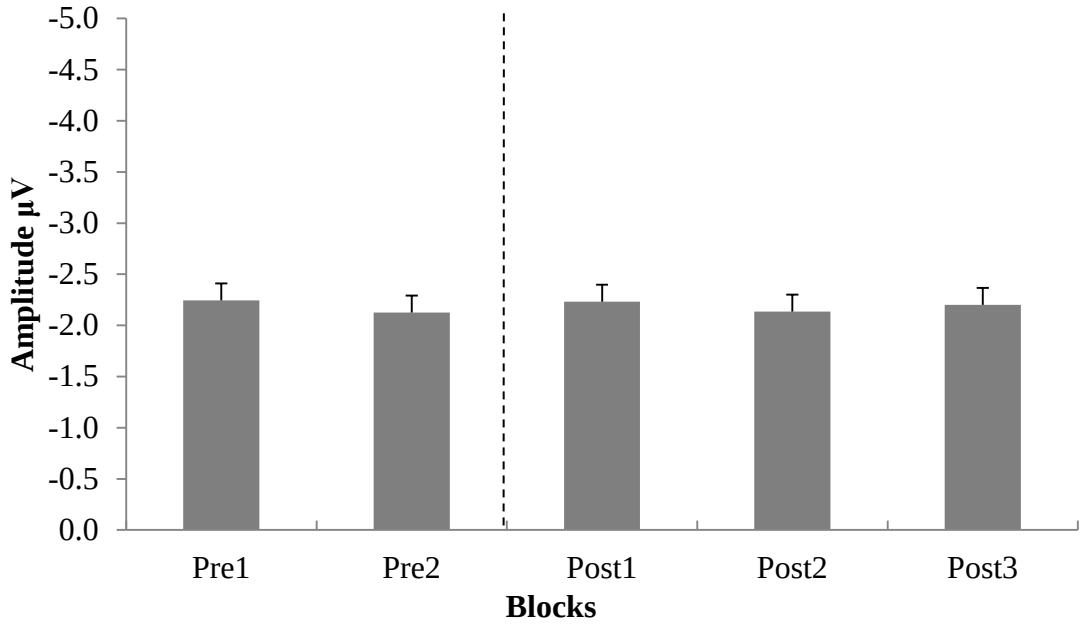

Figure 19. The amplitude change of the N1b component. The vertical dashed line indicates when participants immersed their hand in water. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

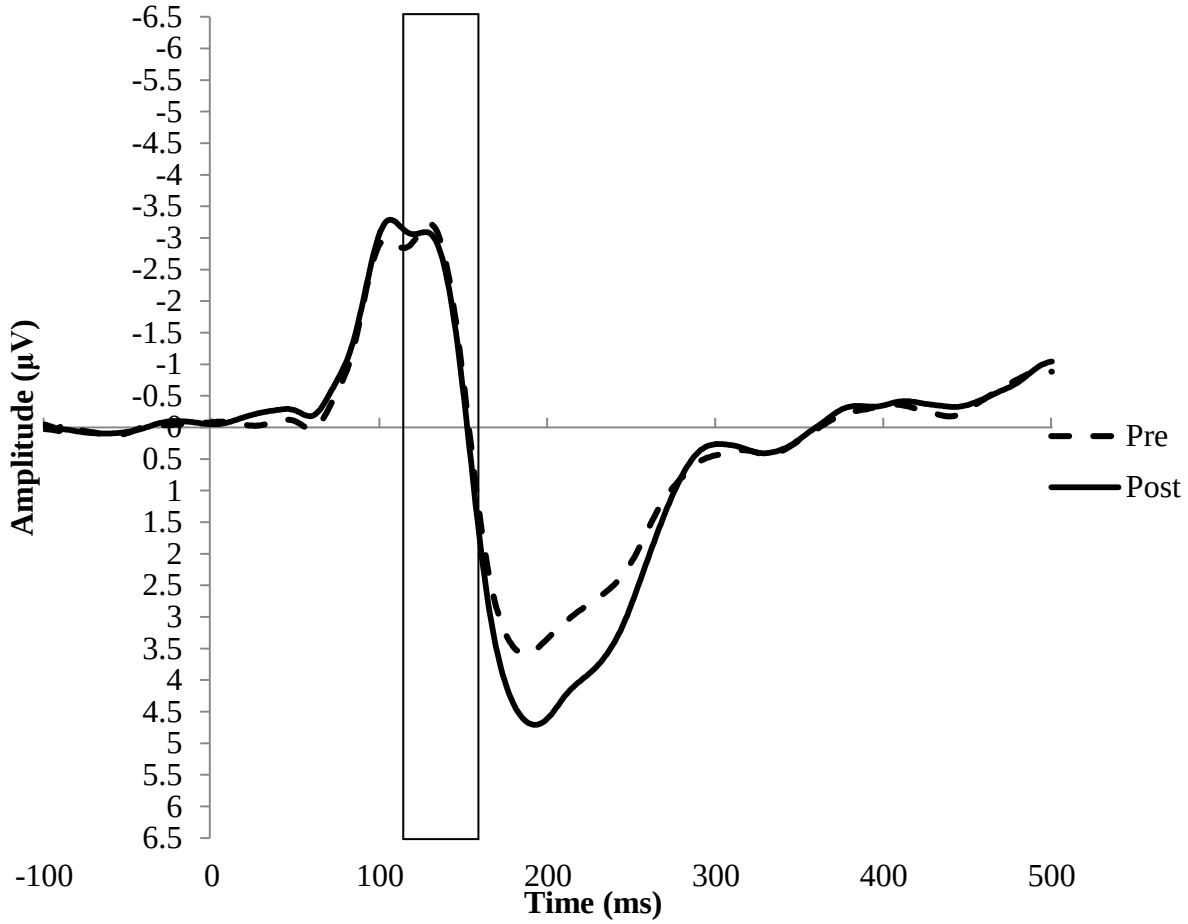

Figure 20. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the average N1b time window (116 – 159ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,52)} = 1.746$, $p > .05$, $\eta^2 = .118$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,13)} = 3.514$, $p > .05$, $\eta^2 = .213$). Furthermore, none of the other contrasts reached significance.

For some of the saliva samples obtained from participants, the cortisol level was below 5.0 nmol/L. For these sample readings, the analysis from the lab was simply recorded as <5.0 nmol/L by default. Because these samples do not have an exact reading, they were recorded as "blank" and not included in the following analysis.

The level of cortisol measured at various points during the experiment was collapsed to obtain an average of the cortisol level prior to and following induction. A paired samples t-

test was conducted and found that the cortisol level prior to (*M*=9.57, *SD*=3.10) and following (*M*=8.01, *SD*=1.55) induction did significantly differ ($t_{(10)} = 2.27$, $p = .047$). This suggested that by asking participants to submerge their non-dominant hand in a bucket of ice temperature water does show a significant change to their level of cortisol (as seen in Figure 21 below).

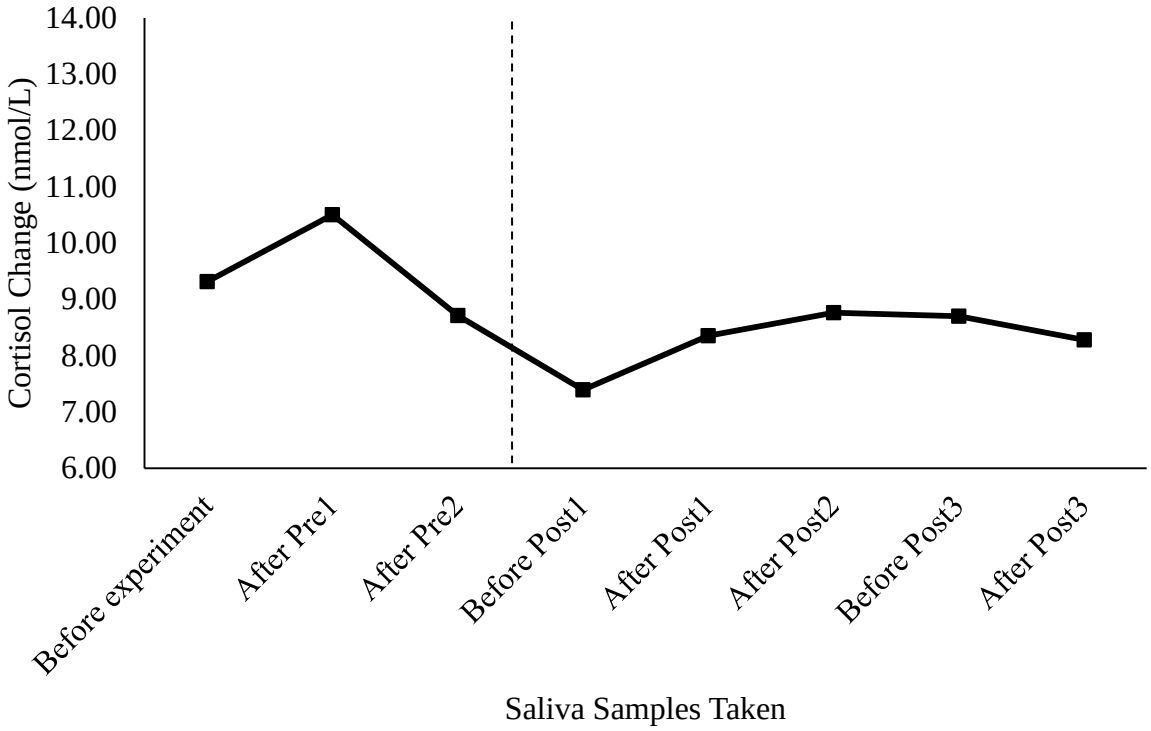

Figure 21. The cortisol level analysed from the saliva samples taken at various points during experiment six. The vertical dashed line indicates when participants immersed their hand in water.

Studies that examined cortisol level commonly analysed only the level of cortisol prior and following the experimental condition (e.g. Kirschbaum et al., 1996; Newcomer et al., 1994). Therefore, a second paired samples t-test was conducted to compare the level of cortisol recorded following Pre2 (*M*=9.40, *SD*=3.26) and before Post1 (*M*=7.60, *SD*=1.45). The results showed that the level of cortisol did not significantly change ($t_{(8)} = 1.96$, $p = .086$). Although, there was a trend for a reduction in the level of cortisol difference following

participant immersing their non-dominant hand in a bucket of ice temperature water for 3mins. This finding corresponds to the results found in the first paired samples t-test that was just presented.

4.2 Experiment Seven

This set of experiments were concerned with investigating how the level of cortisol in human participants might moderate the degree of potentiation achieved. As the method chosen to manipulate the level of cortisol is the cold-pressor technique, it was important that another control experiment should also be conducted to ensure that simply asking participants to immerse their non-dominant hand in the bucket of water will not in and of itself cause changes to the degree of potentiation that can be achieved or significantly alter the participants' level of cortisol. This would help ensure that any relative changes observed following the cold-pressor technique is actually due to the method used to manipulate cortisol.

Experiment seven was conducted as the next control experiment and replicated the protocols of experiment six except for the fact that the water was at a comfortable room temperature and the induction stimuli were also presented between the VEP blocks labelled Pre2 and Post1.

4.1.1 Methods

4.2.1.1 Participants

A new group of males (14) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 39 years (M = 23.79, SD = 5.42). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 70 to 100, with an average quotient of 89.29 (SD = 9.17). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

4.2.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master computer monitor (model: S24B350) (resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The default screen resolution was set by E-Prime of 640 x 480 pixels. All the participants maintained a viewing distance of 57cm from the monitor.

4.2.1.3 Procedure

Experiment seven was conducted as a control experiment to ensure that by simply asking participants to immerse their non-dominant hand in the bucket of water would not by itself prevent hLTP or substantially alter participants' level of cortisol. Experiment one has established that both design one and two could successfully induce visual hLTP. Therefore, only design one was used for efficient examination of the questions of interest in experiment seven.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment one, during the pre-induction and post-induction blocks VEP was recorded while both eyes were viewing the checkerboard stimulus. Participants were instructed to immerse their non-dominant hand in a bucket of room temperature water for 3mins after Pre2 and before the induction block.

During various points of the experiment, all the participants were instructed to chew on a cotton swab for 2mins until it is completely soaked with their saliva. This was to keep track of each participants' cortisol level throughout the experiment. Eight saliva samples were taken from each participant at the following times points: (1) before the experiment began, (2) after Pre1, (3) after Pre2 before the induction block, (4) after the induction block, (5) after Post1, (6) after Post2, (7) at the end of the delay before Post3, (8) and after Post3.

Participants were instructed to rinse their mouth with water before the experiment began to reduce the possibility of contaminating the saliva samples with food or drinks consumed earlier in the day. Furthermore, the level of cortisol tend to be highest when people first wake up in the morning and steadily decline throughout the day (e.g. Alderson & Novack, 2010; Akil et al., 1999; Pruessner et al., 1997). Therefore, in attempt to obtain more stable cortisol recordings all the data collection for the experiment were performed after 12pm. This is also commonly done by other studies investigating the effects of cortisol (e.g.

Andreano & Cahill, 2006; Cahill et al., 2003). The cortisol level present in each saliva sample must be at least 5.0 nmol/L and above for an actual reading to be given. If the cortisol level is below 5.0 nmol/L in the saliva sample, analysis from the lab will simply be recorded as <5.0 nmol/L by default.

4.2.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

4.2.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved” or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant

eye, and hemisphere never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3 and Pre1/Pre2/Pre3/Post1/Post2) as a within subjects factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared pre-induction to post-induction blocks and this is the critical test for hLTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 component was also analyzed in a similar way to the amplitude of the N1b component.

4.2.2 Results

The analysis of amplitude of the N1b component revealed a main effect for block ($F_{(1.965,25.540)} = 27.634$, $p < .001$, $\eta^2 = .680$). The contrast comparing the pre-induction to post-induction blocks was significant ($F_{(1,13)} = 49.665$, $p < .001$, $\eta^2 = .793$). Furthermore, none of the other contrasts reached significance. This indicated that in this control experiment where participants placed their non-dominant hand in a bucket of room temperature water there was a significant increase in the amplitude of the N1b component following induction (see Figure 22 and 23 below).

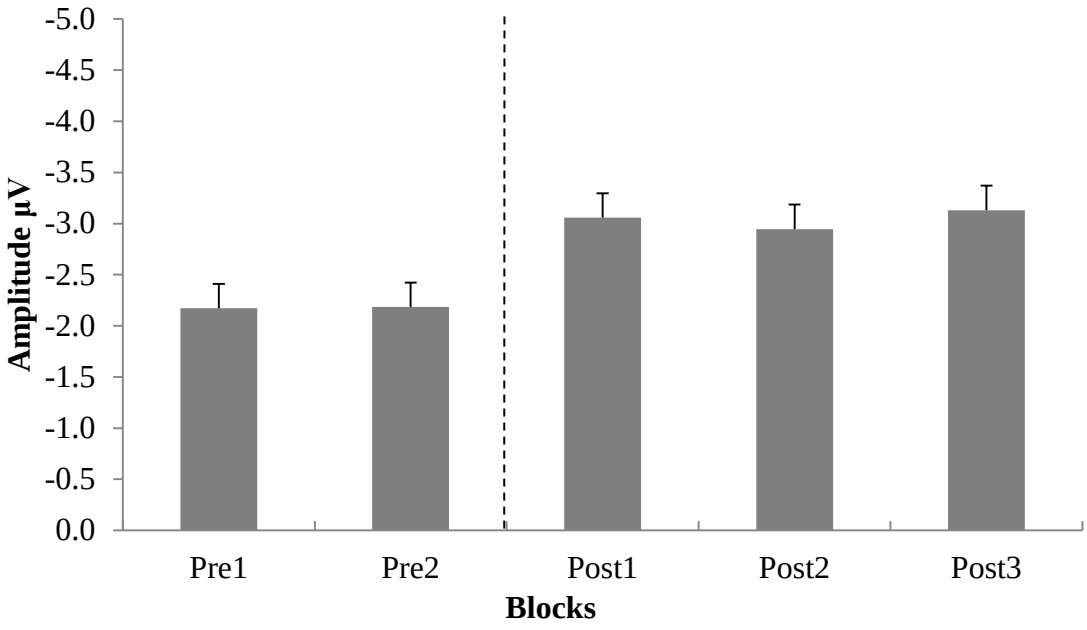

Figure 22. The pre-induction and post-induction amplitude change of the N1b component. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

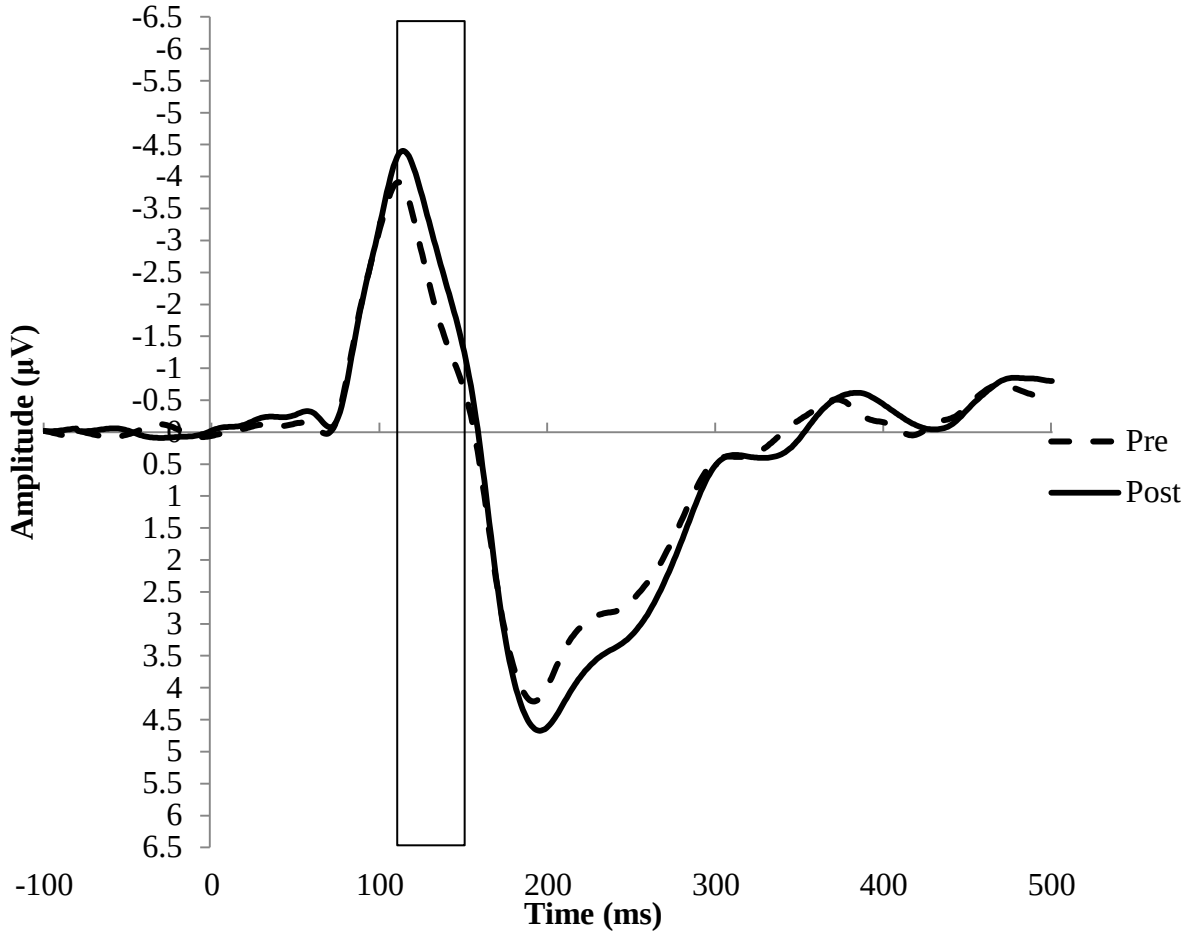

Figure 23. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the average N1b time window (111 – 148ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,52)} = 1.019$, $p > .05$, $\eta^2 = .073$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,13)} = 1.406$, $p > .05$, $\eta^2 = .098$). Furthermore, none of the other contrasts reached significance.

For some of the saliva samples obtained from participants, the cortisol level was below 5.0 nmol/L. For these sample readings, the analysis from the lab was recorded as <5.0 nmol/L by default. Because these samples do not have an exact reading, they were recorded as "blank" and not included in the following analysis.

The cortisol levels measured at various points during the experiment was collapsed to obtain an average of the cortisol level prior to induction and following induction. A paired

samples t-test was conducted and found that the cortisol level prior to induction (*M*=10.73, *SD*=5.58) and following induction (*M*=10.11, *SD*=8.77) did not significantly differ ($t_{(9)} = .54$, $p > .05$). This suggested that merely asking participants to submerge their non-dominant hand in a bucket of water does not cause a significant change to their level of cortisol (as seen in Figure 24 below).

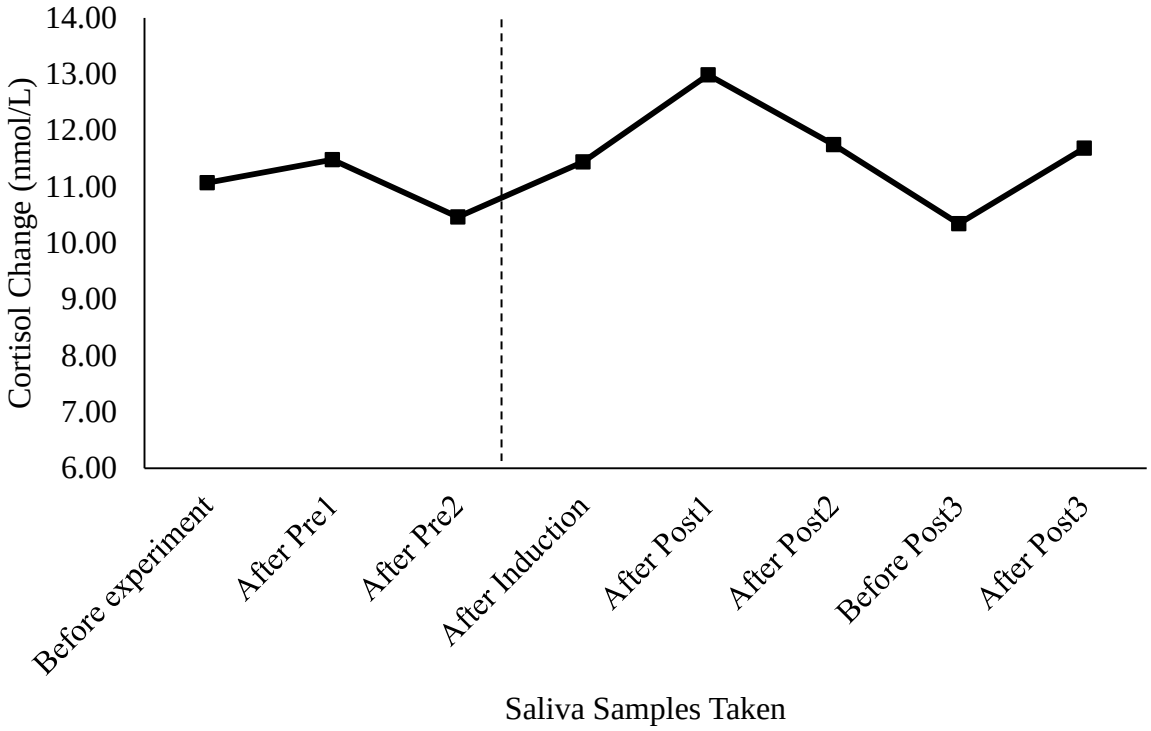

Figure 24. The cortisol level analysed from the saliva samples taken at various points during experiment seven. The vertical dashed line indicates when participants immersed their hand in water.

Studies that examined cortisol level commonly only analyzed the level of cortisol prior to and following the experimental condition (e.g. Kirschbaum et al., 1996; Newcomer et al., 1994), therefore a second paired samples t-test was conducted to compare the level of cortisol recorded following Pre2 (*M*=11.63, *SD*=9.47) and after induction (*M*=11.44, *SD*=10.20). The results showed that the level of cortisol in each participant did not change significantly after participants immersed their non-dominant hand in a bucket of room

temperature water for 3mins ($t_{(7)} = .46$, $p > .05$). Again, this suggested that merely asking participants to submerge their non-dominant hand in a bucket of water does not cause a significant change to their level of cortisol.

4.3 Experiment Eight

The key aim of this set of experiments was concerned with investigating how the level of cortisol might moderate the degree of potentiation achieved. Experiment six established that simply immersing the hand in ice temperature water does not lead to a change in the N1b component. Then experiment seven showed that immersing the hand in room temperature water does not prevent hLTP in response to rapid visual stimulus.

The next experiment (eight) examined whether or not immersing participants' non-dominant hand in ice temperature water influenced the magnitude of hLTP that could be achieved, presumably through the modulation of the level of cortisol. Firstly, experiment eight used the basic experimental paradigm of experiment one design one. Secondly, like experiment six, the cold-pressor technique was used in attempt to alter the level of cortisol in each participant. Prior to the presentation of the LTP inducing stimuli, participants were instructed to immerse their non-dominant hand in a bucket of ice temperature water. Also, like experiment six and seven, experiment eight followed the protocol used in experiment six and seven for the collection of saliva samples to monitor each participant's level of cortisol throughout the experiment.

4.3.1 Methods

4.3.1.1 Participants

A new group of males (14) gave their informed consent prior to participating in the experiment. All the participants reported normal, or corrected to normal vision. The participant's ages ranged from 18 to 25 years (M = 20.57, SD = 2.06). Half of the participants were right eye dominant and the other half were left eye dominant as determined using the Miles test (Porac & Coren, 1976). All the participants were classified as right-handed by having a laterality quotient of 50 or greater on the Edinburgh Inventory (Oldfield, 1971). The participants' laterality quotient ranged from 60 to 100, with an average quotient of 85.36 (SD = 13.37). All the participants were reimbursed with $20 petrol vouchers for their participation in the experiment. The University of Auckland Human Participants Ethics Committee approved the experimental procedures.

4.3.1.2 Stimuli

A flashing circular checkerboard stimulus was presented to participants during the experiment. The stimulus had a diameter subtending 8° of visual angle and was presented on a grey background at full contrast (refer to Figure 2). The presentation of the stimulus was controlled using E-Prime version 2.0.8.22 Psychology Software and presented on a Samsung Sync Master computer monitor (model: S24B350) (resolution: 1920 x 1080 pixels, refresh rate: 60Hz). The default screen resolution was set by E-Prime of 640 x 480 pixels. All the participants maintained a viewing distance of 57cm from the monitor.

4.3.1.3 Procedure

Experiment eight was conducted to examine how the change to the level of cortisol might influence the level of potentiation that could be achieved. Experiment one had

established that both design one and two could successfully induce visual hLTP. Therefore, only design one of experiment one was utilized for efficient examination.

Participants were allocated into design one as described in Chapter 2 (refer to Table 3). Like experiment one, during the pre-induction and post-induction blocks VEP was recorded while both eyes were viewing. All the participants were instructed to immerse their non-dominant hand in a bucket of ice temperature water for 3mins after Pre2 and before the induction block.

During various points of the experiment, all the participants were instructed to chew on a cotton swab for 2mins until it is completely soaked with their saliva. This was to keep track of each participants' cortisol level throughout the experiment. Like experiment seven, eight saliva samples were taken from each participant at the following times points: (1) before the experiment began, (2) after Pre1, (3) after Pre2 before the induction block, (4) after the induction block, (5) after Post1, (6) after Post2, (7) at the end of the delay before Post3, (8) and after Post3.

Participants were instructed to rinse their mouth with water before the experiment began to reduce the possibility of contaminating the saliva samples with food or drinks consumed earlier in the day. Furthermore, the level of cortisol tend to be highest when people first wake up and steadily decline throughout the day (e.g. Alderson & Novack, 2010; Akil et al., 1999; Pruessner et al., 1997). Therefore, in attempt to obtain more stable cortisol recordings all the data collection for the experiment were performed after 12pm. This is also commonly done by other studies investigating the effects of cortisol (e.g. Andreano & Cahill, 2006; Cahill et al., 2003). The cortisol level present in each saliva sample must be at least 5.0 nmol/L and above for an actual reading to be given. If the cortisol level is below 5.0 nmol/L in the saliva sample, analysis from the lab will be recorded as <5.0 nmol/L by default.

4.3.1.4 Electroencephalographic Recording

EEG was recorded continuously with 1000Hz sampling rate and 0.1 – 100Hz analogue band-pass filter, using 128- channel Ag/AgCl electrode nets (Electrical Geodesics Inc., Eugene, OR, USA). All electrode impedances were below 40kΩ, this is an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). The recordings were taken in an electrically-shielded room. EEG was acquired using a common vertex (Cz) reference and later re-referenced to the average reference off-line.

4.3.1.5 Data Analysis

Electroencephalographic recordings were segmented into epochs comprising of a 100ms pre-stimulus baseline and a 500ms period post-stimulus onset. From all waveforms, DC offsets were calculated from the pre-stimulus baseline and were removed. The correction of eye-movement artifacts were made on all segments using the method suggested by Jervis, Nichols, Allen, Hudson, and Johnson (1985). Epoch is discarded if either eye have “moved” or “blinked. Trigger and stimulus synchronization accounted for the 8ms delay the hardware filters imposed upon the EEG signals. For each individual participant, the average over the N1b time window was obtained from two clusters of seven electrodes centred on approximately P7 and P8 under the 10-20 system (Luu & Ferree, 2000), as seen in Figure 4.

In a preliminary analysis, dominant eye (left and right), hemisphere (left and right), and block (Pre1/Pre2/Post1/Post2/Post3) were involved as factors in the analysis. Dominant eye, and hemisphere never reached significance as main effects or interaction. Therefore, the data was reanalyzed with only block (Pre1/Pre2/Post1/Post2/Post3) as a within subjects factor. If sphericity cannot be assumed on F-statistics, Greenhouse-Geisser corrections were utilized.

Planned contrasts were employed to test critical predictions. For design one (refer to Table 1), the first contrast compared the pre-induction blocks for stability and was predicted to be non-significant. Contrast two and three investigated the linear and quadratic trends over the post-induction blocks to determine if there is any decrease over blocks due to repeated testing which could potentially result in long-term depression (Teyler et al., 2005). The last contrast compared the pre-induction to post-induction blocks and this is the critical test for hLTP. None of the pre and post stability contrasts reached significance and so only the post-pre contrast testing for hLTP will be presented.

To investigate the odds of any change to the N1b component being due to effects of altered attention or general cortical excitation, the amplitude of the P1 component was also analyzed in a similar way to the amplitude of the N1b component.

4.3.2 Results

The analysis of amplitude of the N1b component revealed a main effect for block ($F_{(4,52)} = 18.212$, $p < .001$, $\eta^2 = .583$). The contrast comparing the pre-induction to post-induction blocks was significant ($F_{(1,13)} = 45.621$, $p < .001$, $\eta^2 = .778$). Furthermore, none of the other contrasts reached significance. This indicated that in this experiment where participants placed their non-dominant hand in a bucket of ice temperature water there was a significant increase in the amplitude of the N1b component following induction (see Figure 25 and 26 below).

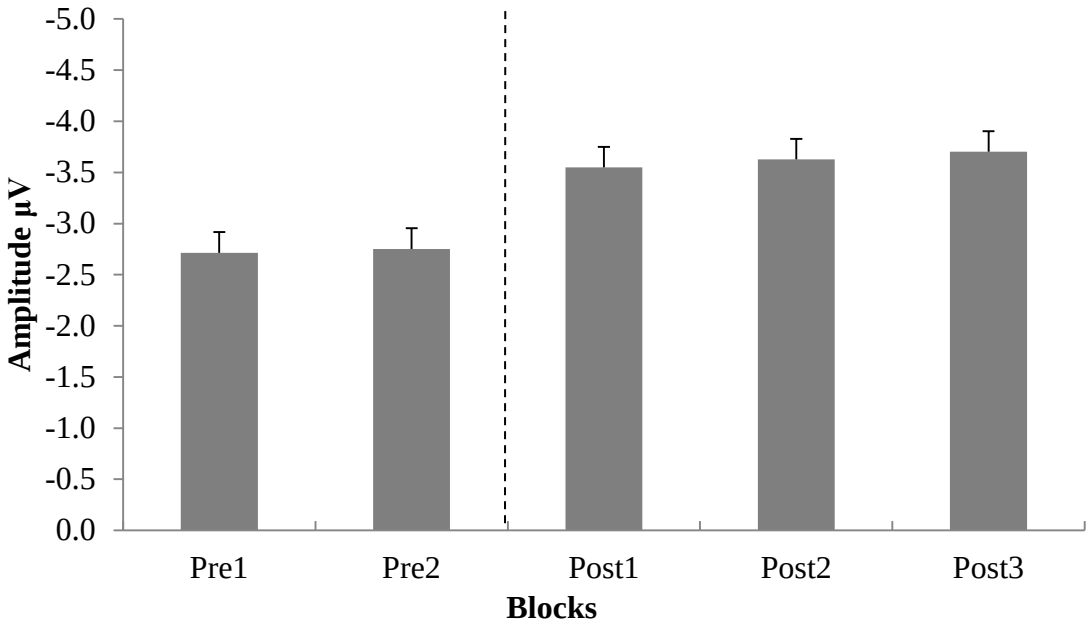

Figure 25. The pre-induction and post-induction amplitude change of the N1b component. The vertical dashed line indicates when the induction block was presented. The error bars represent confidence intervals for the pre-post difference and are calculated for within-subject designs as suggested by Masson and Loftus (2003).

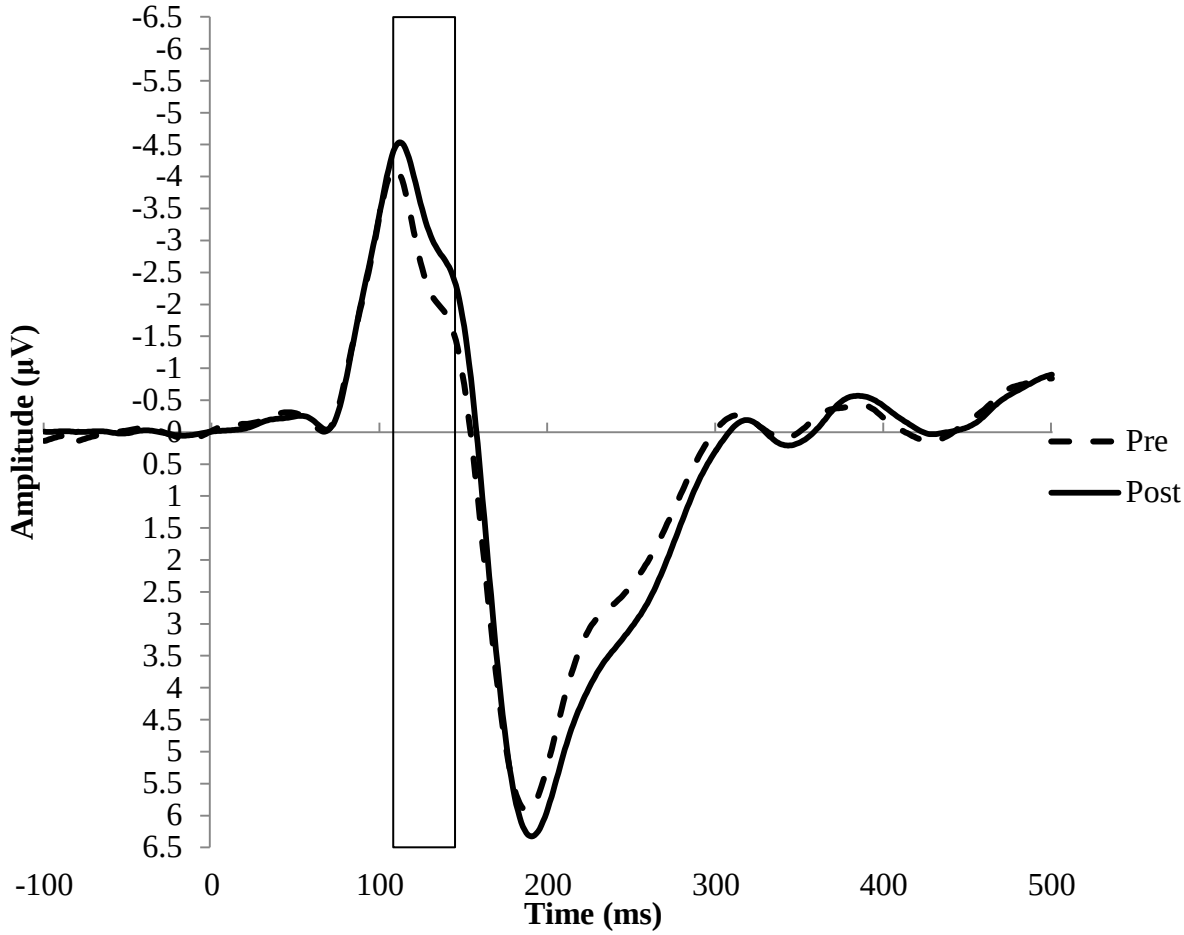

Figure 26. The pre-induction (dashed line) and post-induction (solid line) VEPs when collapsed over all the critical electrodes. The transparent bar shows the N1b time window (109 – 144ms).

The analysis of the amplitude of the P1 component revealed no main effect for block ($F_{(4,52)} = 2.496$, $p > .05$, $\eta^2 = .161$). The contrast comparing the pre-induction to post-induction blocks was non-significant ($F_{(1,13)} = 2.155$, $p > .05$, $\eta^2 = .142$). Furthermore, none of the other contrasts reached significance.

For some of the saliva samples obtained from participants, the cortisol level was below 5.0 nmol/L. For these sample readings, the analysis from the lab was simply recorded as <5.0 nmol/L by default. Because these samples do not have an exact reading, they were recorded as "blank" and not included in the following analysis.

The cortisol levels measured at various points during the experiment was collapsed to obtain an average of the cortisol level prior to induction and following induction. A paired

samples t-test was conducted and found that the cortisol level prior to induction (*M*=8.51, *SD*=3.02) and following (*M*=6.96, *SD*=2.13) induction did significantly differ ($t_{(10)} = 2.90$, $p = .017$). This suggested that asking participants to submerge their non-dominant hand in a bucket of ice temperature water does show a significant change to their level of cortisol (as seen in Figure 27 below).

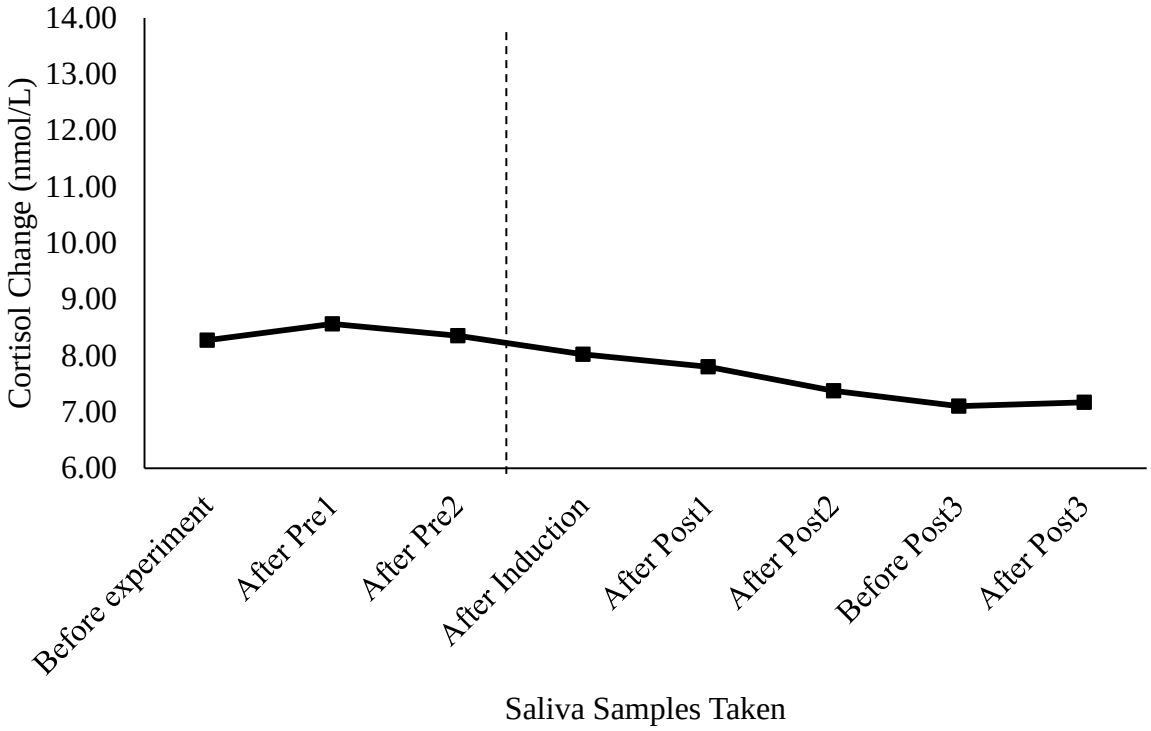

Figure 27. The cortisol level analysed from the saliva samples taken at various points during experiment eight. The vertical dashed line indicates when participants immersed their hand in water.

Studies that examined cortisol level commonly only analysed the level of cortisol prior and following the experimental condition (e.g. Kirschbaum et al., 1996; Newcomer et al., 1994). Therefore, a second paired samples t-test was conducted to compare the level of cortisol recorded following Pre2 (*M*=9.43, *SD*=2.99) and before Post1 (*M*=8.03, *SD*=2.75). The results showed that the level of cortisol in each participant did change significantly after participants immersed their non-dominant hand in a bucket of ice temperature water for 3mins

($t_{(7)} = 3.80$, $p = .007$). Again, this suggested that asking participants to submerge their non-dominant hand in a bucket of ice temperature water does result in a significant change to their level of cortisol.

Furthermore, a Pearson correlation test was conducted to compare the average change in the cortisol level with the change in the amplitude of the N1b component prior to and following induction. However, there was a non-significant, positive, and moderate relationship between the two ($r_{(11)} = .262$, $p > .05$). A second Pearson correlation test was conducted to compare the change in the cortisol level difference with the change in the amplitude of the N1b component prior to and following induction. However, again there was a non-significant, positive, and moderate relationship between the two ($r_{(8)} = .283$, $p > .05$). Refer to Figure 28 below.

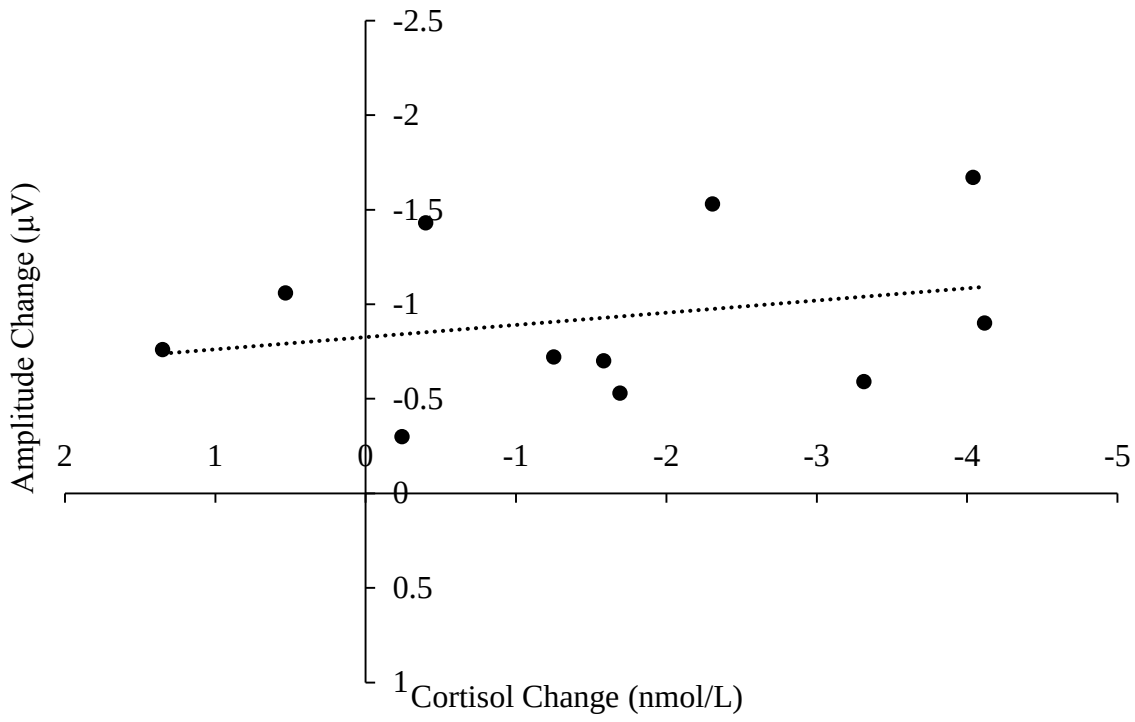

Figure 28. The relationship between the average change in the cortisol level with the change in the amplitude of N1b component prior to and following induction for experiment eight.

4.4 Comparison

There was a significant increase in the amplitude of the N1b component following rapid sensory stimulation in both experiment seven (room temperature water condition) and experiment eight (ice temperature water condition). Therefore, the amplitude difference before and following the induction block for both experiments were further analyzed. An independent samples t-test was conducted, the analysis revealed that there was no significant difference in the change of amplitude of the N1b component following induction between experiment seven and experiment eight ($t_{(26)} = .02$, $p > .05$) , see Figure 29 below. This meant that there was not a significant difference in the magnitude of potentiation achieve between the receiving a room temperature water condition as compared to ice temperature water condition prior to high-frequency sensory stimulation.

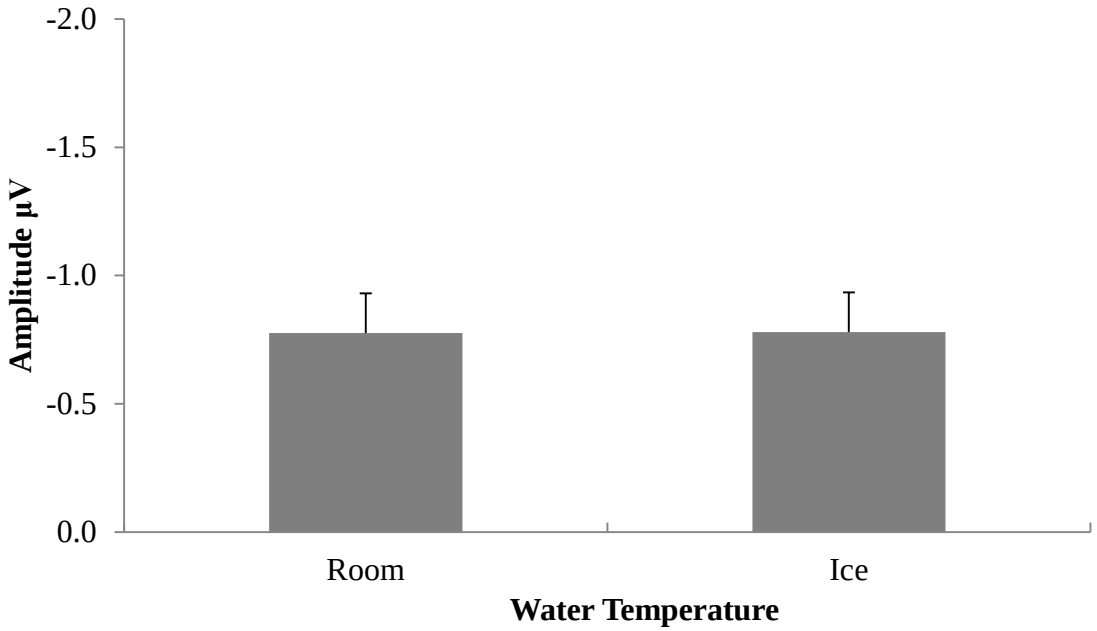

Figure 29. The amplitude change of the N1b component between the experiments that received room temperature water to the experiment that received ice temperature water prior to the induction block. The error bars represent confidence intervals for between-subject designs as suggested by Masson and Loftus (2003).

Furthermore, a Pearson correlation test was conducted to examine if there is a significant association between the difference in the level of cortisol with the change in the amplitude of the N1b component prior to and following the induction block for both experiments. There was a non-significant, positive, and weak relationship between the two ($r_{(21)} = .203$, $p > .05$), see Figure 30 below. This suggest that the level of cortisol present does not have a significant relationship with the magnitude of potentiation achieved.

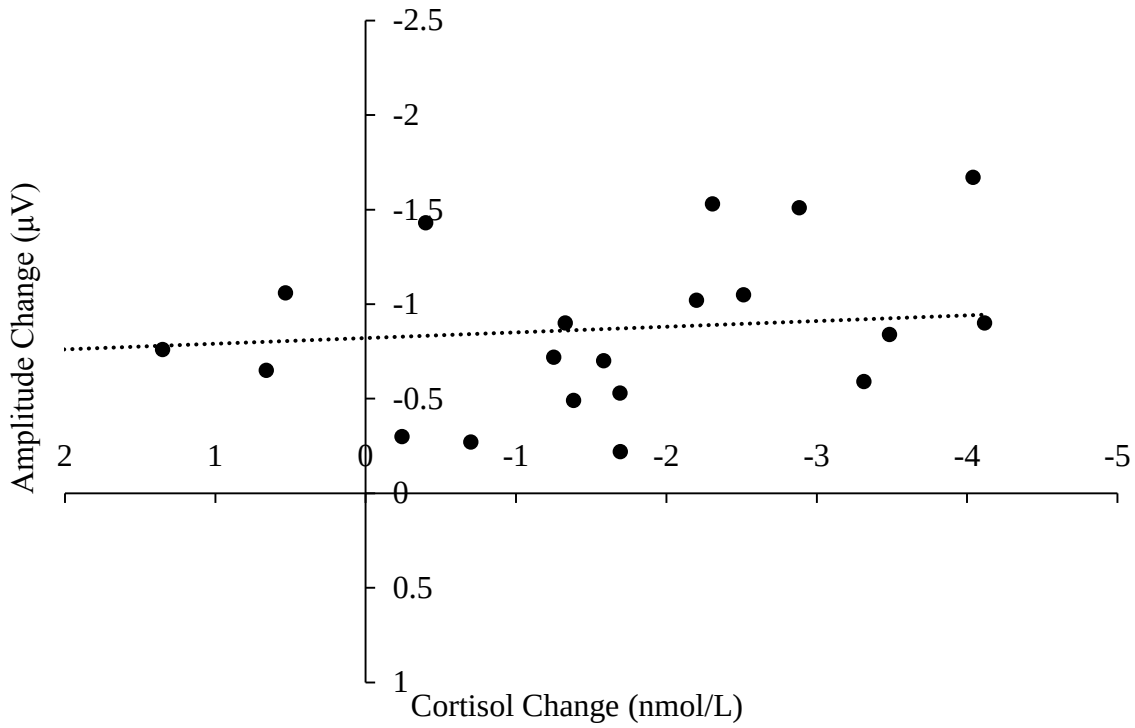

Figure 30. The relationship between the difference in the level of cortisol with the change in the amplitude of the N1b component prior to and following the induction block for experiment seven and experiment eight.

4.5 Discussion

A fair number of studies have been conducted over the years that examined the relationship between adrenal steroids with learning and memory performance. However, there are far fewer studies conducted to examine the association between stress hormones with LTP in healthy human. For this reason, the relationship between the level of cortisol with sensory induced LTP was explored in healthy human participants using the non-invasive paradigm as initially presented by Teyler et al. (2005).

This set of experiments, which examined the relationship between cortisol with hLTP employed the experimental protocols as carried out in experiment one design one. Firstly, this was to make the comparison between all the experiments conducted as part of this thesis easier. Secondly, as experiment one design one closely resembles the original non-invasive paradigm it should also allow for more straightforward comparison of this set of experiments to the prior non-invasive hLTP studies. To alter the level of cortisol in each participant, the cold-pressor technique was chosen as opposed to other slightly more intrusive methods such as oral administration of cortisol. This was to stay consistent with the effort to make the methodology as non-intrusive as possible. The cold-pressor technique involved instructing each participant to immerse their non-dominant hand in a bucket of ice temperature water. The discomfort caused by the low temperature of the water should alter the level of cortisol in participants. However, there were limitations to employing the cold-pressor technique to alter cortisol which will be discussed shortly. To monitor the level of cortisol during the experiment, each participant was instructed to chew on a cotton swab at various points during the experiment to collect their saliva samples for further analysis.

The main aim of this set of experiments was to examine the influence of cortisol on the magnitude of potentiation that could be achieved. Therefore, it was important to first

establish that the method used to alter the level of cortisol would not itself cause significant changes to the amplitude of the N1b component.

Experiment six followed the protocol as carried out in experiment one design one with the exception that the induction block was not presented to participants. This allowed direct examination of the cold-pressor technique. As predicted, when no rapid sensory stimulation was presented to participants, there was no significant change observed in the amplitude of the N1b component prior to and after each participant had submerged their non-dominant hand in a bucket of ice temperature water condition. The level of cortisol analysed through the saliva samples collected showed a decrease after the ice temperature water condition. This direction of change in the level of cortisol will be discussed shortly.

Furthermore, it was important to establish that by merely asking participants to place their non-dominant hand in a bucket of water would not influence the level of cortisol or directly alter the magnitude of potentiation that can be measured. Therefore, experiment seven was conducted as another control experiment. Experiment seven also followed the protocol as carried out in experiment one design one. Just before the induction block, participants were instructed to submerge their non-dominant hand in a bucket of room temperature water. As expected, the participants' level of cortisol prior to and after submerging their hand in a bucket of room temperature water did not significantly change. Moreover, there was a significant increase in the amplitude of the N1b component.

Finally, the key experiment examined the relationship between the level of cortisol with hLTP. Experiment eight also followed the protocol as carried out in experiment one design one. Prior to participants receiving the induction block, all these participants were instructed to immerse their non-dominant hand in a bucket of ice temperature water. Participants' level of cortisol prior to and after the ice temperature water condition did significantly decrease. Again, this direction of change in the level of cortisol will be discussed

shortly. Moreover, there was a significant increase in the amplitude of the N1b component following induction.

To examine whether or not there is a relationship between the changes in level of cortisol with the magnitude of potentiation achieved, two correlation tests were conducted on the results reported in experiment eight. The first correlation test compared the average difference in the level of cortisol prior to and following the water condition with the change in the amplitude of the N1b component. The second correlation test compared the difference in the level of cortisol immediately prior to and immediately following the water condition with the change in the amplitude of the N1b component. While neither test reached significance, there was a positive and moderate relationship between cortisol difference and the change in the amplitude of the N1b component. This potentially implies that when there is a lower level of cortisol, the amplitude of the N1b component become more negative. In other words, this suggests that when participants are less stressed (i.e. lower level of cortisol), there is a larger magnitude of potentiation achieved (i.e. more negative amplitude of the N1b component). However, it is important to emphasise that this relationship was not significant, therefore this is a speculation of how these two are associated.

Furthermore, the results gathered from experiment seven (room temperature water) were combined with the results gathered from experiment eight (ice temperature water) for further analysis. The analysis did not show a significant difference in the degree of potentiation achieved between experiment seven with experiment eight. A correlation test was also conducted to compare the results reported in both experiment seven and experiment eight. Again, the relationship between the change in the amplitude of the N1b component and the change in the cortisol level was not significant. Although, a weak positive correlation was found. Therefore, this also suggest that when participants are less stressed the magnitude of

potentiation achieved is higher. However, again, the relationship was not significant so this association is an assumption.

Nonetheless, this set of experiments still showed that rapid sensory stimulation can successfully induce visual hLTP. Therefore, the results gathered from this set of experiments is consistent with the findings from the first set of experiments conducted as part of this thesis showing that the paradigm can achieve what it is meant to. Furthermore, these results replicated the findings as reported in prior non-invasive hLTP studies (i.e. Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005).

While the current results did not show a significant difference in the amplitude of the N1b component found between the experiment that received the room temperature water condition and the experiment that received the ice temperature water condition, there does seem to be a trend emerging. That a decrease in the level of cortisol is associated with a larger magnitude of potentiation achieved. In other words, it is possible that less stress is related with enhanced memory performance in healthy human participants. Therefore, this provides some support for the literature that suggest raising the level of stress can be associated with a decline in learning and memory performance in humans (e.g. Kirschbaum et al. 1996; Newcomer et al., 1994). In relation to the inverted U shaped function as described earlier (i.e. Diamond et al., 1992; Fehm-Wolfsdorf et al., 1993; Het et al., 2005; Kovacs et al., 1976; Kovacs et al., 1977; Lupien & McEwen, 1997; Roozendaal, 2002; Roozendaal & McGaugh, 1996; Roozendaal et al., 1999; Sauro et al., 2003; Vaher et al., 1994a; Vaher et al., 1994b; Yerkes & Dodson, 1908), these findings appear to be support for the moderate level of cortisol being correlated with optimum learning and memory performance. Again, it is important to note that because the relationship was not significantly correlated, this association is a speculation.

Taking a shift to focus on the limitation of this set of experiments, the cold-pressor technique did not produce results that were initially anticipated. It was assumed that the cold-pressor technique would results in an increase in the level of cortisol. However, from the analysis there was a trend for the level of cortisol to decline as the experiment progressed. This could have potentially occurred due to various factors.

Participants may have begun the experiment feeling relatively anxious due to a couple of reasons. Firstly, before the experiment started participants may not be fully aware of what might happen during the experiment. Therefore, participants may have felt relatively more concerned about the procedure of the experiment. Secondly, as participants were brought into a laboratory environment, this could have made participants feel relatively uneasy just by being in an unfamiliar environment. However, as the experiment progressed participants understanding of the procedure may have resulted in them feeling a lot calmer. Therefore, this may have contributed to making it more difficult to cause substantial elevation to the level of cortisol in participants and in-turn finding a decline in the level of cortisol as the experiment progressed.

Furthermore, in comparison to prior studies that also examined the relationship between cortisol with learning and memory formation (i.e. Abercombie, Speck, & Monticelli, 2006; Buchanan & Lovallo, 2001; Buchanan, Tranel, & Adolphs, 2006; Cahill, Gorski, & Le, 2003; Jelicici, Geraerts, Merckelbach, & Guerrieri, 2004; Payne et al., 2007; Payne et al., 2006; Wirkner, Weymar, Low, & Hamm, 2013), there is not a huge variation with the protocols used to elevate cortisol in this set of experiments with the prior studies. Prior studies conducted on humans typically recruited university students, with participants' age range approximately between 18 to 25 years old. Furthermore, these studies typically excluded participants that took medication that might influence the level of cortisol (e.g. Andreano & Cahill, 2006; Cahill et al., 2003). These studies also informed participants to not engage in

extreme physical activity prior to testing. Lastly, data collection were typically carried out later in the day to help obtain more stable readings on cortisol level. As cortisol normally declines steadily from the time participants' initially wake up in the day (e.g. Alderson & Novack, 2010; Akil et al., 1999; Pruessner et al., 1997). These were also protocols followed by this set of experiments, so it does not appear to contribute a great deal to explaining why this pattern of change in cortisol level was found.

Although, a fair speculation was made by Vedhara et al. (2000) who pointed out that because participants were mainly recruited from the university, it means that the sample consist predominately of university students. Therefore, it would be fair to hypothesize that there might be semester related variations in the level of cortisol. The semester related variation in the level of cortisol will depend on whether or not students had assessments during the time course of the academic year. Therefore, whether or not students had assessments during the time of data collection may have influenced the general level of cortisol present in the participant. Thus, in-turn influencing the level of cortisol that can be further elevated using the cold-pressor technique.

In addition, for the studies that have employed the cold-pressor technique (e.g. Buchanan et al., 2006; Cahill et al., 2003), they had recommended that for future investigation to use oral administration of cortisol as another option to significantly and more reliably alter the level of cortisol in participants. Similarly, the studies that used other psychological stressors (e.g. public speaking) in attempt to raise the level of cortisol has also recommended pharmacological manipulations to change the level of stress hormones present in participants (e.g. Abercombie et al., 2006; Jelicici et al., 2004).

Therefore, future investigation of the relationship between cortisol and sensory induced LTP could employ oral administration of cortisol as another method to increase the level of stress hormones. Furthermore, in addition to using saliva samples to monitor the level

of cortisol during the experiment, future studies can also keep track of participants' heart rate and blood pressure. This could help determine the level of influence that the change in cortisol is having on the participant throughout the experiment. Additionally, future studies can also include questions that ask participants to rate their level of stress. Earlier studies that have kept track of these factors during the experiment were able to obtain a more comprehensive view of the degree of influence the stressor had on each participant (e.g. Payne et al., 2006; Sauro et al., 2003; Wirkner et al., 2013).

Chapter 5: General Discussion

5.1 Summary of Findings

In 2005, Teyler and colleagues was one of the first to report that it was possible to non-invasively induce and measure LTP in healthy human participants using EEG. This was achieved by rapid sensory stimulation to induce LTP combined with taking VEP recordings to measure the effect that has occurred. The comparison of the VEP recordings prior to and following rapid sensory stimulation showed that there was a selective and significant increase in the amplitude of the N1b component. Following on from that finding, hLTP (i.e. sensory induced LTP) was used to describe the significant increase in evoked potentials following the non-invasive high-frequency sensory stimulation. Sensory induced LTP appears to be analogous to the cellular LTP as reported in earlier animal studies (e.g. Abraham et al., 2002; Malenka & Nicoll, 1999; Malenka 2003). Furthermore, studies that were conducted following Teyler et al. (2005) have also shown that successful potentiation can be achieved through rapid sensory stimulation (e.g. Clapp et al., 2005a; Clapp et al., 2006; McNair et al., 2006; Ross et al., 2008; Zaehle et al., 2007). In other words, these non-invasive studies suggest that the original paradigm as presented by Teyler et al. (2005) does achieve what was intended to. Hence, the non-invasive paradigm appears to be a promising methodology to study LTP in healthy human participants.

In comparison to the literature on cellular LTP, far fewer studies have been conducted to examine hLTP. Due to this, the overarching aim of this thesis was to further explore sensory induced LTP using healthy human participants. This thesis consisted of two key aims. The first aim was to further explore where visual hLTP is occurring in the brain. The second aim of this thesis was to examine the relationship between the level of cortisol with the magnitude of potentiation that could be achieved.

Prior to examining the two key aims of this thesis, experiment one was conducted to try and replicate the findings reporting by the prior non-invasive studies (e.g. Teyler et al., 2005). Furthermore, as all the experiments that were conducted as part of this thesis were based off the protocols employed in experiment one, it was also important to ensure that rapid visual stimulation could result in successful induction of sensory induced LTP.

Experiment one had two designs that varied in the number of pre-induction and post-induction VEP recording blocks. Results obtained from both design one and design two showed a significant increase in the amplitude of the N1b component following rapid visual stimulation. The potentiation found remained evident over an hour following the induction phase. Furthermore, while previous studies have shown specificity to the LTP-inducing stimulus (i.e. McNair et al. 2006; Ross et al., 2008), this experiment is the first experiment done that manipulated when the LTP-induction block occurred by varying the number of VEP recordings done prior to and following induction. Thus, while experiment one was conducted to ensure that the experimental protocols employed could replicate visual hLTP as seen in prior non-invasive studies (e.g. Teyler et al., 2005), experiment one also demonstrated that hLTP is tied to the presentation of the visual tetanus and not a simple change over time due to the repeated presentation of the baseline stimuli.

Experiment one established that the protocols employed could replicate the findings from the prior non-invasive studies (e.g. Teyler et al., 2005). Therefore, the first set of experiments that were set out to examine the first aim of this thesis used variations of the protocols from experiment one to include the methodology of inter-ocular transfer.

The findings gathered from this set of experiments showed that the method used during the pre-induction and post-induction VEP recording was not the key to eliciting a change in the amplitude of the N1b component. Hence, successful potentiation did not depend upon whether the participant viewed the checkerboard stimuli with one eye only (i.e.

monocular viewing) or with both eyes (i.e. binocular viewing) during the pre-induction and post-induction VEP recording blocks. In other words, the experiments that had either monocular or binocular viewing of the stimuli during pre-induction and post-induction blocks but with monocular viewing during the induction block did not successfully induce visual hLTP. However, viewing the checkerboard stimuli with both eyes during the induction block was the determining factor that resulted in a significant increase in the amplitude of the N1b component. There was evidence of successful potentiation following rapid stimulation to both eyes when VEP recordings were done with either the checkerboard stimuli being viewed with one eye only (i.e. monocular viewing) or with both eyes (i.e. binocular viewing).

Therefore, the first set of experiments showed that the occurrence of visual hLTP requires the processing of a binocular input. Both animal (e.g. Barlow et al., 1967; Burkhalter & Van Essen, 1986; Maunsell & Van Essen, 1983; Nikara, Bishop, & Pettigrew, 1968; Pettigrew et al., 1968; Poggio, 1995; Poggio & Poggio, 1984) and human (e.g. Blake & Levinson, 1977; Blake & Wilson, 2011; Grill-Spector & Malach, 2004; Neri, 2004; Parker, 2007; Parker & Cumming, 2001) studies indicated that the binocular neurons are found in the visual neocortex and not in the ascending visual pathways. Thus, visual hLTP should be occurring in the visual cortical region as opposed to the ascending visual pathways. Results from this set of experiment are consistent with the current literature that also suggests visual hLTP is occurring in the visual cortical regions.

The second set of experiments examined the other key aim of this thesis. Like the first set of experiments, the second set of experiments were also based off the protocols as done in experiment one. In order to manipulate the level of cortisol in participants during the second set of experiments, the protocols used in experiment one was combined with the cold-pressor technique. The cold-pressor technique required participants to immerse their non-dominant

hand in a bucket of ice-temperature water. All the participants underwent the water condition prior to receiving the induction block.

The findings gathered from the second set of experiments showed that the cold-pressor technique reduced the level of cortisol as analyzed from saliva samples collected from each participant. While there was no significant correlation between the level of cortisol with the magnitude of potentiation achieved, there was a trend for a positive relationship emerging. The findings indicated that there is a trend for the relationship that as the level of stress hormones decreased, the degree of potentiation achieved increased. In other words, less stress is potentially correlated with better learning and memory performance. In relation to the inverted U shaped function (i.e. Diamond et al., 1992; Fehm-Wolfsdorf et al., 1993; Het et al., 2005; Kovacs et al., 1976; Kovacs et al., 1977; Lupien & McEwen, 1997; Roozendaal, 2002; Roozendaal & McGaugh, 1996; Roozendaal et al., 1999; Sauro et al., 2003; Vaher et al., 1994a; Vaher et al., 1994b; Yerkes & Dodson, 1908), these findings is potentially support for the moderate level of cortisol being correlated with optimum learning and memory performance. However, it is worthy to note that this relationship was not significant, therefore this meant that this pattern is currently a speculation of how these two are associated.

Furthermore, as expected the second set of experiments showed that rapid sensory induction can induce visual hLTP. The successful potentiation reported from the second set of experiments were consistent with prior non-invasive studies (e.g. Teyler et al., 2005) and with the earlier experiments that were conducted as part of this thesis.

Overall, the findings gathered from examining both aim one and aim two of this thesis showed that the non-invasive paradigm is successful in eliciting visual hLTP. Furthermore, binocular viewing of the checkerboard stimuli are required to significantly increase the amplitude of the N1b component. Moreover, potentially less stress (i.e. lower level of

cortisol) is associated with better learning and memory formation (i.e. increased magnitude of potentiation achieved).

5.2 Clinical Implications of Human Long-Term Potentiation

The experiments that were conducted as part of this thesis replicated the finding from prior non-invasive studies. The findings showed that rapid sensory stimulation could achieve successful potentiation when it was intended to. Furthermore, the effect can be measured non-invasively through EEG. Therefore, the findings gathered from this thesis indicates the potential of applying this knowledge and technique in the clinical settings.

There are studies that have been conducted to examine the underlying causes to various neurocognitive disorders, such as depression, Alzheimer's disease or schizophrenia (e.g. Chapman et al., 1999; Gisabella et al., 2005; Kim, Song, & Kosten, 2006; Lau & Zukin, 2007; Lewis & Gonzalez-Burgos, 2008; Nestler, 2001; Rowan et al., 2003; Shankar et al., 2008; Vetencourt et al., 2008). These studies have reported evidence to suggest that these disorders may be partially due to impairments in neuroplasticity and network connectivity within the brain. These studies have reported difficulties to successfully induce LTP in patients diagnosed with depression, Alzheimer's disease or schizophrenia (e.g. Chapman et al., 1999; Gisabella et al., 2005; Kim, Song, & Kosten, 2006; Lau & Zukin, 2007; Lewis & Gonzalez-Burgos, 2008; Nestler, 2001; Rowan et al., 2003; Shankar et al., 2008; Vetencourt et al., 2008).

Normann, Schmitz, Furmaier, Doing and Bach (2007) examined the efficiency of neuronal communication and the brains neuroplasticity in patients diagnosed with major depression. Normann et al. (2007) compared the response of patients to a group of healthy control participants after presenting checkerboard reversals at 2hz.

In comparison to the healthy control participants, Normann et al. (2007) found that patients diagnosed with major depression achieved significantly smaller VEP amplitudes. Furthermore, when healthy control participants were administered serotonin reuptake inhibitor for an extended period of time the amplitude increased.

Several key points could be drawn from Normann et al.'s (2007) study. Firstly, the serotonin reuptake inhibitor can potentially enhance neuroplasticity if taken over an extended period of time. Secondly, the reduction in the magnitude of potentiation observed in patients diagnosed with major depression may be even more substantial if these patients were not taking serotonin reuptake inhibitor. In other words, the effects of depression on the brains plasticity might be concealed to a certain extent when patients are treated with this anti-depressant. Moreover, patients diagnosed with major depression still shows a clear sign of LTP impairment even while taking anti-depressant. Therefore, this implies that there should be more to the current method of treatment for patients diagnosed with depression. Potentially suggesting anti-depressants and other forms of treatment is necessary.

Nevertheless, the findings from Normann et al.'s (2007) study did signify the potential to utilize the non-invasive paradigm as a tool to assess the effectiveness of existing and novel treatments for patients diagnosed with depression. In addition, the non-invasive paradigm could possibly be used to examine the degree of impairment of the brains neuroplasticity in patients diagnosed with depression.

Additionally, there are several studies that have also reported LTP impairment in patients diagnosed with other neurocognitive disorders such as Alzheimer's disease (e.g. Chapman et al., 1999; Rowan et al., 2003; Shankar et al., 2008). The difficulty in eliciting LTP in patients' diagnosed with Alzheimer's disease most probably reflects the neurological changes that has occurred in these patients brain (e.g. Arendt, 2001; Arendt, Bruckner, Gertz, & Marcova, 1998; Mesulam 1999). Consequently, this also signifies the potential to apply the

rapid sensory stimulation paradigm to induce hLTP in the clinical setting to explore and assess various neurocognitive disorders.

The difficulty to successfully inducing LTP has not been limited to patients diagnosed with depression and Alzheimer's disease. In 2009a, Cavus et al. examined visual hLTP in patients diagnosed with schizophrenia. In comparison to the group of healthy control participants, Cavus et al. (2009a) reported that the magnitude of potentiation achieved in patients diagnosed with schizophrenia is also significantly lower. Therefore, Cavus et al. (2009a) findings also highlighted the potential to use the non-invasive paradigm in the clinical setting not only for patients diagnosed with depression or Alzheimer's disease but also for patients diagnosed with schizophrenia.

There appears to be a relationship between the degree of potentiation that could be achieved with various neurocognitive disorders which includes major depression (Normann et al., 2007), schizophrenia (Cavus et al., 2009a), and Alzheimer's disease (e.g. Chapman et al., 1999; Rowan et al., 2003; Shankar et al., 2008). In comparison to the healthy control participants, the magnitude of potentiation that could be achieved in patients diagnosed with these neurocognitive disorders appear to be significantly smaller.

Therefore, this highlights the potential for the non-invasive paradigm to help extend the knowledge in regards to these neurocognitive disorders. Furthermore, also suggesting that the non-invasive paradigm can be applied to the clinical setting as the protocols are a much more convenient method to examine neuroplasticity (Kirk et al., 2010; Teyler et al., 2005; Zaehle et al., 2007). For example, the non-invasive paradigm can be used to assess the effectiveness of novel and existing treatments for various neurocognitive disorders. With further research, the non-invasive paradigm could also potentially be used for the diagnosis of various neurocognitive disorders.

5.3 Concluding Remarks

Aristotle described memory being like a wax tablet (Sorabji, 2004). That memory could be retrieved due to imprints and could be modified just like wax could be shaped. However, Aristotle also pointed out that as an individual ages it becomes more difficult to alter memory as neural connections in the brain become more set. In a similar way, this is analogous to how wax becomes harder over time. While it is becoming less common to view memory formation as impressions in Aristotle's wax tablet, there is continuing support that it is possible to investigate the neuropsychological changes that occur in the medium of memories by remotely measuring the electrical activity of the brain to examine hLTP.

The use of rapid sensory stimulation to induce visual hLTP combined with taking VEP recordings to measure the change in the amplitude of the N1b component has shown to be successful in achieving what this non-invasive paradigm is intended to. That is to induce LTP-like effect by rapid sensory stimulation. This non-invasive paradigm could potentially be applied to the clinical setting as a tool for several neurocognitive disorders. This includes but not limited to enhancing the understanding, the diagnosis, and the evaluation of existing and novel treatments for various neurocognitive disorders. Furthermore, sensory induced LTP could be a method to help extend the knowledge currently known about the cortical functions in various human sensory and cognitive disorders.

From here on, further examination of hLTP is highly recommended. This could potentially reveal more of the non-invasive paradigms' utility. As a result, further investigation of sensory induced LTP could in turn lead to findings that could be useful to science and beneficial to the wider human population.

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