The EEG Profile of Hemispatial Neglect and Neurofeedback as an Intervention.

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I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning.

Date

Name

Signed

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ABSTRACT

There is evidence to suggest that interventions targeting alertness could be effective in the rehabilitation of hemispatial neglect. Alertness correlates in the EEG with decreased *theta* and increased *beta* activity and training up *beta*/*theta* ratios using EEG neurofeedback has resulted in particularly beneficial results in children with ADHD with recognised deficits of alertness. Experiment I showed that neglect patients had significantly reduced *beta* activity compared to age-matched controls, consistent with an alertness deficit underpinning neglect and suggesting that the symptoms of neglect could be ameliorated by the same neurofeedback training protocol applied in ADHD.

The effectiveness of EEG neurofeedback training of *beta* power with a *theta* inhibit has not been investigated in older adults or stroke patients. Therefore, Experiment II used EEG neurofeedback training to enhance *beta* in older adults. Compared to controls, the neurofeedback group showed significantly increased *beta* activity in the post-assessment quantitative EEG, demonstrating that older adults can modulate their EEG through neurofeedback training and laying the foundations for extending training to neglect patients.

Experiment III employed the same training protocol in seven neglect patients. EEG activity was monitored in regular training sessions conducted over a six-week period and it was found that normalization of baseline EEG activity was associated with a remediation of impairments across several outcome assessments. Detailed analysis of across- and within-session EEG data found that a sub-group of patients showed evidence of spontaneous increases in *beta* activity that were related to

additional improvements in outcome measures. However, there was no evidence that EEG modulation was due to the neurofeedback training.

In sum, this thesis reports two novel findings. Firstly, neglect is associated with an EEG profile that is consistent with an alertness deficit. Secondly, recovery in severely impaired neglect patients is associated with enhanced beta activity.

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CHAPTER 1: GENERAL INTRODUCTION

1.1. Neglect: The Syndrome

Stroke is one of the leading causes of death and disability in the western world (Sudow & Warlow, 1997). With over two-thirds of right hemisphere stroke patients suffering from the debilitating effects of hemispatial neglect (Bowen, McKenna & Tallis, 1999) a greater understanding of this condition and the development of effective rehabilitation interventions are vital. A small percentage of patients who present with neglect in the acute stages post-stroke do spontaneously recover completely (approximately 9%) and around 43% of patients show some improvement in a 2-week period post-stroke (Farne, Buxbaum, Ferraro, Frassinetti, Whyte, Vermonti et al , 2004). There remains a large percentage of patients who are left with debilitating symptoms which can greatly hamper the rehabilitation of other neurological deficits that may be unrelated to neglect, such as hemiplegia (Kalra, Perez, Gupta & Wittink, 1997). Despite the fact that neglect is the best single predictor of poor recovery from stroke (Sea, Henderson & Cermak, 1993), there remains no satisfactory consistent form of rehabilitation for this deficit.

Hemispatial neglect is a complex neurological disorder, most commonly occurring after right hemisphere stroke, which manifests as an inability to attend to stimuli presented in the contralesional side of space (e.g. Heilman, Bowers, Valenstein & Watson, 1987; Mesulam, 1999; Husain & Rorden, 2003). Hemispatial neglect is equally likely to occur in the immediate acute phase after a left or right hemisphere

stroke, but in its enduring form is most prevalent after right hemisphere damage (Stone, Halligan & Greenwood, 1993). The disorder is usually characterized by a bias to orientate towards objects and events to the patient's ipsilesional side while ignoring those to the contralesional side. It is important to clarify that whilst neglect can often impact on sensory processing, it occurs in the absence of any primary sensory or motor deficit such as hemianopia (contralesional visual loss) or hemiplegia (contralesional paralysis of the body). Typically patients will only eat food on the ipsilesional side of the plate, dress the ipsilesional side of the body and, in severe cases, not acknowledge contralesional body parts as their own (Husain & Rorden, 2003). When asked to copy a figure or draw a clock from memory, neglect patients will only detail the ipsilesional side of these figures without any conscious awareness that the contralesional side is completely missing (Marshall & Halligan, 1993). When asked to search a display for specific targets, neglect patients will tend to explore the ipsilesional side of the display repetitively, finding it hard to disengage and move to search the contralesional side (Husain & Rorden, 2003). Neglect can be defined in one or more frames of reference, ego-centric (viewer-centred) or allo-centric (environmentally-centred or object-centred) and in a variety of sensory modalities (Milner & McIntosh, 2005). Viewer-centred neglect is defined for patients who fail to attend to stimuli on the contralesional side of their midline, whereas object-centred neglect is defined for patients who fail to attend to the contralesional side of the stimulus, regardless of the position of the stimulus relative to patient. Object-centred neglect often becomes clear when the patient is only able to read the ipsilesional side of individual words despite scanning these words from the contralesional to the ipsilesional side of the page.

In addition to the lateralized spatial bias, neglect is also characterised by additional impairments not attributable to a spatial bias. For example, neglect patients have a more severe and protracted attentional blink than healthy individuals (Husain & Rorden, 2003; Corbetta & Shulman, 2011, for review). Visual and auditory studies report that neglect patients show impaired performance on both sides of space, suggesting a general reduction in capacity for processing stimuli regardless of spatial location (Duncan, Bundesen, Olson, Humphreys, Chavda & Shibuya, 1999; Battelli, Cavanagh, Intriligator, Tramo, Henaff, Michel & Barton, 2001). Neglect patients continuously re-search the ipsilesional side of space, revisiting items they have already cancelled out, indicating an impaired working memory that exacerbates an existing spatial bias (Malhourta, Coulthard & Husain, 2009).

Of most interest to this thesis is the finding that neglect patients commonly present with symptoms associated with decreased alertness, such as an inability to sustain attention, increased reaction times, worsening symptoms with sedatives, along with an improvement in symptoms with stimulants (Lazar, Fitzsimmons, Marshall, Berman, Bustillo, Young et al, 2002; Malhorta et al, 2009; Buxbaum, Ferraro, Veramonti, Farne, Whyte, Ladavas et al, 2004). Samuelsson, Hjelmquist, Jensen, Ekholm and Blomsrand (1998) showed neglect patients had significantly increased reaction times on an auditory task and that improvement in neglect symptoms over time correlated with a reduction in these reaction times. The deficits described here show that neglect is associated with an impairment in task-related sustained attention, usually attributed to decreased tonic alertness.

Further evidence to support a link between spatial attention and alertness is provided by observations that reduced alertness following sleep deprivation or time-on-task induces mild neglect-like symptoms, defined as a significant rightward shift in attention, in healthy adults (Manly, Dobler, Dodds & George, 2005). Since healthy participants usually have a slight bias to the left (pseudoneglect) (Bowers & Heilman, 1980), it has been proposed that reduced levels of alertness are sufficient to induce a rightward shift in visuospatial attention in the healthy population. Importantly, it points to a functional relationship between alertness and spatial attention rather than just an association. One clinical group that has provided further evidence for a relationship between alertness and spatial attention is ADHD. Children diagnosed with ADHD, who perform consistently poorly on sustained attention measures, often exhibit a similar rightward spatial bias (Manly, Robertson & Verity, 1997; Dobler, Anker, Gilmore, Robertson, Atkinson & Manly, 2005: Manly, Cornish, Grant, Dobler & Hollis, 2005; Dobler, Manly, Verity, Woolrych & Robertson, 2003). George, Dobler, Nicholls and Manly (2005) presented a case study of an 8-yr-old child with clinically diagnosed ADHD. The child had a rightward spatial bias which became more exaggerated with boredom, induced by the repetition of the same star cancellation task 40 times. This provides further support for a functional relationship between alertness and spatial attention.

The literature discussed thus far clearly points to a link between alertness and spatial attention both in non-clinical populations and patients with hemispatial neglect. Further evidence for this link comes from neuroimaging findings implicating a dysfunction alertness network as the primary cause of neglect (Corbetta, Kincade, Lewis, Snyder & Sapir, 2005).

1.1.1. Aetiology of hemispatial neglect

Multiple brain regions have been implicated in spatial neglect, an unsurprising finding given the complex range of symptoms and individual variability associated with the syndrome. Whilst there is some disagreement about and variability in patient selection across studies, it is generally accepted that neglect is most common after damage to regions that receive blood from the middle cerebral artery (MCA). The major cortical regions identified as common to neglect include the right temporo-parietal junction (TPJ) and the superior temporal gyrus (STG) (Vallar, 2001; Karnath, Feber & Himmelbach, 2001). More recent studies taking advantage of more advanced structural imaging techniques have identified three main cortical areas that appear to be abnormal in neglect patients. These cortical areas constitute the perisylvian network and include the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior/middle temporal and ventrolateral frontal cortices (Rengachary, He, Shulman & Corbetta, 2011; Karnath, Rennig, Johannsen & Rorden, 2011; Committeri, Pitzalis, Galati, Patria, Pelle, Sabatini et al, 2007).

He, Snyder, Vincent. Epstein, Shulman and Corbetta (2007) have extended this work using functional connectivity MRI to investigate the roles of two attentional networks; the dorsal attentional network and the ventral attentional network. The dorsal attentional network (DAN) is activated during spatial orienting and incorporates the intra-parietal sulcus/superior parietal lobule and the frontal eye field/dorsolateral prefrontal cortex. This dorsal network is bilateral, functioning with equal weight in both the right and left hemisphere. The ventral attentional network (VAN) is activated during non-spatial attentional processing and incorporates the

temporoparietal junction and the ventral frontal cortex, the areas common to neglect cited above. Unlike the DAN, the VAN is strongly lateralized to the right hemisphere and is thought to mediate alertness. He et al (2007) reported that left-sided neglect was a result of structural damage to the VAN which interacts to cause functional disruption to the right side of the DAN resulting in an imbalance represented by hyperactivity of the left DAN. This hyperactivity of the left DAN manifests itself as an attentional bias toward the right and inattention of the left, consistent with Kinsbourne's (1987) original theory of hemispheric competition. Support for this hypothesis comes from a study which showed that applying suppressive Transcranial Magnetic Stimulation (TMS) to the left fronto-patietal network of neglect patients correlated with a reduction in the spatial bias (Koch, Oliveri, Cherran, Ruge, Lo Gerfo et al, 2008). Similarly, repetitive TMS can induce a spatial bias in healthy participants by temporarily impairing the parietal cortex in one hemisphere thus disinhibiting the contralateral cortex and creating a shift in attention (Hilgetag, Theoret & Pascual-Leone, 2001).

The work of He et al (2007) in particular suggests that the spatial bias which is often used to diagnose neglect is not the root of the problem. Instead the spatial bias is the result of a dysfunctional VAN and disrupted non-spatial alertness system, located within the damaged right hemisphere. However, rehabilitation interventions, as we will now see, have focussed on the spatial aspect of neglect with limited success.

1.1.2. Spatially lateralized rehabilitation interventions

Over the last 50 years, rehabilitation therapies have focused on trying to re-align the spatial bias that is the most obvious symptom of neglect. Simple visual scanning training techniques are still widely used in clinical settings and require patients to find specific targets in a perceptually demanding display. The aim of this technique is to encourage the patient to explore the neglected side of space by giving feedback and repeated practice sessions. This technique has been shown to improve related tasks, such as reading and visual search, but fails to generalize to other affected modalities and tasks (Schindler, Kerkoff, Karnath, Keller & Goldenberg, 2002). Significantly however, visual scanning training has been shown to complement neck-muscle vibration with improved performance on visuomotor tasks reported up to two months after the treatment (Schindler et al, 2002).

Several bottom-up approaches have aimed to induce shifts in spatial representations with the advantage that they do not require any patient awareness of the deficits in the way top-down approaches do. The brain uses cues from the vestibular, visual and proprioceptive systems in order to establish the body's position in space. Since the perceived midline is shifted over to the right in neglect patients, techniques that target these systems have had promising, if transient, beneficial effects. Sensory stimulation techniques include caloric vestibular stimulation, optokinetic stimulation and neck muscle vibration (for a review see Luaute, Halligan, Rode, Rossetti & Boisson, 2006).

In line with the neuroanatomical network hypothesis of a damaged ventral system and spared dorsal system discussed in the previous section, goal-directed action research supports the existence of an intact dorsal network in neglect. According to Milner and Goodale's (2006) model, the dorsal stream is responsible for real-time guidance of action towards a target (in the 'where' stream) and the ventral stream is responsible for the processing of perceptual features (in the 'what' stream). Milner and Goodale hypothesised that neglect is a fundamental consequence of a failure of the ventral stream to construct *high* level perceptual representations rather than a dysfunction of the dorsal stream. Robertson, Nico and Hood (1995, 1999) showed that when patients were instructed to grasp the centre of a rod, rather than simply point, deviation to the right was reduced. This suggests that prehensive movements towards an object allow 'leakage' of information about spatial qualities via the unaffected dorsal stream and provides support for He et al's (2007) functional connectivity findings.

Another bottom-up approach, the left limb activation method, was developed based on observations that encouraging neglect patients to use the contralesional limb improved perception of the affected side by activating the pre-motor circuits of the lesioned hemisphere. Robertson and North (1992) found that activation of the left finger in left space significantly improved performance on cancellation tasks. This improvement did not occur in conditions where the right limb was activated (alone or simultaneously) or when the left limb was activated in the right-hemispace. Since this effect was not conditional on the left finger being visible it was not simply an effect of left-sided visual cueing.

Prism adaptation is a method aimed at redistributing the bias in spatial attention through sensory-motor remapping. This procedure, first introduced by Rossetti, Rode, Pisella, Farne, Boisson and Perenin (1998), requires the patient to wear prismatic goggles which induce an optical deviation toward the ipsilesional (right) side of space for several minutes. Whilst wearing these prisms, patients perform pointing movements toward visual targets placed in front of them. In order for the patient to compensate for the fact that the straight ahead object now appears to be towards the right they must make compensatory movements towards the left under the guidance of the trainer. Over repeated trials, patients achieve more accurate pointing movements as though their sensorimotor coordinates have shifted towards the neglected left hemispace. When the goggles are removed, patients are left with a post-prismatic after-effect during which they continue to make pointing deviations towards the left for a period of up to two hours. Several studies have reported a significant reduction in neglect symptoms on a variety of tests such as straight ahead pointing, cancellation tests, postural balance, wheelchair navigation and mental representation (Pisella, Rode, Farne, Boisson & Rossetti, 2002; Tilikete, Rode, Rossetti, Pichon & Boisson, 2001; Frassinetti, Angeli, Meneghello, Avanzi & Ladavas, 2002; Ladavas, Bonifazi, Catena & Serino, 2011). However, contradictory findings have also been reported whereby no beneficial effects were achieved through prism adaptation (Rousseaux, Bernati, Saj & Kozlowski, 2006; Ferber, Danckert, Joanisse, Golta & Goodale, 2003; Turton, O'Leary, Gabb, Woodward & Gilchrist, 2009). Procedural differences, the time post-stroke of the patients, the duration of treatment and the post-assessment time are all confounding effects that could account for the varied results (for a review see Ladavas et al, 2011). Whilst prism adaptation has proven to be the most widely researched intervention, very few

studies have reported significant long-term remediation of deficits. This suggests that lateralized interventions may not tackle the root cause of neglect and provides motivation to focus research on non-lateralized interventions.

1.1.3. Non-spatially lateralized rehabilitation interventions

A few studies have aimed to devise rehabilitation strategies that attempt to improve the alertness deficit associated with the syndrome. Before discussing this literature, it is important to distinguish two types of alertness. Tonic alertness refers to the intrinsic, long-term control of arousal level independent of external cues. Phasic alertness refers to the brief increase of arousal level in response to an unpredictable warning stimulus. Attempts to improve tonic alertness without the use of pharmacology have not been explored; however, phasic alerting strategies have proven to be effective. Bottom-up phasic alerting, using exogenous unexpected tones just before the presentation of a stimulus, have reduced, and in some cases, eliminated the spatial bias in neglect patients and reduced the protracted attentional blink (Robertson, Mattingley, Rorden & Driver, 1998; Van Vleet & Robertson, 2006; Chica, Theibaut de Schotten, Toba, Malhorta, Lupianez & Bartolomeo, 2011). These studies provide further evidence for an interaction between alerting networks and spatial orienting networks and for the idea that the manifestation of spatial neglect involves alertness deficits. The fact that even a severely damaged attention system can adapt and respond so effectively to a warning cue to ameliorate an extreme spatial bias bodes well for the future of treatment therapies. Phasic alerting ameliorates neglect transiently for events presented immediately following the

warning stimulus but in order to have a more lasting effect, a method aimed at improving tonic alertness is needed to produce more sustained improvements.

A recent attempt simultaneously to improve both phasic and tonic alertness in neglect patients was conducted by Van Vleet and DeGutis (2012). The same authors had previously used a visual sustained attention training task which required patients to maintain an alert and ready state (tonic alertness) whilst having to inhibit responses to unexpected targets (phasic alertness) (DeGutis & Van Vleet, 2010). Results from this initial work showed that after nine days of training, the spatial bias was almost eliminated and patients also improved on measures of non-spatial selective attention. In order to establish whether improvements in tonic alertness were the source of improvements in neglect, Van Vleet and DeGutis (2012) modified their training method to an auditory sustained attention training task. They hypothesised that if the training was truly due to an enhancement of intrinsic alertness, rather than simply using a visual training paradigm to improve performance on a visual task, the training stimulus modality should be irrelevant. The results of this study corroborated their previous findings that this phasic and tonic training intervention improved spatial and non-spatial attention in neglect patients and generalized across sensory modalities. The work by Van Vleet and DeGutis provides an encouraging foundation on which to further develop effective rehabilitation techniques which aim to regulate intrinsic tonic alertness and thus reduce the spatial bias in neglect. One intervention that suggests itself as a possible candidate for the rehabilitation of non-spatial alertness is EEG neurofeedback. Support for the application of EEG neurofeedback in neglect rehabilitation is discussed in the following section.

1.2. Quantitative EEG and Neurofeedback

1.2.1. Quantitative Electroencephalography (EEG)

Quantitative EEG is a scientifically established method used to map electrical brain activity across the scalp. It involves the extraction of pre-defined frequency bands by Fast Fourier Transformation (FFT) from the raw EEG signal recorded from electrodes precisely positioned over the scalp. These pre-defined frequency bands vary from 0.5-50 Hz (cycles per second) and are expressed in the form of amplitude (μV) or power (μV^2). Power can be defined in terms of absolute or relative power. Absolute power is defined as the total mean power of a frequency band and represents a direct measure of the activity recorded directly beneath the sensor, without consideration for the physical characteristics of the skull. Relative power is defined as the ratio (or percentage) between the absolute power of a frequency band and the absolute power of the total spectrum, representing a proportional measure independent of skull thickness, skin resistance and non-brain sources of electrical activity (Demos, 2005, p.102). Quantitative EEG can be used as a tool to identify different brainwave signatures associated with different cognitive processes and has been used to explore local and general disturbances in cerebral function in clinical disorders. Whilst exact bandwidths vary in the literature, it is generally agreed that:

***Delta* (0.5-4 Hz):** Increased *delta* waves are an indication of reduced cortical activation and are prominent during sleep in healthy individuals. *Delta* activity diminishes as a function of age. Abnormally *high* levels of *delta* activity can indicate brain injury or clinical psychopathology.

***Theta* (4-8 Hz):** Like *delta*, *theta* waves are predominant during sleep, increasing in stage 1 and 2 of sleep and in rapid eye movement (REM) where it is believed to play a role in the consolidation of recent memory (Greenberg & Pearlman, 1974). During wakefulness *theta* waves can also be an indicator of alertness levels; increased *theta* activity correlates with decreased levels of alertness and decreased performance (Strijkstra, Beersma, Drayer, Hablesma and Daan, 2003). Several clinical conditions have reported associations with increased *theta* activity, including ADHD, Epilepsy and traumatic brain injury. *Theta* has also been linked to working memory, specifically increased activity arises in the encoding and retrieval of information in working memory (Klimesch, Doppelmayr, Schimke & Ripper, 1997)**.**

***Alpha* (8-12 Hz):** This band is often referred to as the brain 'idling rhythm' since it is predominant during states of relaxation, when the brain is not under any cognitive demands. This band is often referred to as the brain 'idling rhythm' since it is predominant during states of relaxation, when the brain is not under any cognitive demands. However, alpha is not simply considered to be a reflection of idling, it is also considered to represent active inhibition processes based on the findings that increased alpha power has been observed in tasks where a learned response must be withheld and also over brain areas that are task irrelevant. Interestingly, alpha power is associated with performance dependent on the task being used. For example, better performance on a demanding perception task is related to lower alpha power during a pre-task interval (Erenoglu et al, 2004); this points to the theory that perceptual performance is enhanced if the cortex is already activated. Conversely, performance on a memory task is related to *high*er alpha power in a pre-task interval, suggesting that memory performance is enhanced if the

cortex is deactivated prior to the task and hence memory retrieval is the dominant process without interference from other cognitive processes (Klimesh, Sauseng & Hanslmayr, 2007).

An '*alpha* peak' is usually observed over parietal and occipital regions during eyes-closed conditions. The frequency at which this peak, the peak *alpha* frequency (PAF), occurs within the *alpha* frequency range has been associated with cognitive capacity and memory performance; *high*er peak frequencies indicating superior cognitive performance (Klimesch, 1997, 1999). *Alpha* is often segregated into lower *alpha* (7-9.5 Hz), implicated in attentional processes, and upper *alpha* (9.5-12 Hz), implicated in semantic memory processes.

Sensory-Motor Rhythm, *SMR* (12-15 Hz): This rhythm, also referred to as low-*beta*, is so called because it is localized to the sensorimotor cortex. It is associated with motor stillness and cognitive vigilance, a state often likened to a cat being ready to pounce. Disorders, such as ADHD, with symptoms of hyperactivity and impulsivity, have been associated with decreased levels of *SMR* activity (Lubar, 1991), discussed in more detail in the next chapter. Increased *SMR* has been reported in paraplegics and quadriplegics in whom lower-motor neurons have been damaged (Lubar & Shouse, 1976).

***Beta* (15-18 Hz):** This faster wave activity is usually of low-voltage and often goes unnoticed unless it is specifically investigated. *Beta* activity tends to increase during *high* level cognitive processes involving focussed attention and problem solving. Increasing evidence exists to suggest the *beta* activity is linked to alertness and vigilance and is discussed in more detail in proceeding sections.

***High beta* (20-30 Hz):** Due to the *high* frequency of this wave, it can easily be confused with muscle artefact, (EMG). *High beta* activity is associated with peak performance and cognitive processing; however this is rarely trained up during neurofeedback protocols. This is because excessive *high beta* activity can be a marker for anxiety, stress and mood-related conditions. The most common cause of excess *high beta* activity is pharmacologic, particularly caused by benzodiazepines and barbiturates (Libenson, pg 187, 2010). Similarly, sedatives or anaesthetic medications and cortical injuries can result in reduced levels of *high beta* activity (Libenson, pg 188, 2010)

1.2.2. Quantitative EEG and stroke

In contrast to the extensive number of studies using fMRI and similar imaging techniques to investigate stroke, there have been very few studies concentrating on the electrophysiological nature of stroke and particularly hemispatial neglect. Brain injury in general has been associated with increased *delta* activity, accompanied by a decrease in activity in the *alpha* and *beta* bands (Niedermeyer, 2005). Quantitative EEG, recorded in the acute post stroke phase, has been shown to be predictive of patient outcome in several studies (Finnigan, Rose, Walsh, Griffin, Jante, McMahon et al, 2004; Finnigan, Walsh, Rose, & Chalk, 2007). Finnigan et al (2004) recorded quantitative EEG in 13 patients 48 hours post stroke and assessed each patient on the National Institute of Health Stroke Scale (NIHSS), a scale that provides a measure of stroke-related deficits, at 48 hours and then again 30 days later. The patient group included both left and right hemisphere stroke patients with a range of lesion locations. Analyses showed that increased *delta*/*alpha* ratio (driven by increased *delta*) at 48 hours was correlated with worsening scores on the 30-day NIHSS whilst

increasing *alpha* power was correlated with improved scores. Giaquinto, Cobianchi, Macera and Nolfe (1994) monitored EEG in 34 patients with ischaemic stroke in the left or right middle cerebral artery territory over a six month period. The greatest rate of recovery was reported during the first three months post stroke with a significant decrease in *delta* power over the injured hemisphere compared with baseline along with increased *theta* and *alpha* activity. There was no statistically significant difference in EEG activity at six months compared to three months suggesting that spontaneous improvement occurred in the first three months only. There was no change in *beta* activity over the six month period of testing, a finding that will be returned to later in the thesis. Mean values of *delta* and *theta* power revealed hemispheric asymmetries with *high*er power in the injured hemisphere than in the non-injured hemisphere. Their results supported previous findings that the greatest improvement in EEG occurred in the first few months after stroke. This study also found that patients with more severe clinical impairments had much more *delta* and less *alpha* relative power than patients with milder impairments. In another study, EEG recorded from a 53 year old subcortical stroke patient was compared to that of a group of 12 age-matched controls. Results showed that the patient had increased absolute *delta*, *theta*, *high*er *theta*/*beta* ratios, and decreased relative *beta* activity on the side of the infarct (Molnar, Csuhaj, Horvath, Vastagh, Gaal, Czigler et al, 2006). The usual reactivity observation of increased *beta* power on eyes opening was reported not to occur in this stroke patient in either hemisphere but was reduced to a greater extent over the damaged hemisphere. Similarly, the usual reactivity observation of decreased *alpha* activity as a result of opening the eyes was not produced in the patient on either side. The authors suggest this might a general

consequence of stroke causing the derangement of *alpha* generators (Juhasz, Kamondi & Szirmai, 1997).

In addition to quantitative EEG studies investigating general stroke correlates, it has also been established that quantitative EEG can be used as a tool to identify stroke patients with aphasia (Finitzo, Pool & Chapman, 1991) and can even indicate the future prognosis of such patients in terms of extent of aphasia recovery (Szelies, Mielke, Kessler & Heiss, 2002; Jabbari, Maulsby, Hotzappel & Marshall, 1997). In these studies, not only are EEG abnormalities reported over brain regions directly related to speech, specifically increased *delta* and *theta* power over left frontal and temporal regions, but also over distant brain regions, with greatly reduced occipital *alpha* power in the left hemisphere in comparison with the right. This suggests that functional disturbances outside the infarct region also play a key role in the manifestation of stroke-related deficits.

1.2.3. Quantitative EEG and neglect

Although limited in number, studies focusing on stroke patients with neglect have found consistent activation patterns and asymmetries. Watson, Andiola and Heilman (1977) conducted one of the first studies to investigate EEG patterns in neglect patients with the aim of determining whether focal lesions associated with the disorder were associated with abnormal EEG patterns remote from the lesion. This study compared EEG profiles of 23 neglect patients (20 with right hemisphere lesions, 3 with left hemisphere lesions) with 21 aphasic patients (all with left hemisphere lesions). The findings showed that neglect was associated with a diffuse increase of *delta* and *theta* activity across the whole of the damaged hemisphere

compared to aphasia which was associated with increased *delta* and *theta* activity over the focal lesioned area only. Demeurisse, Hublet and Paternot (1998) compared EEGs one month post stroke of 33 patients with right hemisphere stroke, 16 of whom presented with neglect, 17 of whom presented with no neglect. They found that *delta* activity was *high*er in patients with neglect than in patients without neglect; however this effect was not region specific. They also found significantly increased *delta* activity in posterior regions on the right compared to the left in patients with neglect. It was concluded that the left/right ratio between *delta* activity in posterior regions might be more suitable than absolute *delta* power values to discriminate patients with neglect from those without neglect.

In a follow-up study Colson, Demeurisse, Hublet and Slachmuylder (2001) investigated differences in *delta* and *theta* activity in 33 right-sided stroke patients with and without clinical neglect. They found that patients with neglect had increased levels of both *theta* and *delta* in right parieto-temporal regions (overlapping with the right TJP already implicated in neglect), a pattern that distinguished this group from the non-neglect group. These differences were found in the absence of any differences in CT and/or MRI localization between the two groups and therefore *high*light the advantage quantitative EEG may have over other imaging techniques in identifying neurophysiological markers of neglect. EEG recordings were carried out in the eyes-closed condition only and absolute power were analysed. Since only *theta* and *delta* activities were reported in the study it was unclear what the pattern of activity was in the *high*er EEG bands.

To summarize, the majority of EEG studies on stroke and neglect are few and far between and have focused on the pattern of increased slow wave activity extending over the damaged hemisphere. However, few have considered the pattern of activity at the *high*er end of the frequency spectrum, largely due to an increased chance of artefact contamination due to muscle activity (Finnigan et al, 2004). Activity at the *high*er end of the spectrum has the potential to be more informative and could provide a greater insight into the neurophysiology of neglect, impacting on potential interventions.

1.2.4. Quantitative EEG and ADHD

Based on the findings that ADHD is associated with a shift in spatial attention in the same direction is neglect, as already outlined, it follows that there may be similarities in the EEG profile of ADHD and neglect patients. Electrophysiological ADHD research has consistently reported an abnormal EEG pattern during resting state conditions, specifically, increased activity of *theta* waves and decreased activity of *beta* waves often summarised by an increased *theta*/*beta* ratio (Snyder & Hall, 2006). Research has gone as far as to identify very specific EEG patterns that are related to subtypes of ADHD (Clarke, Barry, McCarthy & Selikowitz, 2001).

Mann, Lubar, Zimmerman, Miller and Muenchen (1992) compared QEEGs of children with ADHD and control children and reported an increase in slow wave activity, specifically increased *theta* in frontal locations, and a decrease in fast wave activity, specifically decreased *beta* in posterior locations. These differences were observed in a rest condition and during a cognitive task. Later studies verified these findings and extended the analyses to find that the *theta*/*beta* ratio, recorded from Cz

at rest, could be used to identify children who had been clinically diagnosed with ADHD (Lubar, Swartwood, Swartwood & Timmermann, 1995; Chabot & Serfontein, 1996; Monastra, Lubar, Linden, Van Deusen, Green, Wing et al, 1999). Bresnahan and Barry (2002) showed that an elevated *theta*/*beta* ratio in the eyes open condition could be used to distinguish adults who met the clinical criteria for ADHD (n = 50) compared with those who demonstrated only a few symptoms related to the disorder (n = 50). Since parallels have already been drawn between ADHD and neglect, the *theta*/*beta* ratio should be investigated in neglect.

1.2.5. The relationship between tonic alertness and EEG

As previously mentioned, terms used to describe aspects of alertness are used inter-changeably in the literature by different groups of scientists but can logically be categorised into two main categories: 'on-task' and 'off-task'. Sustained attention, concentration and vigilance all refer to maintaining an alert state whilst being 'on-task' since they cannot be described in any other context. Arousal, on the other hand, refers to the more intrinsic state of alertness that can be measured off-task physiologically. Sustained attention or vigilance tasks, typically lengthy monotonous tasks, require alertness to be maintained tonically at a certain level in order to enable responding to relatively rare, uninteresting target stimuli. As noted above, a decline in tonic alertness is indexed by increased reaction times and increased error rates on sustained attention tasks. Several physiological measures have been used in the past to reflect states of tonic alertness and arousal such as skin conductance level (SCL), heart rate variability (HRV) and respiratory rate (RR). Continuous EEG can also be used as a measure of tonic alertness. Previous studies have shown correlations of declining levels of alertness with increased levels of *theta*

and *high beta* power (Matthews, Davies, Westerman & Stammers, 2000; Paus, Zatorre, Hofle, Caramanos, Gotman, Petrides & Evans, 1997; Knott, Bakish, Lusk, Barkely & Peruginni, 1996; Makeig & Jung, 1996). A decrease in *beta* activity with time-on-task has also been reported suggesting this could also be used as an index of tonic alertness (Valentino, Arruda, Gold, 1993; Oken, Salinsky & Elsas, 1996). Arruda, Amoss, Coburn and McGee (2007) recorded quantitative EEG in healthy participants whilst they carried out an auditory continuous performance task. They reported *beta* power activity over the right hemisphere to be predictive of performance with an accuracy of 65%, with increased *beta* activity relating to improved performance. Arruda et al (2007) concluded that these results suggest that task-related *beta* activity could be a marker of tonic alertness.

The behavioural and EEG literatures already discussed suggest that ADHD children could have a similarly disrupted attentional system as neglect patients. The hypoarousal of the central nervous system (CNS) model has been put forward to account for the deficits of sustained attention associated with ADHD (Satterfield & Cantwell, 1974). ADHD has been consistently linked to an elevated *theta*/*beta* ratio and given the hypoarousal account of ADHD this ratio is often considered an index of alertness. However, contradictory evidence for this relationship has been put forward by Barry, Clarke, McCarthy, Selikowitz, Rushby and Ploskova (2004) in their study investigating EEG correlates with central nervous system (CNS) arousal in healthy participants. This study investigated whether the *theta*/*beta* ratio was a true marker of *arousal* by correlating this ratio with the electrodermal measure of skin conductance level (SCL), the gold standard measure of arousal. Barry et al (2004) found that elevated CNS arousal, as measured by SCL, was not associated

with *theta*, *beta* or the *theta*/*beta* ratio but instead was associated with significantly decreased *alpha* activity. Based on these findings, the authors postulate that a clear distinction needs to be defined between activation and arousal, terms often used synonymously. They suggested that the *theta*/*beta* ratio represents a substrate of task-related *activation* involved in cognitive/attentional tasks whilst *alpha* represents a more general state of *arousal*. Therefore, impaired performance on cognitive/attention tasks is put down to a task-related processing deficit, which could be defined as an *alertness*, rather than an *arousal*, deficit per se. A later study by the same group extended research into ADHD children. Compared to a control group, ADHD children had significantly lower SCL (interpreted as reduced arousal), increased *theta* and *theta*/*beta* ratio and decreased *alpha* and *beta* activity. In support of the earlier findings, SCL correlated negatively with *alpha* activity and showed no relationship with *theta*/*beta*. Interpretation of these findings taken together is difficult. They suggest that increased arousal (as measured by SCL) is associated with decreased *alpha* activity, as shown in both healthy and ADHD children. However, ADHD children are reported to have decreased levels of *alpha* activity in comparison to age-matched controls which would imply they have *higher* arousal levels. In an attempt to reconcile this, Loo, Hale, Hanada, James, McGough, McCracken and Smalley (2009) suggest that attenuation of *alpha* power may reflect the need to increase arousal and cortical activation in order to comply with the demands of an experimental situation in ADHD, specifically the requirement to remain still throughout the recording of the EEG in order to avoid artefact contamination. Further support for this theory of increased task-induced cortical activation comes from research showing that ADHD children exhibited decreased levels of *alpha* activity during mathematical calculations in comparisons to controls

(Swartwood, Swartwood, Lubar & Timmermann, 2003). Therefore, it remains unclear whether reduced *alpha* activity in ADHD reflects a general *hyper*active arousal state, contrary to the hypoarousal model, or a task-induced need for activation in order for ADHD patients to perform at the same level as age-matched controls. Given that ADHD is associated with lower SCL (Barry, Clarke, McCarthy, Selikowitz, MacDonald & Dupuy, 2012), it seems that the latter relationship is more likely.

1.2.6. EEG Neurofeedback

The method of using EEG as a form of biofeedback was introduced by Barry Sterman in 1968. In an early study, Wyricka and Sterman (1968) successfully managed to train cats via food reward to increase *SMR* activity. Sterman was later asked by NASA to investigate the effect of varying degrees of exposure to monomethylhydrazine, an epileptogenic fuel compound. Fifty laboratory cats were injected with the compound and all but ten developed epileptic seizures. The ten cats that showed resistance to seizures happened to be the cats that had been involved in the *SMR* up-training study, providing the first evidence that training EEG can influence the activity of the cortex. In 1971, Sterman went on to investigate the effects of up-training *SMR* activity in an epileptic sufferer, with the result of a reduction in seizure activity. This finding led the way for further research into the use of EEG manipulation in epilepsy (for a review see Sterman & Egner, 2006).

Sterman's findings showed that EEG feedback, or neurofeedback, could be successfully used to influence cortical activity and behaviour in humans.

Neurofeedback training works on the principle of teaching individuals to increase or decrease specific EEG frequencies in order to promote normalization of activity in a dysfunctional brain or to optimize activity in a normal brain. Neurofeedback is based on the principles of operant conditioning where learning is achieved by rewarding EEG changes in the desired direction. This is achieved by presenting the individual with an online representation of their brain activity in the form of a simple audio-visual display, such as a computer game or graphical representation. When the individual successfully increases or decreases specific brain frequencies as required by a particular training protocol they receive a positive audio-visual reward. This positive reinforcement gradually leads to better self-regulation of brain activity through learning achieved over repeated training sessions. Whilst neurofeedback training can be applied to clinical populations with clearly disrupted EEG profiles, it can also be used to promote specific EEG frequencies in the healthy population, as has been reported in several optimal performance studies.

1.2.7. EEG Neurofeedback Training in the Healthy Population

Several neurofeedback studies have reported an association between enhancement in power of Sensory- Motor Rhythm (*SMR*) and *beta* bands with performance on various measures of attention in young healthy adults. In one study, 22 student participants (mean age = 22.1) were trained on an *SMR* and *beta* neurofeedback training protocols with the aim of improving aspects of attention (Egner & Gruzelier, 2001). Participants completed ten 30-minute sessions of neurofeedback training, consisting of consecutive 15-minute periods of *SMR* and *beta* training. Comparison of performance on a continuous performance task, the Test of Variables of Attention (TOVA), in the pre and post assessments revealed a significant reduction in

commission errors after the training sessions, reflecting a decrease in impulsiveness. Further analysis showed that successful enhancement of *SMR* during the neurofeedback training sessions was *high*ly positively correlated with this reduction in commission errors. Both *SMR* and *beta* learning was associated with an increased P300b event-related potential in response to an auditory oddball task, thought to reflect attentional processing.

In order to disentangle specific aspects of attention that are changed with each specific neurofeedback training protocol, Egner and Gruzlier went on to conduct a similar study, again with young healthy adults, but this time participants were allocated to only one training group, *SMR* or *beta* training, and compared to a control group (Egner and Gruzelier, 2004). *SMR* training was associated with reduced omission errors, improved perceptual sensitivity (indexed as d prime) and reduced time variability. *Beta* training was associated with reduced reaction times (often used as a measure of arousal or alertness) and increased P300b amplitudes at central and parietal locations. However, despite showing improvements in attentional processing as a function of neurofeedback, there were no associated EEG changes in the pre- and post-assessments. Therefore, caution must be taken when interpreting these data as it is difficult to assign causality to the behavioural changes without associated EEG changes.

Vernon, Egner, Cooper, Compton, Neilands, Sheri et al (2003) also found supporting evidence for the beneficial effects of *SMR* training in healthy young adults. Their cohort consisted of 30 undergraduate medical students with an average age of 22.1

yr. Participants were randomly allocated to the control group, *theta* group or *SMR* group. The control group was simply assessed on the pre and post measures over the same time course as the two neurofeedback groups. Participants in the *theta* group were required to enhance *theta* whilst simultaneously inhibiting *delta* and *alpha* activity. Participants in the *SMR* group were required to enhance *SMR* activity whilst inhibiting *theta* and *beta* activity. Their results showed that only the *SMR* group were able to modulate their *SMR* activity in the directions of the training protocol whereas the *theta* group failed to show any signs of learning. Alongside this successful EEG modulation, the *SMR* group also showed signs of behavioural improvement on several cognitive assessments including improved accuracy on a continuous performance task (CPT) and improved accuracy on a working memory task. The control and *theta* group did not show any change in either of these measures in the post assessment. These data support the previous finding of Egner and Gruzelier (2001) that young healthy adults are able to successfully modulate their EEG through an *SMR*-based training protocol after just 8 sessions. The data also supports previous findings that *SMR* training can influence aspects of attentional processing.

1.2.8. Neurofeedback Training in older adults

Neurofeedback research has not only focused on cohorts of young healthy adults. It has also been applied to various clinical conditions such as ADHD and autism, epilepsy, anxiety and schizophrenia. The encouraging results from these studies suggest that the application of neurofeedback is not limited to *high* functioning brains. Despite a significant amount of interest in cognitive decline in elderly

subjects and how to prevent this, very few studies have focused on the impact of EEG-neurofeedback training and performance on cognitive tasks in the elderly. Based on the findings from healthy young adults and clinical groups, it would seem that this is an area that needs to be explored. Previous research suggests that the EEG spectral patterns and frequency band power levels change as a function of age. Evidence suggests there is a general shift in the frequency spectrum toward lower frequencies with decreased *alpha* and *beta* activity and increased *theta* activity (Matejcek, 1980; Nakano, Miyasaka, Ohtaka & Ohomori, 1992; Williamson, Harold, Morrison, Rabheru, Fox, Wands, Wong & Hachinski, 1990). Research into the application of neurofeedback in older adults is limited and the small number of existing studies has focussed on *alpha* and *theta* training due to the links between these bands and memory (Klimesch, Vogt & Doppelmayer, 2000). Angelakis, Stathopoulou, Frymiare, Green Lubar and Kounios (2007) investigated several neurofeedback protocols on individual healthy participants aged between 70-78 yr. The main aim of this study was to investigate whether elderly participants could be trained to increase their individual 'peak *alpha* frequency' (PAF) which is known to decrease as a function of age and correlated to mental performance. Only six participants were recruited for this study, three of whom were trained to increase their PAF (experimental group), two of who were trained to increase their *alpha* amplitude (control group) and one of whom was given sham feedback. A minimum of 31 sessions (maximum of 36 sessions) were completed by all participants. Participants in both the PAF training group and the *alpha* amplitude training group showed improvements in the relevant learning indices across sessions and each protocol was associated with improvements on specific cognitive assessments which included the "n back" task and a GO/No-Go oddball task. However, in another study

Lecomte and Juhel (2011) found that whilst six of ten elderly subjects were able to successfully increase *alpha* power through neurofeedback training, this was not associated with improvements on the memory assessments from the Signoret Memory Battery. This study only included four sessions of neurofeedback training, however, so it remains unclear whether the four participants who did not show successful EEG modulation might have been successful with more sessions and whether with more sessions there would have been memory improvements. Becerra, Fernandez, Roca-Stappung, Diaz-Comas, Galan, Bosch et al, (2012) explored the effectiveness of a *theta* protocol which rewarded decreased *theta* activity in healthy elderly subjects. Fourteen healthy adults, aged between 60-84 years, were recruited and allocated to a neurofeedback training group (who received *theta*-based neurofeedback training) or a control group (who received sham neurofeedback training). All participants received 30 training sessions over a period of twelve weeks. True neurofeedback training was associated with reduced *theta* activity and improved performance in verbal processing. However, both groups improved on the memory subtest of the NEUROPSI. The authors had no explanation for the improved performance in the sham group other than a placebo effect. In sum, there is evidence to suggest that elderly brains are capable of modulating the EEG activity through EEG neurofeedback training, although it remains unclear whether this modulation translates to behaviour as of yet. Interestingly none of the studies cited here have investigated training *beta* activity in older adults, a surprising find given the promising results this protocol has received in healthy young adults.

1.2.9. Neurofeedback in Clinical Populations

Of particular relevance to this thesis are neurofeedback protocols which involve rewarding increases of mid-range *SMR* and *beta* waves whilst simultaneously inhibiting *theta* waves. This form of training has received particular attention in the field of ADHD since this condition is associated with abnormally *high* levels of *theta* and low levels of *SMR* and *beta* activity. Several studies have reported behavioural, cognitive and neurophysiological improvements as a result of *beta* and *SMR* reward protocols in children and adolescents with ADHD (Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Monastra, V., Monastra, D. & George, 2002; Fuchs, Birbaumer, Lutzenbergen, Gruzelier & Kaiser, 2003; Kropotov, Grin,Yatsenko, Ponomareev, Chuko, Yakovenko & Nikishena, 2005). Beauregard and Levesque (2006) aimed to investigate whether behavioural improvements associated with neurofeedback in ADHD children was correlated with changes in neural activity as recorded by fMRI. An experimental group of 15 children undertook 20 sessions of EEG neurofeedback training (*SMR* and *beta* up training and *theta* down training) whilst 5 children were allocated to the control group and received no intervention. In addition to several behavioural tasks, pre and post assessment sessions included an fMRI recording whilst participants completed the Counting Stroop task and a Go/No-Go task. fMRI data from the pre assessment task showed no difference between the intervention and control groups but confirmed previous findings that ADHD is associated with a lack of activation in the anterior cingulate cortex (ACcd) during selective attention tasks (Bush, Frazier, Rauch, Seidman, Whalen, Jenike et al, 1999). However, the experimental group showed a significant increase in activation in this region in the post assessment, a finding that correlated with improved performance on the Stroop task. Increased activation of the ACcd was observed alongside increased activation

of the left caudate and the left substantia nigra in the experimental group. Since these regions are components of the anterior cingulate-striatal circuit that control dopamine, the authors postulate that neurofeedback led to neuromodulation of a dysfunctional dopaminergic system thought to play an active role in attention and ADHD symptomology. Arns, Ridder, Strehl, Breteler and Coenen (2009) conducted a meta-analysis of 15 studies investigating neurofeedback training as an intervention for symptoms of ADHD. They concluded that the current status of neurofeedback as a treatment for ADHD was Level 5, meaning it was considered to be efficacious and specific. To summarize, neurofeedback training protocols aimed at reducing *theta* and increasing *SMR* and *beta* activity have shown to improve aspects of tonic alertness and sustained attention in ADHD.

Neurofeedback has also been successfully applied to patients with mild and traumatic brain injury suggesting that a damaged brain is also able to benefit from this intervention. For example, Ayers (1993) allocated 12 patients with mild head injury to an EEG neurofeedback training AND psychotherapy group and six patients to a psychotherapy group. The neurofeedback training group received a protocol involving enhancement of *beta* (15-18 Hz) and suppression of *theta* (4-7 Hz). Patients from the neurofeedback training group showed a reduction in symptoms and reported progression in therapy, whist no improvements were reported in the control group. Keller (2001) evaluated the effectiveness of EEG neurofeedback training in enhancing remediation of attention deficits in patients with closed head injuries who were still in the phase of spontaneous recovery (mean time recruited post injury was 3.8 months). Patients recruited had a variety of lesions including: bilateral haematoma, frontoparietal haematoma, temporal lobe contusions, frontotemporal

lobe contusions and bilateral contusions. Twelve patients were allocated to an EEG neurofeedback training group and received training to increase *beta* activity (13-20 Hz) whilst nine patients were allocated to a computerized attention training task. Both groups improved performance on the computer tasks but the neurofeedback training group also improved on the paper-and-pencil cancellation task. The only significant improvement across both assessments however was reported for the neurofeedback group, who had significantly reduced reaction times on the post assessment continuous performance task. The authors therefore concluded that neurofeedback is a promising method for the treatment of attentional disorders in patients with traumatic brain injuries and that neurofeedback training was suitable for use with patients in the early phase of rehabilitation. However, within the neurofeedback training group, eight patients learned to increase their *beta* amplitudes whilst four patients showed a decrease in *beta* amplitude. Interestingly, the eight improvers started the training with significantly lower *beta* amplitudes than the four patients who failed to show improvement with training. This suggests that initial baseline EEG measures may be predictive of the ability to train through neurofeedback. Another interesting finding reported by Keller (2001) was that patients in the neurofeedback group as a whole became more proficient across sessions at increasing *beta* activity within session. Keller therefore postulates that an improved ability to maintain *beta* above threshold during the training sessions corresponds to post training improvements on sustained attention measures. Unfortunately Keller did not report group differences within the neurofeedback training group so it is not possible to draw conclusion about the differential effects of increasing or decreasing *beta*on behavioural performance. This issue will be considered later in this thesis.

Neurofeedback has also been found to improve memory in patients with brain injury and improve attention and response accuracy on a performance task and decrease errors in a problem solving task (Thornton, 2000). In addition to these behavioural improvements, Tinius and Tinius (2000) also reported more normalized EEGs in patients treated with neurofeedback for traumatic brain injury.

Rozelle and Budzynski (1995) reported a case study of a stroke patient who embarked on a 6-month period of neurofeedback training one year after a left-hemisphere stroke. Two neurofeedback training protocols were employed, the first trained the patient to inhibit *theta* activity and the second to increase *beta* activity (15-21 Hz). Post-assessment measures indicated that the patient's resting state EEG contained reduced levels of *theta* activity which coincided with improved speech fluency, balance, coordination, attention and concentration and reduced levels of anxiety and depression. Similarly, Laibow, Stubblebine, Sandground and Bounias (2001) conducted a study to investigate the effectiveness of EEG neurofeedback training in a group of 29 unselected patients with a variety of brain injuries that presented at their clinic. Patients were classified in terms of their clinical syndrome to one of six groups: motor dysfunction, cognitive dysfunction, psychosocial disorders, pain dysfunction, pain related syndrome and neuropsychiatric disorders. All patients were trained to reduce slower waves (2-7 Hz) and faster waves (24-32 Hz) whilst simultaneously increasing mid-range waves (15-18 Hz). A sub group of seven patients included in this study had suffered a stroke, and this group showed a significant increase in *alpha* power alongside a decrease of *theta* power.

1.2.10. Considerations when Designing and Interpreting a Neurofeedback Study

The neurofeedback literature, whilst showing promising effects of training, must be interpreted with some caution for several reasons. Firstly, there is a lack of consistency across studies in terms of variables analysed and reported. Very few studies provide details about EEG changes across the spectrum within training sessions and across training sessions, which would provide insightful information into the mechanisms involved during the neurofeedback process. Studies reporting only pre and post behavioural improvements only provide suggestive indications of a causative effect of neurofeedback training. Recognising the methodological flaws which infiltrate the neurofeedback literature, Dempster and Vernon (2009) suggest a more consistent approach to reporting neurofeedback session data which involves evaluating baseline measures, across session learning *and* within session learning. Therefore, the protocols devised for this thesis will attempt to provide a detailed account of all relevant EEG variables in order to be able to make informed conclusions regarding the effectiveness of neurofeedback training.

The other critical factor to consider when designing a neurofeedback study is control. It is important to note that most of the clinical studies reviewed here attempted to have some kind of control group but none were in the form of double-blind, randomized, sham-controlled studies. The latter experimental design is usually considered to be ideal but has been criticized in its application to clinical groups because when a standard treatment is available it is considered to violate ethical principles to withhold this from a patient. However, such ethical issues are not relevant to *high* functioning adults. Logemann, Lansbergen, van Os, Bocker and

Kenemans (2010) aimed to investigate whether previous findings relating neurofeedback training with improved aspects of attention in healthy participants could be observed in a double-blind sham-controlled study. Participants were randomly allocated to neurofeedback treatment group (n = 14) or a control group who received sham feedback (n = 13). Individualized training protocols were employed for the training group based on quantitative EEG measures. The investigators predicted that the neurofeedback training group would show decreased inattentiveness and impulsivity after training relative to the sham group as well as changes in the specific EEG frequency bands being trained. The study incorporated a halfway interim assessment and as a consequence of this assessment, the study was ceased in accordance with ethical guidelines because no trend was evident in terms of changes in behavioural performance or EEG in the experimental group. This study *high*lighted one important factor that needs to be considered when designing a neurofeedback study. In Logemann et al's (2010) study 10 of the 14 participants in the neurofeedback group and 10 of the 12 participants in the sham group thought they had been allocated to the sham feedback group. This could explain the lack of effective neurofeedback learning since it is likely that training relies on active engagement of the participant during each training session. With regards to sham studies, Becerra et al (2012) reported a placebo effect in the sham group, which showed improved performance in the post assessment, suggesting that those allocated unknowingly to a sham group could have used the same cognitive strategies employed by those in the true neurofeedback group. In order to circumvent the unknown effects of sham groups, the neurofeedback protocol in Experiment II of this thesis used a control group who underwent the same pre and post assessment measures as the neurofeedback group but received no intervention.

1.3 Overview and Research Questions

The literature covered thus far allows major conclusions to be drawn:

(i) Neglect is a complex neurological disorder with both spatial and non-spatial deficits, both of which are likely to interact to exacerbate symptoms.

(ii) Whilst interventions addressing the spatial element of the disorder have their place in rehabilitation, there is scope to develop interventions that focus on non-spatial attention, namely tonic alertness.

(iii) EEG correlates of tonic alertness in healthy and clinical disorders have been reported. Specifically, reduced *theta* and increased *beta* are associated with *high*er levels of alertness in ADHD, a condition also associated with a shift in spatial attention. However, there is a distinct lack of EEG investigations into neglect, so the underlying EEG profile relating to the disorder is largely unknown.

(iv) EEG *beta*/*theta* neurofeedback has improved various aspects of attention and alertness in both healthy and clinical populations through neuromodulation of EEG activity. This method has been extensively researched in application to ADHD and a number of studies have reported a reduction in attention-related and behavioural symptoms with neurofeedback.

(v) The EEG neurofeedback literature focussing on enhancing *beta* protocols is sparse in the fields of healthy older adults and brain injury.

Overview of Experimental Chapters

EXPERIMENT I

Based on the literature reviewed in this chapter, the aim of Experiment I was to investigate the EEG profile of neglect. It was predicted that neglect patients would show a distorted EEG profile similar to that of ADHD with elevated levels of slow wave frequencies (*theta*) and diminished levels of *high*er frequencies (*beta*). If this prediction is correct, it suggests that neglect patients may benefit from the arousal-based EEG neurofeedback training protocol that has been successfully used as a therapeutic intervention for children and adolescents with ADHD.

EXPERIMENT II

The aim of Experiment II was to determine whether healthy older adults, within the general age range of most stroke patients, are capable of modulating their EEG to the same extent as has previously been shown in healthy young adults. If so this provides further support for the application of EEG neurofeedback to neglect patients of a similar age.

EXPERIMENT III

The first aim of Experiment III was to determine whether neglect patients can successfully modulate their EEG through neurofeedback training and whether any learning is associated with a reduction in symptoms related to the disorder.

To date, there have been no studies investigating neurofeedback as a viable therapy for stroke or neglect, other than single case studies, so the data presented here was intended to act as a preliminary investigation on which to build future research. It was predicted that not all patients would benefit from neurofeedback training. Therefore of particular interest was identifying predictor variables, such as neglect severity, which determine how patients respond to the intervention. The second major aim of this study was to provide a continual assessment of EEG activity over a six-week period in patients with neglect within the 3-month acute period after stroke. This would allow insightful associations to be made between EEG activity and behavioural recovery.

CHAPTER 2

EXPERIMENT I

2.1. Research Questions and Hypotheses

The aim of this experiment was to determine whether hemispatial neglect is associated with an abnormal EEG profile. Previous studies investigating quantitative EEG correlates with stroke have generally focussed on slow frequency analyses (Molnar et al, 2006; Szelies et al, 2002; Colson et al, 2001). It is clear that stroke, and general brain injury, results in an increase in *delta* and *theta* power but little emphasis has been placed on the effects of stroke on *high*er frequency bands. This study aims to investigate the effects of right hemisphere stroke, specifically in patients with left-sided neglect, on all frequency bands.

Given the links between ADHD, alertness and spatial attention discussed in Chapter 1, particular parallels between the EEG profile of ADHD and neglect will be considered in this study. Previous studies investigating the EEG of ADHD have consistently found evidence of a general slowing of EEG. Specifically, there is an increase of *theta* activity and a corresponding decrease of *beta* activity, often calculated as a *theta*/*beta* ratio (Monastra et al, 1999). Based on quantitative EEG data from ADHD and indications that neglect is associated with reduced levels of tonic alertness, it was predicted that, compared to healthy age-matched controls, neglect patients would have a distorted EEG signature with excessive *delta* and *theta* power and reduced *SMR* and *beta* power. If this was proven to be the case, it would support the use of an alertness-based intervention for neglect.

An additional EEG variable that might distinguish neglect patients from age-matched controls is peak *alpha* frequency. Peak *alpha* frequency is an EEG measure that reflects the wave frequency of the maximum power within the *alpha* band (8-13 Hz), not to be confused with *alpha* amplitude or power across the *alpha* band. It usually lies between 10-11 Hz in healthy adults but has been shown to decrease as a function of age and vary amongst individuals (Klimesch, 1997; Posthuma, Neale, Boomsma & de Geus, 2001). Klimesch, Schimke, Ladurner & Pfurtscheller (1990) suggested that peak *alpha* frequency variations *within* individuals reflect attentional demands or alertness. Further evidence for a correlation between peak *alpha* frequency and alertness comes from studies reporting increased peak *alpha* frequency on administration of stimulants including caffeine and nicotine (Newman, Stein, Trettau, Coppola & Uhde, 1992; Knott, 1988). Reduced peak *alpha* frequencies have been reported in several clinical groups including Alzheimer's disease (Passero, Rocchi, Vatti, Burgalassi & Battistini, 1995), schizophrenia (Canive, Lewine, Edgar, Davis, Miller, Torres & Tuason, 1998) and chronic fatigue (Billiot, Budzynski & Andrasik, 1997). Juhasz et al (1997) recorded peak *alpha* frequencies in 40 patients with hemispheric stroke. This patient group was sub divided into 4 groups according to lesion location and extension: 1. Large cortico-subcortical parietal infarct in the middle cerebral artery regions. 2. Circumscribed haemorrhages or infarcts in the territory of the temporal branches of the middle cerebral artery. 3. Small haemorrhages or infarcts in the basal ganglia. 4. Multiple white substance lacunae. Patients were classified as presenting with asymmetric peak *alpha* frequency if there was a 0.5 Hz difference between the left and right hemisphere, otherwise patients were classified as symmetric. Interestingly, 11 of the 15 patients allocated to the symmetric group were large parietal lesion patients whilst 6 of the 7 recruited to the

asymmetric group were basal ganglia lesion patients. Based on the literature presented here certain predictions can be made about how peak *alpha* frequency will be affected in neglect patients. Since neglect is associated with decreased alertness, a reduced peak *alpha* frequency would be expected and since patients are most likely to come under the group of large parietal lesions, it would be expected that any reductions in peak *alpha* frequency compared to healthy controls would be bilaterally affected.

The main hypotheses of this study were:

Hypothesis 1 – Hemispheric Differences

Quantitative EEG differences will be reported for neglect patients and age-matched controls in the form of relative power in order to control for individual differences in skull thickness and other confounding variables that may result in individual variations in absolute EEG power. Mean relative power values will be extracted for *delta*, *theta*, *alpha*, *SMR*, *beta* and *high beta* frequency bands and calculated over left (F3, C3, P3) and right (F4, C4, P4) hemispheres. It is predicted that there will be no hemispheric asymmetries in any frequency bands in the control group. It is predicted that hemispheric asymmetries will be found in the patient group, with increased *delta* and *theta* activity over the damaged hemisphere and decreased *SMR* and *beta* activity compared to the undamaged hemisphere (Demeurisse et al, 1998; Watson et al, 1977). The same predictions are made for the eyes-open and eyes-closed conditions.

Hypothesis 2 – Across Group Differences

Mean relative power values will be analysed across groups for each hemisphere separately. It is predicted that patients will have significantly increased *delta* and *theta* activity and decreased *SMR* and *beta* activity compared to controls in both hemispheres. This difference is predicted to be more pronounced for the right hemisphere than the left hemisphere. The same predictions are made for the eyes-open and eyes-closed conditions.

Hypothesis 3 – Peak *Alpha* Frequency

It is predicted that patients will have a reduced peak *alpha* frequency compared to controls, extracted from the eyes-closed condition. The peak *alpha* frequency is predicted to be reduced in both hemispheres (Juhasz et al, 1997). This would support previous research indicating a link between alertness and peak *alpha* frequency (Klimesch et al, 1990).

2. 2. Methods

2.2.1. Participants

Patient Group

Nine right hemisphere stroke patients with left-sided neglect (five males and four females; mean age = 65 years; SD = 9.57) were recruited from stroke units in South London and Kent (Kings College Hospital, St Thomas' Hospital, University Hospital Lewisham and William Harvey Hospital (East Kent)). Patients gave informed

written consent to participate in the study which was given full ethical approval by East Kent Hospital's Trust along with local approval from each NHS site. All patients met the following criteria;

Inclusion/Exclusion Criteria

In order to be considered for this study patients had to fulfil the following inclusion and exclusion criteria.

Include if yes to all:

1) ≤ 12 weeks since stroke
2) Clinically assessed spatial neglect
3) Pre-stroke Modified Rankin Score 0,1 or 2

Exclude if yes to any one:

1) Age <18 years
2) Severe communication problems
3) Lack of consent from patient or next of kin
4) Expected survival <12 weeks
5) Visual/spatial deficits pre-date stroke
6) Inability to participate in assessment/training

A note on patient recruitment

When patients were recruited for this study they consented to take part in Experiment I and Experiment III. Because the quantitative EEG employed in this experiment was a lengthy procedure and could not be done at the bed-side, not all patients could take part in this assessment immediately after consent (i.e. at Time 1 of Experiment III). Acute patients were recruited for this study for several reasons. Firstly, recruiting neglect patients is fraught with difficulty but acute patients will pass through hospital stroke units and be identified by the clinical team, whereas, chronic neglect patients no longer in the medical system would be considerably harder to identify. Secondly, all stroke patients will have current neuroimaging scans enabling identification of lesion size, shape and location. Scans taken at the chronic stage, apart from being impractical, will typically show anatomical changes which have occurred as a result of normalization after injury (Karnath & Rorden, 2012). This can result in misinterpretation of lesion anatomy and the misclassification of damaged and undamaged regions. Finally, acute studies allow the brain to be assessed before it has had time to functionally reorganise.

Age-Matched Control Group

Eighteen age-matched control participants (six males and 12 females; mean age = 65.72 years; SD = 8.53) volunteered to take part in the study and gave informed written consent. All control participants were without any neurological or psychiatric history. Written consent was obtained from each participant in accordance with the Helsinki Declaration, and the study was given full ethical approval from the College Research Committee at Goldsmiths, University of London.

2.2.2. Patient Neuropsychological Assessments

Behavioural Inattention Test

Visual neglect was assessed by the conventional part of the Behavioural Inattention Test (BIT) (Wilson et al, 1987). This battery consists of three cancellation tasks of varying perceptual difficulty (line, star and letters), a line bisection task, 2 figure copying tasks and a representation drawing task. The accepted cut-off point for clinical neglect is a score of 129/146, with scores less than 129 indicating visual neglect. All patients scored under 129 so were classified as having clinical neglect (see Table 2.1 for individual scores and Appendix 1 for example scoring sheet).

National Institute of Health Stroke Scale

Patients were assessed for general stroke severity by the National Institute of Health Stroke Scale (NIHSS). This scale measures several aspects of brain function including consciousness, vision, sensation, movement, speech and language. A score greater than 16 is considered to indicate poor prognosis and a *high* probability of severe disability or death. The scoring system used to categorize stroke is: 0 = no stroke, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-42 – severe stroke (see Table 2.1. for individual scores and Appendix 2 for example scoring sheet). All patients recruited scored 5 or more on the NIHSS so were classified as having suffered a moderate or severe stroke.

Table 2.1. Demographic and Clinical Data for the Patient Group

Patient	Gender	Age (yr)	Stroke	Lesion Location	No. of days since stroke	BIT	NIHSS
HB	M	62	Haemorrhage	Right Fronto-Parietal	90	19	11
RT	M	55	Infarct	Right Parietal, Temporo-occipital	47	14	17
KS	M	50	Infarct	Right MCA	75	41	16
KH	M	66	Haemorrhage	Right Fronto-Parietal	26	129	10
JM	F	68	Infarct	Right MCA	29	23	13
BS	F	72	Infarct	Right MCA	64	108	5
PS	F	76	Infarct	Right MCA	12	43	6
GL	M	63	Infarct	Right MCA	16	127	5
JH	F	73	Infarct	Right MCA	15	91	15

Scores on the Behavioural Inattention Test (BIT) and National Institute of Health Stroke Scale (NIHSS) are presented. No. of days since stroke gives the number of days between stroke onset and quantitative EEG recording

Given the range of scores reported on the BIT and NIHSS and the number of days since stroke, correlations were conducted to find out whether any of these variables correlated with each other. There was no significant relationship between number of days since stroke and scores on the BIT or NIHSS. However, there was a significant correlation between scores on the BIT and scores on the NIHSS ($r = -0.695$, $p = 0.038$) indicating *high*er scores on the BIT, i.e. less severe neglect, correlated with lower scores on the NIHSS, i.e. less severe stroke-related symptoms, as would be expected.

2.2.3. Quantitative EEG Acquisition

Quantitative EEG was recorded from all participants using the 21-channel Mitsar amplifier system and 19-channel electrode cap (ElectroCap). The cap was placed on the scalp according to the 10-20 system. Electrodes were referenced to linked earlobes and the ground electrode was placed 1.5 cm anterior to the central frontal (Fz) electrode. Electrodes placed on Fp1 and Fp2 recorded electro-oculogram (EOG) data to identify eye blink and horizontal eye movements. All impedances were under 5 kΩ throughout the recordings. Recordings were referenced to an average-weighted montage. Data were digitised at a sampling rate of 250 Hz and passed through a 0.5-30 Hz bandpass filter. Recording, digitisation and subsequent off-line data processing were carried out with Mitsar and WinEEG software. Artefact reduction was done via several methods. Firstly, a pre-programmed Independent Component Analysis (ICA) method was used to identify and correct for eye blinks. Artefacts were then marked and rejected for any amplitude over 100 μV. Recordings were conducted in a quiet room for 3 min in the eyes-open and eyes-closed conditions. One patient found it difficult to keep his eyes closed so his data could not be included in the eyes closed condition. The analysis focuses on the 9 most robust and artefact-free electrode locations (Fz, Cz, Pz, C3, Cz, C4, P3, Pz, P4), all other electrodes were contaminated and unusable in more than one patient so it was preferable to include fewer electrodes in more patients.

FFT analysis was performed and relative power (the ratio between the absolute power of the particular band and the absolute power of the total spectrum) was calculated for *delta* (1.5-4 Hz), *theta* (4-8 Hz), *alpha* (8-12 Hz), *SMR* (12-15 Hz), *beta* (15-18 Hz), *high beta* (20-30 Hz) at each electrode for each condition (eyes-

open and eyes-closed). For the statistical analyses, data was subsequently ln-transformed in order to increase normality (Gasser et al, 1982). In the eyes-closed condition the *alpha* peak frequency in Hz was determined for each electrode from the spectra graphs.

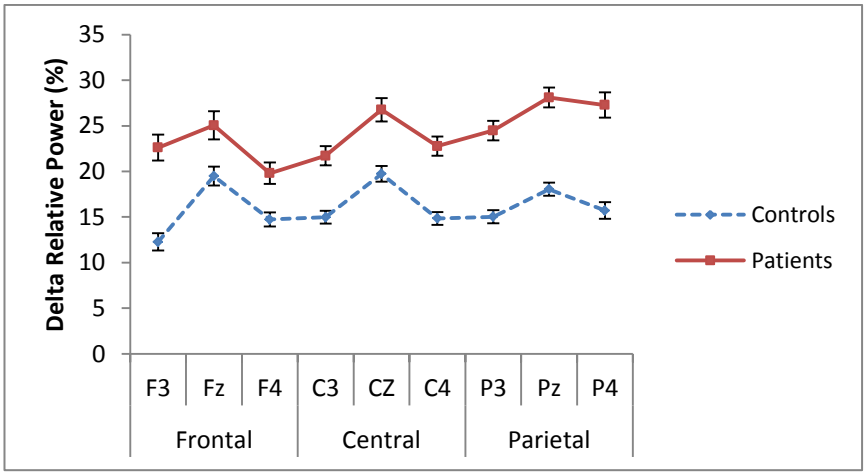
2.3. Results

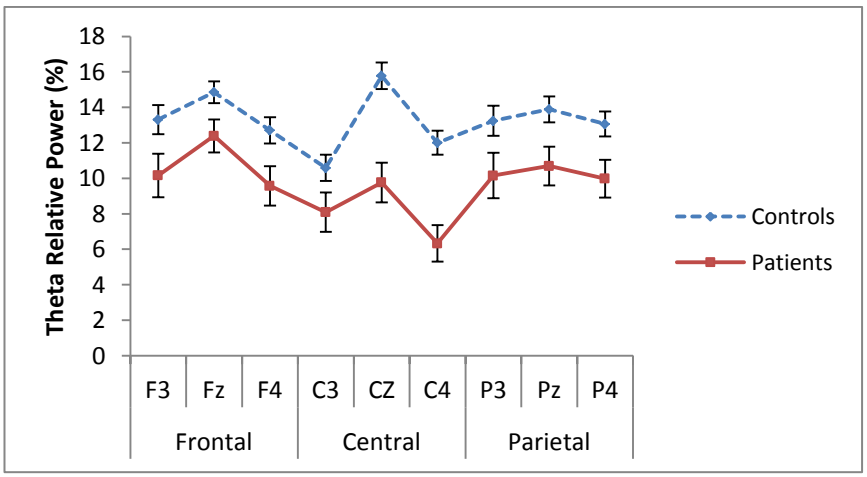
The hypotheses outlined in the introduction are addressed sequentially in this section. Findings are reported separately for eyes-open and eyes-closed conditions. The relative power data is presented in Figure 2.1 and Figure 2.2. In order to normalise the data for statistical analyses, the relative frequency data was ln-transformed. For both conditions, group and electrode comparisons are made with respect to the relative power of all frequency bands (*delta*, *theta*, *alpha*, *SMR*, *beta* and *high beta*). The eyes-closed analysis includes the additional variable of peak *alpha* frequency (PAF) over the left (averaged over F3, C3 and P3) and right hemispheres (averaged over F4, C4 and P4).

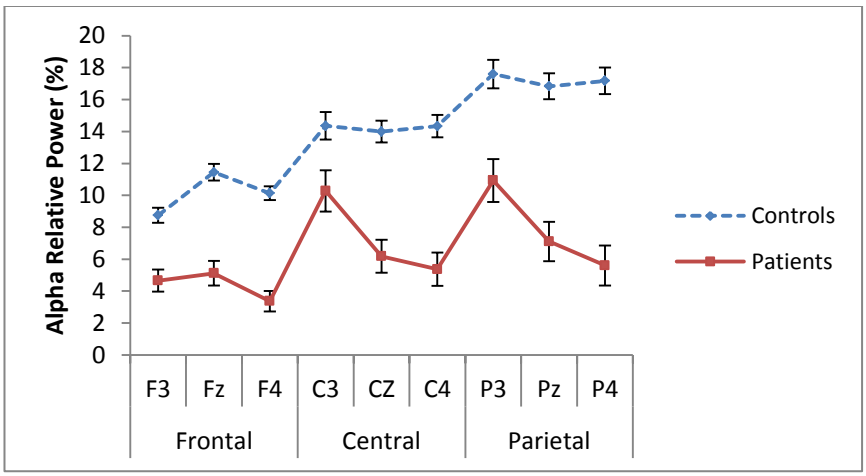
When reporting main effects and interactions from the ANOVA, the p values are Greenhouse-Geisser corrected when the test of sphericity is significant at $p = .05$, leading to non-integer values of degrees of freedom (d.f.) where d.f. > 1. Non-integer d.f. are written to one decimal place, F statistics to two decimal places and p and η_p^2 values to three decimal places. All post hoc t-tests are corrected for multiple comparisons by adjusting the α level accordingly.

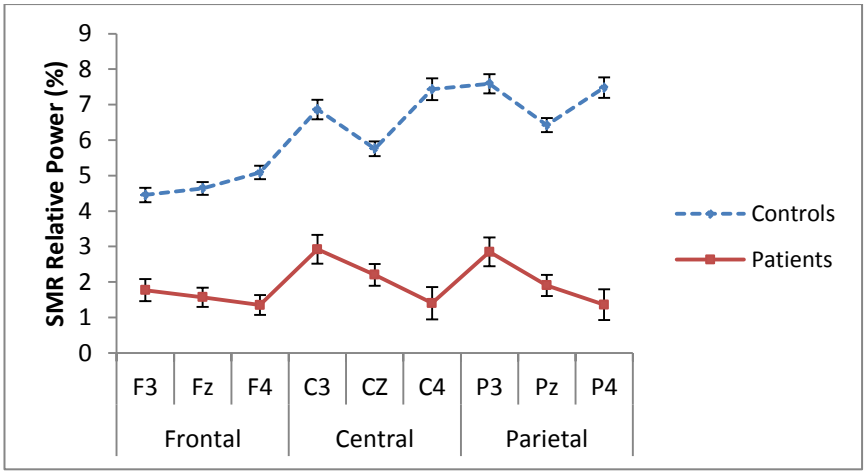
2.3.1. Eyes-Open Condition

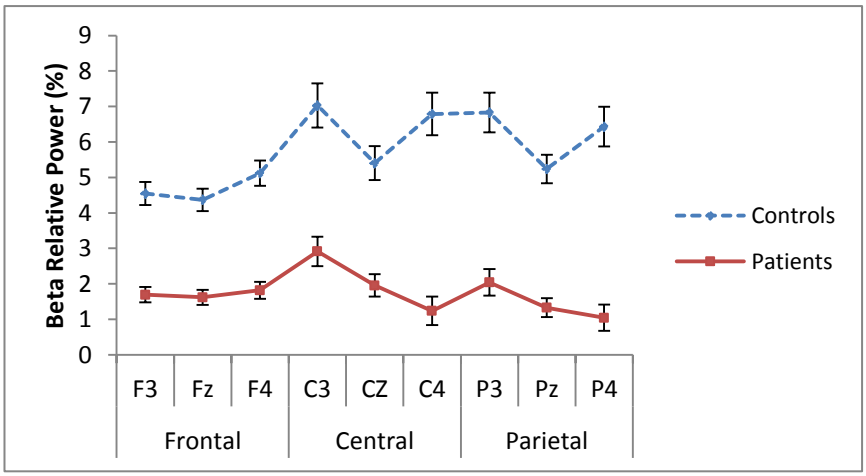
Figure 2.1 displays the relative power for each frequency for each group (control and patient) across frontal, central and parietal electrodes.











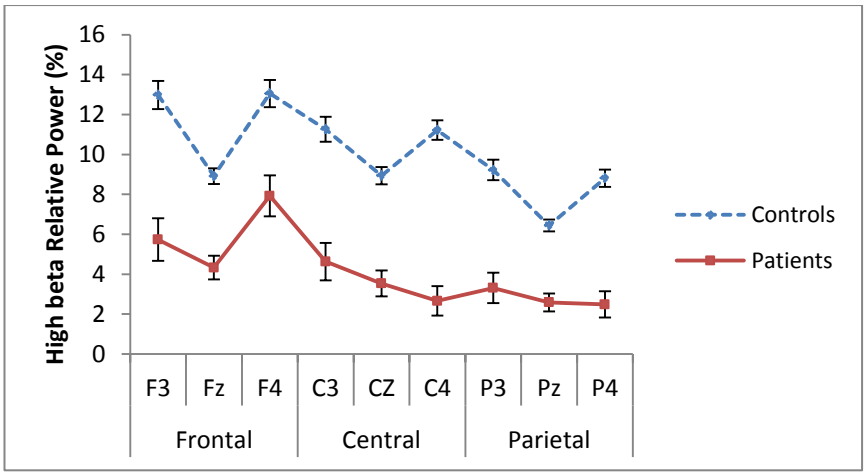


Figure 2.1. Relative power of frequency for patients and controls at each electrode in the eyes open condition

Hypothesis 1 and 2 – Hemispheric and Group Differences in Eyes Open Condition

Having ln-transformed the raw data, the following electrodes were included in the analyses, F3, F4, C3, C4, P3, P4. Central electrodes were omitted from the analyses because left-right hemispheric differences were of particular interest here. A 3 x 2 x 2 mixed-measures ANOVA was conducted separately for each frequency band with within-subjects factors of Area (frontal, central, parietal) and Hemisphere (left, right) and across subjects factor of Group (patient, control). Interactions were further analysed by independent t-tests to investigate significant group interactions at each electrode (alpha level adjusted to correct for 6 comparisons at F3, F4, C3, C4, P3, P4) and paired samples t-tests to investigate significant hemisphere effects within each group (***alpha*** level corrected for 3 comparisons (F3-F4, C3-C4, P3-P4).

Delta

Table 2.2. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *delta*

Frequency	Source	df	F	P	η_p^2
Delta	**Area**	**1.3**	**13.54**	**0.000***	**0.361**
	Area x Group	**2**	**0.79**	**0.462**	**0.032**
	Hemisphere	**1**	**0.66**	**0.424**	**0.027**
	Hemisphere x Group	**1**	**5.10**	**0.033***	**0.175**
	Area x Hemisphere	**1.3**	**0.19**	**0.718**	**0.008**
	Area x Hemisphere x Group	**2**	**0.02**	**0.083**	**0.099**
	Group	**1**	**3.21**	**0.086**	**0.118**

Given the significant Group x Hemisphere interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at F3 (t(25) = -3.27, p = 0.018), C4 (t(24) = 2.93, p = 0.042), P3 (t(25) = -3.49, p = 0.012), and P4 (t(25) = -3.57, p = 0.006) with patients having significantly *high*er *delta* relative power than controls at these locations.

Theta

Table 2.3. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *theta*

Frequency	Source	df	F	P	η_p^2
Theta	**Area**	**1.3**	**13.54**	**0.000***	**0.361**
	Area x Group	**2**	**0.79**	**0.462**	**0.032**
	Hemisphere	**1**	**0.66**	**0.424**	**0.027**
	Hemisphere x Group	**1**	**5.10**	**0.033***	**0.175**
	Area x Hemisphere	**1.3**	**0.19**	**0.781**	**0.008**
	Area x Hemisphere x Group	**2**	**0.02**	**0.083**	**0.099**
	Group	**1**	**3.21**	**0.086**	**0.118**

Despite the significant Group x Hemisphere interaction, independent t-tests conducted at each electrode site to compare groups did not reveal any significant group differences in relative *theta* power at any location. This can be explained by the conservative p value which took into consideration the six multiple comparisons used to detect significant group differences.

Alpha

Table 2.4. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *alpha*

Frequency	Source	df	F	P	η_p^2
Alpha	**Area**	**1.6**	**60.34**	**0.000***	**0.715**
	Area x Group	**2**	**0.86**	**0.431**	**0.034**
	Hemisphere	**1**	**30.85**	**0.000***	**0.562**
	Hemisphere x Group	**1**	**48.22**	**0.000***	**0.668**
	Area x Hemisphere	**1.3**	**8.13**	**0.004***	**0.253**
	Area x Hemisphere x Group	**2**	**0.90**	**0.414**	**0.036**
	Group	**1**	**17.70**	**0.000***	**0.424**

Given the significant Group x Hemisphere interaction, Independent T-Tests were conducted at each electrode site to compare groups. A significant group difference was revealed at F4 ($t(25) = 4.89$, $p = 0.000$), C4 ($t(25) = 4.78$, $p = 0.000$) and P4

(t(25) = 4.95, p = 0.000) with patients having significantly lower *alpha* relative power than controls over all three right hemisphere regions. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *alpha* relative power in the right hemisphere compared to the left hemisphere over frontal (t(8)=3.214, p = 0.036), central (t(8)=5.041, p = 0.003) and parietal regions (t(8)=3.933, p = 0.012).

SMR

Table 2.5. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *SMR*

Frequency	Source	df	F	P	η_p^2
SMR	**Area**	**2**	**30.96**	**0.000***	**0.563**
	Area x Group	**2**	**2.36**	**0.105**	**0.090**
	Hemisphere	**1**	**34.66**	**0.000***	**0.591**
	Hemisphere x Group	**1**	**60.65**	**0.000***	**0.716**
	Area x Hemisphere	**1.3**	**9.52**	**0.002***	**0.284**
	Area x Hemisphere x Group	**2**	**1.63**	**0.206**	**0.064**
	Group	**1**	**53.02**	**0.000***	**0.688**

Given the significant Group x Hemisphere interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at all electrodes; F3 (t(25) = 3.64, p = 0.006), F4 (t(25) = 7.07, p = 0.000), C3 (t(25) = 4.77, p = 0.000), C4 (t(25) = 8.42, p = 0.000), P3 (t(25) = 6.34, p = 0.000) and P4 (t(25) = 9.64, p = 0.000) with patients having significantly lower *SMR* relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the

patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *SMR* relative power in the right hemisphere compared to the left hemisphere over central (t(8)=6.169, p = 0.000) and parietal regions (t(8)=5.618, p = 0.000).

Beta

Table 2.6. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *beta*

Frequency	Source	df	F	P	η_p^2
Beta	**Area**	**2**	**3.38**	**0.042***	**0.124**
	Area x Group	**2**	**2.94**	**0.063**	**0.109**
	Hemisphere	**1**	**19.61**	**0.000***	**0.450**
	Hemisphere x Group	**1**	**23.24**	**0.000***	**0.492**
	Area x Hemisphere	**1.5**	**16.18**	**0.000***	**0.403**
	Area x Hemisphere x Group	**2**	**4.08**	**0.023***	**0.145**
	Group	**1**	**33.40**	**0.000***	**0.582**

Given the significant 3-way interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at all electrodes; F3 (t(25) = 3.83, p = 0.006), F4 (t(25) = 5.02, p = 0.000), C3 (t(25) = 3.37, p = 0.012), C4 (t(25) = 6.63, p = 0.000), P3 (t(25) = 5.03, p = 0.000) and P4 (t(25) = 7.18, p = 0.000) with patients having significantly lower *beta* relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *beta* relative power in the right hemisphere compared to the left

hemisphere over central (t(8)=5.174, p = 0.003) and parietal regions (t(8)=4.126, p = 0.009).

High Beta

Table 2.7. Summary of the 3 x 2 x 2 ANOVA based on ln-transformed mean relative power of *high beta*

Frequency	Source	df	F	P	η_p^2
High Beta	**Area**	**1.3**	**12.43**	**0.000***	**0.341**
	Area x Group	**2**	**1.28**	**0.287**	**0.051**
	Hemisphere	**1**	**2.17**	**0.154**	**0.083**
	Hemisphere x Group	**1**	**3.47**	**0.075**	**0.120**
	Area x Hemisphere	**1.4**	**5.49**	**0.016***	**0.186**
	Area x Hemisphere x Group	**2**	**3.60**	**0.035***	**0.130**
	Group	**1**	**24.38**	**0.000***	**0.504**

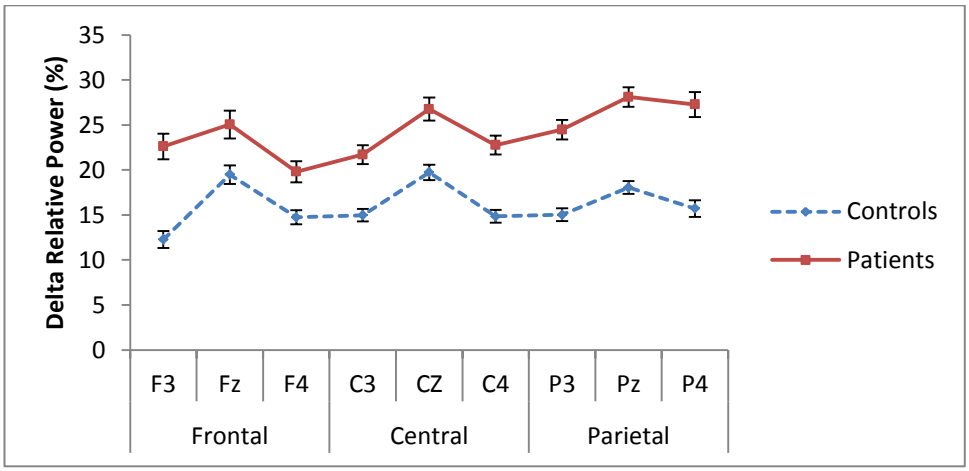
Given the significant 3-way interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at F3 (t(25) = 3.12, p = 0.030), C3 (t(25) = 3.51, p = 0.012), C4 (t(25) = 6.05, p = 0.000), P3 (t(25) = 3.95, p = 0.006) and P4 (t(25) = 5.45, p = 0.000) with patients having significantly lower *high beta* relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *high beta* relative power in the right hemisphere compared to the left hemisphere over central (t(8)=3.357, p = 0.036) regions.

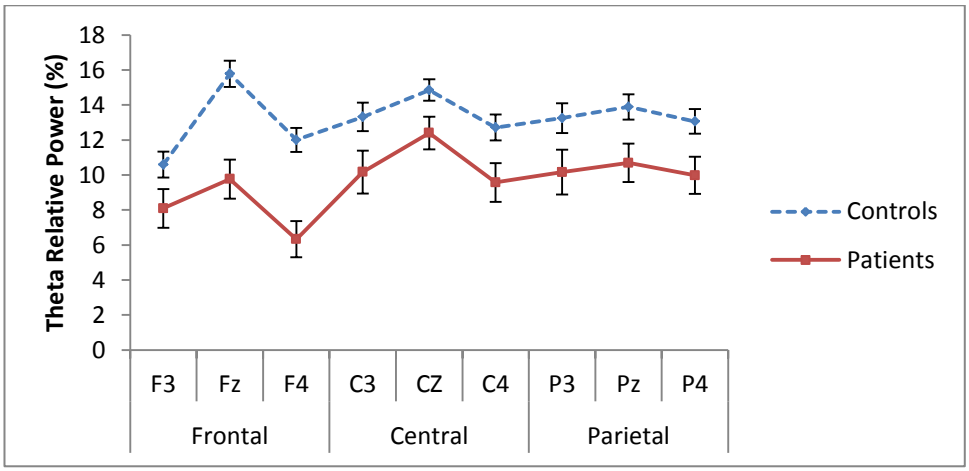
2.3.2. Eyes-Closed Condition

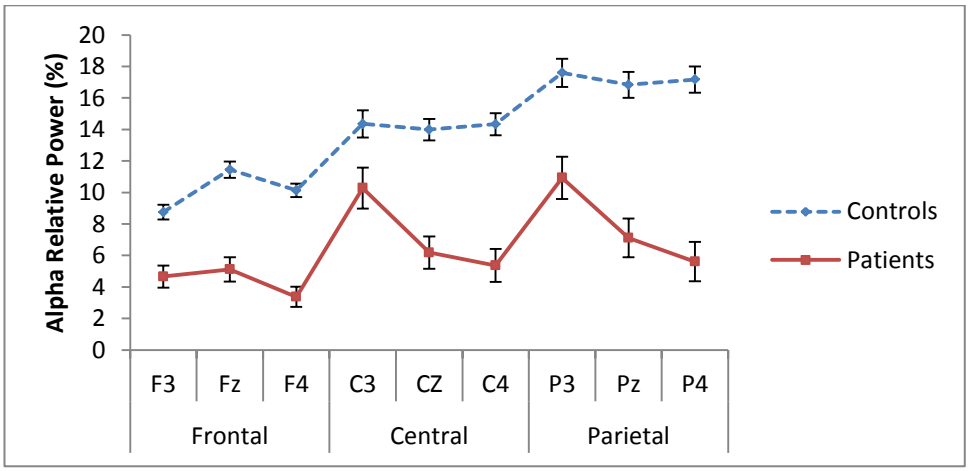
The same analyses were conducted for the eyes-closed condition, group and electrode comparisons are made with respect to the relative power of all frequency bands (*delta*, *theta*, *alpha*, *SMR*, *beta* and *high beta*). The eyes-closed analysis includes the additional variable of peak *alpha* frequency (PAF).

When reporting main effects and interactions from the ANOVA, the *p* values are Greenhouse-Geisser corrected when the test of sphericity is significant at $p = .05$, leading to non-integer values of degrees of freedom (d.f.) where d.f. > 1. Non-integer d.f. are written to one decimal place, *F* statistics to two decimal places and *p* and η_p^2 values to three decimal places. All post hoc t-tests are corrected for multiple comparisons by adjusting the α level accordingly.

Figure 2.2 displays the relative power for each frequency for each group across frontal, central and parietal electrodes.







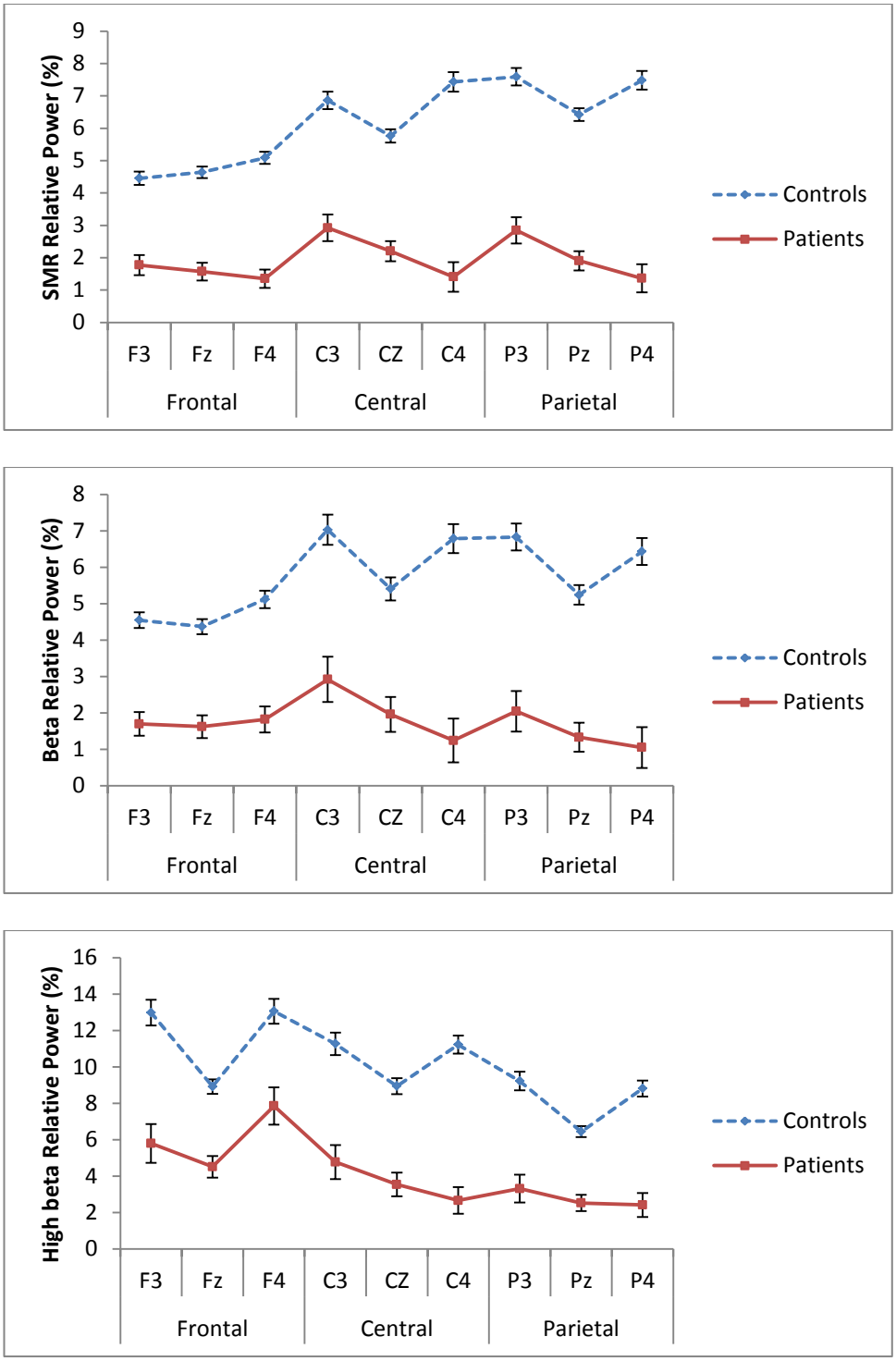


Figure 2.2. Relative power of frequency for patients and controls at each electrode in the eyes-closed condition

Hypothesis 1 and 2 – Hemispheric and Group Differences in Eyes Closed Condition

A 3 x 2 x 2 mixed-measures ANOVA was conducted separately for each frequency band with within-subjects factors of Area (frontal, central, parietal) and Hemisphere (left, right) and across subjects factor of Group. Interactions were further analysed by independent t-tests to investigate group interactions at each electrode (*alpha* level adjusted to correct for 6 comparisons at F3, F4, C3, C4, P3, P4) and paired samples t-tests to investigate hemisphere differences within each group (*alpha* level corrected for 3 comparisons (F3-F4, C3-C4, P3-P4).

Delta

Table 2.8. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *delta* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
Delta	**Area**	**1.54**	**1.28**	**0.287**	**0.053**
	Area x Group	**2**	**5.65**	**0.006***	**0.197**
	Hemisphere	**1**	**6.86**	**0.015***	**0.230**
	Hemisphere x Group	**1**	**2.29**	**0.144**	**0.090**
	Area x Hemisphere	**1.3**	**1.29**	**0.283**	**0.053**
	Area x Hemisphere x Group	**2**	**1.55**	**0.223**	**0.063**
	Group	**1**	**14.00**	**0.001***	**0.381**

Given the significant Group x Area interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at C3 (t(23) = -4.14, p = 0.000), C4 (t(23) = -4.08, p = 0.000), P3 (t(23) = -3.35, p = 0.018), and P4 (t(23) = -4.41, p = 0.006) with patients having significantly *high*er *delta* relative power than controls.

Theta

Table 2.9. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *theta* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
Theta	**Area**	**1.5**	**0.38**	**0.685**	**0.016**
	Area x Group	**2**	**9.64**	**0.000***	**0.295**
	Hemisphere	**1**	**4.49**	**0.045***	**0.163**
	Hemisphere x Group	**1**	**9.49**	**0.005***	**0.292**
	Area x Hemisphere	**2**	**0.48**	**0.620**	**0.021**
	Area x Hemisphere x Group	**2**	**0.59**	**0.556**	**0.025**
	Group	**1**	**0.17**	**0.682**	**0.007**

Despite the significant Group x Hemisphere interaction, independent t-tests conducted at each electrode site to compare groups did not reveal any significant group differences in relative *theta* power. This can be explained by the conservative p value which took into consideration the six multiple comparisons used to detect significant differences.

Alpha

Table 2.10. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *alpha* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
Alpha	**Area**	**2**	**31.90**	**0.000***	**0.581**
	Area x Group	**2**	**0.18**	**0.833**	**0.008**
	Hemisphere	**1**	**44.69**	**0.000***	**0.660**
	Hemisphere x Group	**1**	**56.36**	**0.000***	**0.710**
	Area x Hemisphere	**2**	**7.57**	**0.001***	**0.248**
	Area x Hemisphere x Group	**2**	**5.81**	**0.006***	**0.202**
	Group	**1**	**30.39**	**0.000***	**0.569**

Given the significant 3-way interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at F3 ($t(23) = 3.43$, $p = 0.012$), F4 ($t(23) = 6.26$, $p = 0.000$), C4 ($t(23) = 7.66$, $p = 0.000$) and P4 ($t(23) = 6.65$, $p = 0.000$) with patients having significantly lower *alpha*

relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *alpha* relative power in the right hemisphere compared to the left hemisphere over central ($t(6)=8.36$, $p = 0.000$) and parietal regions ($t(6)=5.23$, $p = 0.018$).

SMR

Table 2.11. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *SMR* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
SMR	**Area**	**2**	**16.89**	**0.000***	**0.423**
	Area x Group	**2**	**0.18**	**0.839**	**0.008**
	Hemisphere	**1**	**42.98**	**0.000***	**0.651**
	Hemisphere x Group	**1**	**37.98**	**0.000***	**0.623**
	Area x Hemisphere	**2**	**3.42**	**0.041***	**0.129**
	Area x Hemisphere x Group	**2**	**2.91**	**0.065**	**0.112**
	Group	**1**	**43.41**	**0.000***	**0.654**

Given the significant Group x Hemisphere interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at all electrodes; F3 ($t(23) = 4.16$, $p = 0.000$), F4 ($t(23) = 6.89$, $p = 0.000$), C3 ($t(23) = 4.13$, $p = 0.000$), C4 ($t(23) = 7.52$, $p = 0.000$), P3 ($t(23) = 5.31$, $p = 0.000$) and P4 ($t(23) = 6.65$, $p = 0.000$) with patients having significantly lower *SMR* relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions.

Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *SMR* relative power in the right hemisphere compared to the left hemisphere over frontal (t(6)=3.56, p=0.036), central (t(6)=6.03, p = 0.003) and parietal regions (t(6)=4.27, p = 0.015).

Beta

Table 2.12. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *beta* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
Beta	**Area**	**2**	**12.35**	**0.000***	**0.349**
	Area x Group	**2**	**0.32**	**0.727**	**0.014**
	Hemisphere	**1**	**34.30**	**0.000***	**0.599**
	Hemisphere x Group	**1**	**27.32**	**0.000***	**0.543**
	Area x Hemisphere	**2**	**3.30**	**0.046***	**0.125**
	Area x Hemisphere x Group	**2**	**2.35**	**0.106**	**0.093**
	Group	**1**	**29.42**	**0.000***	**0.561**

Given the significant interactions, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at all electrodes; F3 (t(23) = 3.99, p = 0.006), F4 (t(23) = 6.30, p = 0.000), C3 (t(23) = 4.09, p = 0.006), C4 (t(23) = 9.14, p = 0.000), P3 (t(23) = 3.49, p = 0.012) and P4 (t(23) = 5.42, p = 0.000) with patients having significantly lower *beta* relative power than controls. Given the significant Area x Hemisphere interaction, paired T-Tests were conducted separately for the control group and the patient group to compare hemisphere differences at each of the three regions. Therefore, paired comparisons included F3-F4, C3-C4, P3-P4. There were no significant hemisphere differences in the control group at any region. However, the paired t-tests revealed patients to have significantly less *beta* relative power in the right hemisphere compared to the left

hemisphere over central (t(6)=5.91, p = 0.003) and parietal regions (t(6)=4.06, p = 0.021).

High Beta

Table 2.13. Summary of the 3 x 2 x 3 ANOVA based on ln-transformed mean relative power of *high beta* in eyes-closed condition

Frequency	Source	df	F	P	η_p^2
High Beta	**Area**	**2**	**7.24**	**0.002***	**0.239**
	Area x Group	**2**	**0.58**	**0.565**	**0.024**
	Hemisphere	**1**	**12.40**	**0.002***	**0.350**
	Hemisphere x Group	**1**	**8.59**	**0.008***	**0.272**
	Area x Hemisphere	**1**	**0.16**	**0.851**	**0.007**
	Area x Hemisphere x Group	**2**	**2.07**	**0.137**	**0.083**
	Group	**1**	**23.10**	**0.000***	**0.501**

Given the significant 3-way interaction, independent t-tests were conducted at each electrode site to compare groups. A significant group difference was revealed at F3 (t(23) = 3.34, p = 0.018), F4 (t(23) = 5.15, p = 0.000, C3 (t(23) = 3.27 , p = 0.018), C4 (t(23) = 6.09, p = 0.000), P3 (t(23) = 3.27, p = 0.018) and P4 (t(23) = 3.79, p = 0.006) with patients having significantly lower *high beta* relative power than controls.

Hypothesis 4) Peak *Alpha* Frequency

A mixed-measures ANOVA was conducted and revealed a significant effect of Group ($F(1,24) = 10.12$, $p = 0.004$, $\eta_p^2 = 0.296$) and a significant Hemisphere x Group interaction ($F(1,24) = 7.06$, $p = 0.014$, $\eta_p^2 = 0.227$). There was no significant main effect of Hemisphere. Post hoc independent t-test revealed a significantly reduced peak *alpha*

frequency in patients over both the left ($t(24) = 2.54$, $p = 0.036$) and the right ($t(24) = 3.76$, $p = 0.002$) hemispheres (see Figure 2.9).

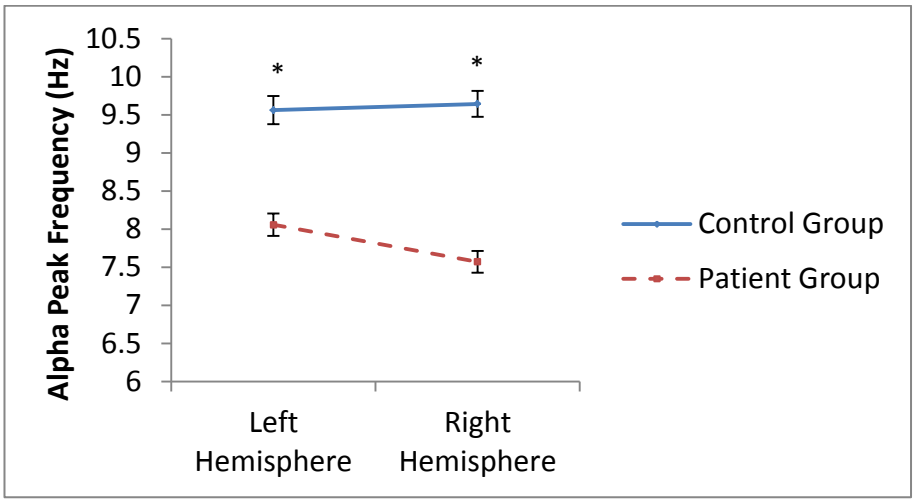


Figure 2.3. Eyes-Closed Condition, a comparison of hemispheric differences in *alpha* peak frequency in patients and controls. Error bars depict +/- 0.5 SEM. * *denotes significant ($p < .05$) group difference.*

2.4. Discussion

2.4.1. The EEG profile of hemispatial neglect

The principle aim of this study was to investigate whether hemispatial neglect is associated with an abnormal EEG profile. The hemispheric analyses within each group revealed that the EEG profile in healthy older adults is symmetrical across both hemispheres with no significant hemisphere differences reported for any frequency band. However, significant hemisphere differences were reported for the patient group with decreased activity in *alpha*, *SMR* and *beta* reported over the right hemisphere in comparison with the left hemisphere. This finding contradicts previous reports that stroke is associated with increased *delta* and *theta* activity over

the injured hemisphere compared to the uninjured hemisphere (Molnar et al, 2006; Demeurisse et al, 1998). Since this is the first study to evaluate differences at the *high*er end of the spectrum; this asymmetrical activity of *alpha*, *SMR* and *beta* over the damaged hemisphere in neglect is a novel finding and one that deserves further investigation.

The across group results revealed that neglect patients had increased levels of *delta* activity and decreased levels of *SMR*, *beta* and *high beta* generalised across both hemispheres with an decrease in *alpha* activity localised to the right hemisphere in both the eyes-open and eyes-closed conditions. Notably, *theta* activity failed to differentiate between groups.. This finding provides support that *beta* activity could be a more informative index of alertness than *theta*, a concept that will be explored in Experiment III.

One of the goals of this study was to determine whether neglect patients had a similarly distorted EEG profile to ADHD children. Similarities were expected because both clinical groups display similar deficits in alertness and spatial attention, as reviewed in the general introduction. Mann et al (1992) compared EEG activity in ADHD children to a control group and found decreased *beta* activity in posterior locations in the ADHD group. The neglect group in Experiment I also showed decreased *beta* activity in comparison to the control group. Mann et al (1992) also reported ADHD children to have increased *theta* activity in frontal locations compared to the control group. The neglect group in Experiment I did not differentiate with respect to the control group with regards to *theta* activity at any location including frontal areas.

Also associated with ADHD is elevated levels of *high beta* activity (Hale, Smalley, Dang, Hanada, Macion, McCracken et al, 2010), a finding that was not reported in the neglect patients studied here. Instead, this study found neglect patients to have decreased levels of *high beta* activity compared to controls. Since *high beta* activity has been postulated to be a marker of hyperactivity (Clark et al, 2001), a common deficit in ADHD, it does not seem surprising that neglect patients had reduced levels of *high beta* given that they do not generally present with symptoms of hyperactivity.

Studies investigating variations in *alpha* peak frequency in healthy individuals have found correlations with cognitive functions and alertness (Klimesch et al, 1990). The eyes-closed condition revealed a reduced peak *alpha* frequency across both hemispheres in the patient group compared to the control group. Juhasz et al (1997) reported large parietal lesions were associated with reduced ipsilateral and contralateral *alpha* peak frequency whilst smaller subcortical lesions were associated with a reduced *alpha* peak frequency over the ipsilateral hemisphere only and with a greater probability of normalizing with recovery. Considering the patients included in this study all had relatively large parietal lesions, the findings support those of Juhasz et al (1997).

In conclusion, neglect patients have an abnormal EEG profile compared to healthy age-matched controls. The most distinguishing features of this abnormal profile is the reduced activity at the *high*er end of the spectrum and a reduced peak *alpha* frequency. In light of previous research linking such EEG distortions to reduced tonic alertness, it can be concluded that this study provides supporting evidence that

neglect is characterised by an impaired alerting system which could benefit from normalization of the EEG.

2.4.2. Implications for Future Research

One of the key aims of clinical quantitative EEG protocols is to keep the recording as quick and simple as possible. This is of paramount importance for a clinical group like neglect since their low arousal and alertness levels and general stroke-related deficits mean participation is limited to a short testing period. Several of these patients were confined to a wheelchair or hospital bed at the time of recording so conducting a full cap quantitative EEG was challenging. The results reported in this study suggest that it may be possible to use a small number electrodes to establish an EEG profile of stroke or neglect since significant effects were observed based on averaging across just two electrodes on the left (C3, P3) and two on the right (C4, P4). This could be reduced even further to just one electrode on either side making the recording procedure much more accessible to a greater number of patients. Both eyes-open and eyes-closed conditions produced the same significant results which also suggests that only one condition may be necessary, potentially reducing the recording time and hence session length still further.

The abnormal EEG profile of neglect reported here has significant implications for neglect rehabilitation in terms of employing interventions that focus on improving the *beta* power or peak *alpha* frequency, given that reduced *beta* activity is suggestive of decreased alertness. One such intervention that has produced promising beneficial results in ADHD patients is EEG neurofeedback. This

intervention uses a protocol which aims to increase *SMR* and *beta* frequencies whilst inhibiting *theta* frequencies. This technique has been repeatedly shown to improve behavioural symptoms of inattention and impulsivity in ADHD to an equivalent or better standard than medication (Fuchs et al, 2003; Monastra et al, 2002). Additionally, physiological data has shown that *SMR* and *beta* training can also induce neurophysiological changes in the form of enhancement of electrical activity specific to certain stages of target processing, specifically P300 ERP components (Kropotov et al, 2005). A study by Beauregard and Levesque (2006) used fMRI to investigate the effects of *SMR* and *beta* neurofeedback training in children with ADHD. Behavioural results showed that, compared to controls, children who received neurofeedback training showed a significant decrease in inattention and hyperactivity and improved performance on selective and sustained attention. The fMRI data showed normalization of neural activity after neurofeedback training in the anterior cingulate–striatal circuit, specific brain regions associated with selective attention and response inhibition. Implications for the use of EEG neurofeedback in the treatment of neglect will be explored in the next two experimental chapters of this thesis.

It is important to note that the patients included in this study were all right hemisphere stroke patients with neglect. Therefore, given there were no patients without neglect, the significant effects found in the analyses can only be associated with right hemisphere stroke but not neglect per se. Further investigative research should supplement these findings with a third group of patients in order to distinguish EEG characteristics between neglect and non-neglect patients. This group would be right hemisphere lesion patients who do not have clinical neglect.

The aim of further investigations would be to establish whether there were any neurophysiological differences that would identify right hemisphere stroke patients with and without neglect in a similar way that left hemisphere stroke patients with and without aphasia have been distinguished based on EEG characteristics alone (Szelies et al 2002).

CHAPTER 3

EXPERIMENT II

3.1. Research Questions and Hypotheses

If hemispatial neglect is associated with a distorted EEG profile as reported in Experiment I, EEG neurofeedback could be an effective candidate for rehabilitation. Whilst neurofeedback was initially perceived as an intervention for clinical conditions, it has more recently assumed a role in the field of optimal performance. Neurofeedback, in the form of various training protocols, has shown promising results in the domains of cognition, sport, music and drama in the healthy population (Gruzelier & Egner, 2005). Of particular interest to this thesis are studies which report significant improvements in various aspects of attention through enhancement of *SMR* and *beta* activity (Egner & Gruzelier, 2001; Egner & Gruzelier 2004; Vernon et al, 2003). These studies report improvements in performance on measures including sustained attention, impulsivity and memory after 8-10 sessions of neurofeedback training. Similar attentional improvements have also been reported in children with ADHD who have undergone a period of neurofeedback training (typically over 20 sessions) promoting an increase of *SMR* and *beta* activity alongside a decrease in *theta* and *high beta* activity (for a review see Arns et al, 2009).

Neurofeedback is attracting increasing interest in the field of attention with regards to its application to both healthy and clinical populations. However, before applying this method to clinical conditions like stroke, often more likely to be represented in

older adults, it is important to establish any age-related effects with regards to the ability to successfully modulate EEG. The majority of studies reporting improvements in attention after neurofeedback have been based on samples of young adults, usually of university age or adolescents, particularly in the field of ADHD. Cognitive decline in older adults has been reported to be associated with a reduction in cerebral blood flow (Kaufer & Lewis, 1999). Alongside this, mild cognitive impairment and early-onset dementia have been associated with increased slow wave activity in the *delta* and *theta* bands (Hartman-Stein & La Rue, 2011, pg 433). Such findings suggest that normalisation of the EEG spectrum could potentially improve cognition in the elderly. A small number of studies have attempted to investigate neurofeedback in the elderly with promising results. Angelakis et al (2007) and Becerra et al (2012) both reported successful EEG modulation in the direction of the specific training protocols implemented but failed to find the predicted improvements in memory. Both protocols focussed on training slower *alpha* and *theta* bands as opposed to using the *beta* and *SMR* training that has proven beneficial in healthy young adults. Therefore, the principle aim of this study was to establish whether healthy older adults are able to modulate specific EEG frequency bands in the *high*er frequency range (*beta* and *SMR*) through EEG-neurofeedback training. The second aim is to investigate whether this EEG modulation is associated with an improvement in behavioural parameters of attention compared to a non-intervention control group after ten training sessions.

Many of the studies to date simply use pre and post assessments as a measure of neurofeedback success and fail to publish detailed data from the neurofeedback sessions themselves. This study aims to investigate across and within session EEG

data to further our understanding of how learning is achieved in order to investigate optimum session duration and number of sessions. Results obtained through this research will provide a foundation on which to further explore the effectiveness of neurofeedback in stroke patients with hemispatial neglect who have an under-active brain and might benefit from an intervention aimed at improving alertness. Therefore, a key point of exploration will focus on baseline 'tonic' changes in EEG across sessions as this can be considered to represent tonic states of alertness in healthy and clinical populations. The aim of neurofeedback training is to eventually modulate specific frequency bands in the brain at the tonic, as opposed to the phasic, level to ensure long-term effects. The idea is that once the brain has been encouraged to function in a more healthy and efficient fashion, it will continue to do so without the need for 'top-up' sessions.

Two training protocols were employed in this study in a replication of a previous study by Egner and Gruzelier (2004); the *beta* protocol required participants to increase *beta* activity without simultaneously increasing *theta* or *high beta* activity and the *SMR* protocol required participants to increase *SMR* activity without simultaneously increasing *theta* or *high beta* activity. The *theta* and *high beta* inhibits were important to include in the training protocols to ensure participants were not simply increasing activity across the spectrum. The training electrode was positioned at CZ because training from this location has previously been proven to produce behavioural and neurophysiological changes in healthy paraticpiants (Egner and Gruzelier, 2004; Vernon, Egner et al, 2003; Ross et al, 2009) and children with ADHD (see meta-analysis by Arns et al, 2009). Each training session was preceded by a 3-min baseline, from which thresholds for each frequency band were set, during

which participants were encouraged to relax. This baseline and thresholding procedure was conducted for every session in order to maintain a constant level of reinforcement. Ten training session were completed by all participants in line with previous studies showing significant learning effects within 10 sessions in the healthy population (Egner and Gruzelier, 2001; Egner and Gruzelier, 2004: Vernon, Egner et al, 2003). In order to maximise learning, sessions were conducted every week day over a two-week period.

To study the effects of neurofeedback training on EEG modulation several EEG variables were extracted from the session data: *beta* or *SMR* activity (depending on the relevant protocol) during baseline and feedback periods and *theta* and *high beta* activity during baseline and feedback periods. To study any interactions between across-session and within-session changes, training sessions from weeks 1-3 are compared to weeks 4-6. Finally, group comparisons will be investigated by analysing differences in resting state EEG and performance on a visual continuous performance task.

The main hypotheses are listed below and will be addressed individually in the results section

Hypothesis 1) Quantitative EEG Analyses – Within Group Changes

Pre and post quantitative EEG recording in the eyes-open condition will be compared for the control and neurofeedback group. No changes are expected for any of the frequency bands in the control group. As a result of the neurofeedback

training, elevated levels of *beta* and *SMR* activity are expected in the NFT group without concurrent changes in *theta* and *high beta* activity given these should be maintained below the thresholds set.

Hypothesis 2) Behavioural Analysis

Attentional processing was assessed in the pre and post assessment sessions by the visual continuous performance task (VCPT). It was predicted that no changes in performance would be observed in the control group but that any improvements would be due to practice effects. However, significant improvements were predicted in the neurofeedback group. Omission and commission error rates are analysed, along with reaction times.

Hypothesis 3) Across Session Analysis

To examine changes in tonic EEG with training, activity during the baseline period at the start of each session will be analysed. It is predicted that across session increases in *beta* and *SMR* activity will be seen in participants who received neurofeedback training. This increased activity will occur without concurrent increases in *theta* or *high beta* activity.

Hypothesis 4) Within Session Analyses

Increased *beta* activity is expected during the feedback period of each *beta* neurofeedback training session. Similarly, increased *SMR* activity is expected to be

seen during the feedback period of each *SMR* neurofeedback training session. No change in *theta* or *high beta* activity will be seen due to the inhibits placed on these frequencies. An interaction between across session and within session changes is expected, with within session performance improving with increasing number of sessions (Keller, 2001). This interaction will be explored by comparing early neurofeedback training sessions (sessions 1-5) with late neurofeedback training sessions (sessions 6-10).

Hypothesis 5) Training Protocol Comparisons

Since each session consisted of running the *beta* NFT protocol followed by the *SMR* protocol, training efficiency was expected to be less for *SMR* than *beta* sessions due to fatigue.

3.2. Method

3.2.1. Participants

Eighteen healthy participants (6 males and 12 females; mean age = 65.72 years; age range = 53 to 83 years, SD = 8.53) volunteered to take part in the study and gave informed written consent. All control participants were right-handed, had normal or corrected vision and were considered to be free from neurological and psychiatric history. Participants had never taken part in a neurofeedback research study or therapy previously. Written consent was obtained from each participant in accordance with the Helsinki Declaration, and the study was given full ethical approval from the College Research Committee at Goldsmiths, University of London.

3.2.2. Design

Once written consent had been obtained, participants were randomly allocated to the neurofeedback group or the control group. Both groups were made up of 3 males and 6 females. The mean age of the neurofeedback group was 66.2 yr and the mean age of the control group was 65.2 yr. All participants were required to attend the pre and post assessment sessions which involved a resting state quantitative EEG recording and a visual continuous performance task (VCPT). Each assessment session lasted approximately 2 hours with the post assessment being conducted two weeks after the pre assessment. During the intervening time the control group received no intervention whilst the neurofeedback group received neurofeedback training sessions. Neurofeedback training sessions were conducted at Goldsmiths,

University of London, or at the participant's home depending on the most convenient option for each individual. Ten sessions were completed over a two-week period and lasted for approximately 1 hr.

3.2.3. Quantitative EEG Acquisition

Quantitative EEG was recorded from all participants using the 21-channel Mitsar amplifier system and 19-channel electrode cap (ElectroCap). The cap was placed on the scalp according to the 10-20 system. Electrodes were referenced to linked earlobes and the ground electrode was placed 1.5 cm anterior to the central frontal (Fz) electrode. Electrodes placed on Fp1 and Fp2 recorded electro-oculogram (EOG) data to identify eye blink and horizontal eye movements. All impedances were under 5 kΩ throughout the recordings. Recordings were referenced to an average-weighted montage. Data were digitised at a sampling rate of 250 Hz and passed through a 0.5-30 Hz bandpass filter. Recording, digitisation and subsequent off-line data processing were carried out with Mitsar and WinEEG software. Artefact reduction was done via several methods. Firstly, a pre-programmed Independent Component Analysis (ICA) method was used to identify and correct for eye blinks. Artefacts were then marked and rejected for any amplitude over 100 μV. Recordings were conducted in a quiet room for 3 min in the eyes-open. The analysis focuses on the 9 most robust and artefact-free electrode locations (Fz, Cz, Pz, F3, F4, C3, C4, P3, P4).

FFT analysis was performed and relative power (the ratio between the absolute power of the particular band and the absolute power of the total spectrum) was calculated for *delta* (1.5-4 Hz), *theta* (4-8 Hz), *alpha* (8-12 Hz), *SMR* (12-15 Hz),

beta (15-18 Hz), *high beta* (20-30 Hz) separately at each electrode for each condition (eyes-open and eyes-closed).

3.2.4. Visual Continuous Performance Task (VCPT)

The VCPT (Psytask user manual, http://www.mitsar-medical.com, Juri D. Kropotov,2009) was selected because it has previously been shown to be sensitive to group differences between ADHD children and healthy controls based on omission errors, commission errors and RT variance (Ogrim, Kropotov, Hestad, 2012; Mueller, Candrian, Grane, Kropotov, Ponomarev and Baschera, 2011; Mueller, Candrian, Kropotov, Ponomarev and Baschera, 2010). During this task the participant sat in front of a presentation screen in a dimly lit room. Each trial consisted of a pair of stimuli. The stimuli were animals, plants or humans. The first in the pair was either an animal or a plant. If an animal was followed by an animal the participant was required to respond; this was labelled a GO trial. If the animal was followed by a plant, the participant was required to withhold a response; this was labelled a NOGO trial. If the first stimulus was a plant it could either be followed by another plant or a human. In both these cases, the participant was required not to respond (see Figure 3.1 for an illustration).

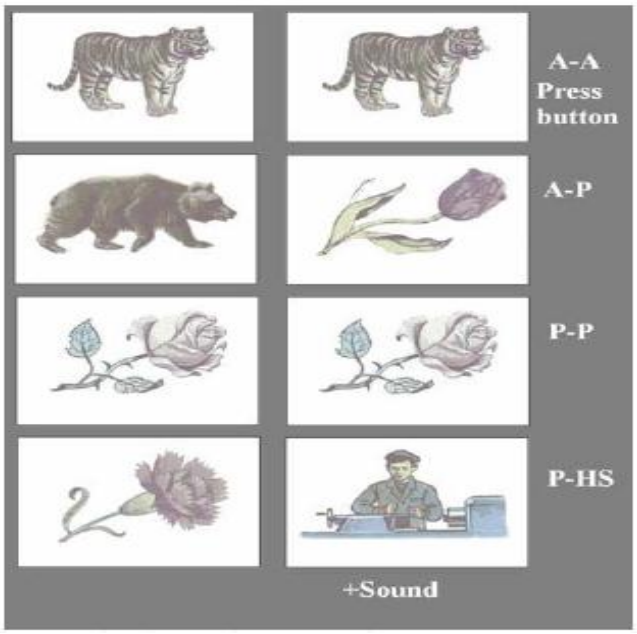


Figure 3.1. Possible trial combinations in the VCPT; A-A is a GO trial, A-P is a NOGO trial, P-P and P-HS are IGNORE trials.

The first stimulus in each pair was always presented in the centre of the screen and the second stimulus in the pair was either be presented to the right or left of centre. Stimulus presentation times were 100 ms and there was an inter-trial interval of 1100 ms. The session consisted of 480 trials with a pseudo-random presentation of 80 pairs of stimuli (120 GO trials, 120 NOGO trials and 240 IGNORE trials).

This GO/NOGO task allowed the extraction of two attentional measures: impulsivity and inattentiveness. Omission errors (failing to report an animal–animal pair) reflect inattentiveness and commission errors (wrongly responding to a trail that was to be ignored, i.e. animal-plant, plant-plant or plant-human trails) reflect impulsivity. Reaction times for the GO trials were also analysed.

3.2.5. Neurofeedback Training Protocols

EEG signals were recorded using the Nexus-4 DC-coupled EEG amplifier (MindMedia, the Nethelands) and the neurofeedback training was carried out with the Biotrace+ software. The active Ag/Cl scalp electrode was placed at Cz (according to the 10-20 international system) for both training protocols, with reference and ground electrodes placed on the mastoids, having used an abrasive gel (NuPrep) to clean the skin and Ten20 conductive gel to act as a glue between the scalp and electrode. The EEG was sampled at 256 Hz and IIR bandpass filtered to extract amplitude values (in μV, peak-peak) for the relevant frequency bands involved in the feedback protocol; *theta* (1.5-4Hz), *SMR* (12-15Hz), *beta* (15-18Hz) and *high beta* (20-30Hz). The exported EEG amplitude data was reviewed for artefact rejection. A voltage-based artefact threshold was implemented to remove eye, muscle and EMG contamination. FFT of the raw data was used to calculate mean amplitudes for each frequency band in terms of 3 minute epochs. The first 3-min epoch related to the baseline period and the remaining five 3-min epochs related to the training periods of the feedback, each separated by a short pause.

Participants in the NFT group were required to take part in 10 sessions of *beta* and *SMR* training over a two-week period. The first 15-min protocol involved enhancement of *beta* power with inhibition of *theta* and *high beta* power and the second 15-min protocol involved enhancement of *SMR* power with inhibition of *theta* and *high beta* power. Each session followed a standardized procedure which began with positioning the electrodes and obtaining a clean raw EEG trace. Each session was preceded by a 3-min baseline, from which thresholds for each frequency

band were set, during which participants were encouraged to relax. The thresholds were set so that, based on the 3-min baseline, the participant would exceed the reward band (*SMR* or *beta*) threshold 70% of the time, would exceed the inhibit threshold for the *theta* band 20% of the time and the *high beta* band 10 % of the time. After the initial baseline period, the online neurofeedback training commenced. Participants were not given any specific instructions on how to control their EEG but were encouraged to maintain an attentive state. The visual and auditory feedback was in the form of a 15-minute video clip from the nature series 'The Blue Planet'. The clip would play continuously when the participant was increasing the reward band (*SMR* or *beta*) above the threshold and when they were keeping the inhibit bands (*theta* and *high beta*) below threshold. If any of these criteria were not met, the DVD would pause, informing the patient they were not maintaining their target amplitudes.

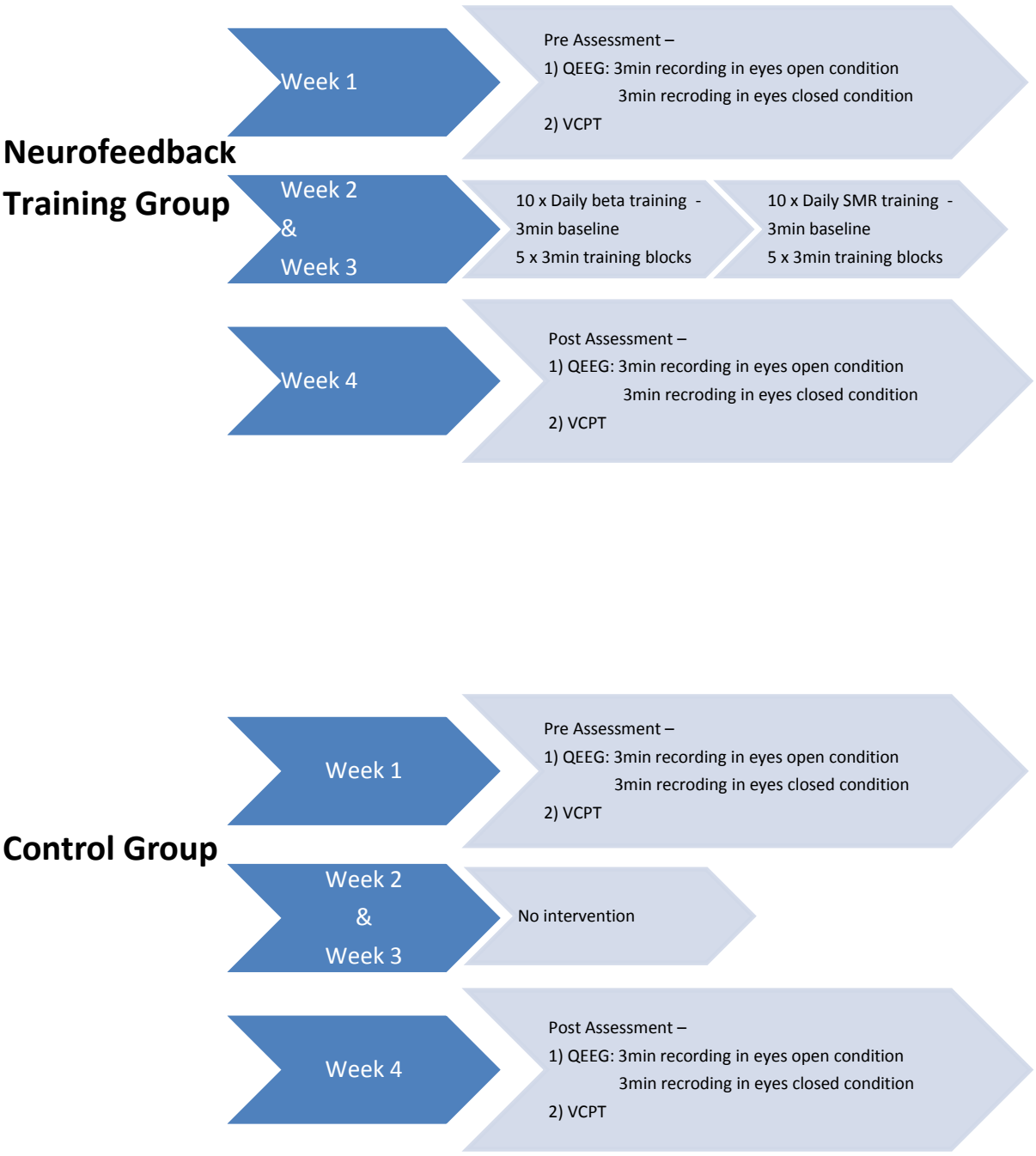


Figure 3.2. **Schematic showing the protocol setup for both groups**

3.3. Results

Each hypothesis outlined in the introduction will be addressed sequentially in this section. The first aim of this study was to investigate whether there were group differences in EEG and performance on the attention task between the control group and the NFT group. Therefore, quantitative EEG data was analysed along with performance on the VCPT. The second set of results presented in this chapter were based on the neurofeedback training data from the intervention group. Each daily session consisted of 15 min *beta* training followed by 15 min *SMR* sessions, each preceded by the 3 min baseline during which the thresholds were set. Data from the *beta* and *SMR* training sessions were analysed separately to investigate specifically related within and across session effects and to see if there were different training effects for each protocol.

When reporting main effects and interactions from the ANOVA, the p values were Greenhouse-Geisser corrected when the test of sphericity was significant at $p = 0.05$, leading to non-integer values of degrees of freedom (d.f.) where d.f. > 1. Non-integer d.f. were written with one decimal place, F statistics with two decimal places and p and η_p^2 values with three decimal places. All post hoc t-tests were corrected for multiple comparisons by adjusting the α level accordingly. Pearson correlations and Linear Trend Analyses were conducted to establish whether there was a significant *linear* change in EEG activity, both across session and within session.

3.3.1. Quantitative EEG Analyses

Hypothesis 1) Quantitative EEG analyses – Within Group Changes

Quantitative EEG recording in the eyes-open condition allowed comparisons between the control and neurofeedback groups to be made based on resting state tonic EEG. Relative power in all frequency bands were compared. No changes are expected for any of the frequency bands in the control group. As a result of the neurofeedback training, elevated levels of *beta* and *SMR* activity are expected in the neurofeedback group without concurrent rises in *theta* or *high beta* activity.

Mean relative power values are presented in Figure 3.3. However, initial analyses showed there were no differences between right and left hemispheres in either group so mean relative power values were averaged across all 9 electrodes for the statistical analyses. A mixed-measures ANOVA was conducted for each frequency band (*delta*, *theta*, *alpha*, *SMR*, *beta*, *high beta*) with within-subjects factors of Assessment (pre, post) and a between-subjects factor of Group (Neurofeedback (n=9) and control (n=9)). The dependent variable was relative power (%).

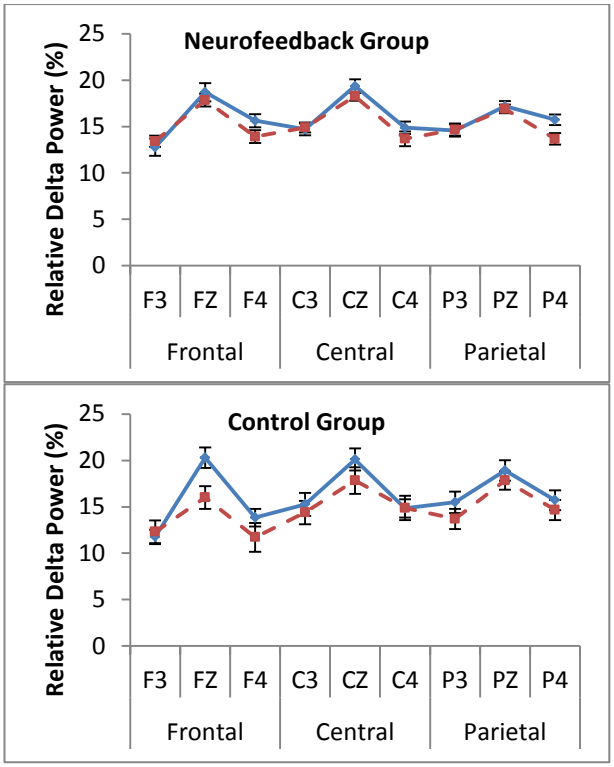


Figure 3.3 **Mean relative delta power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

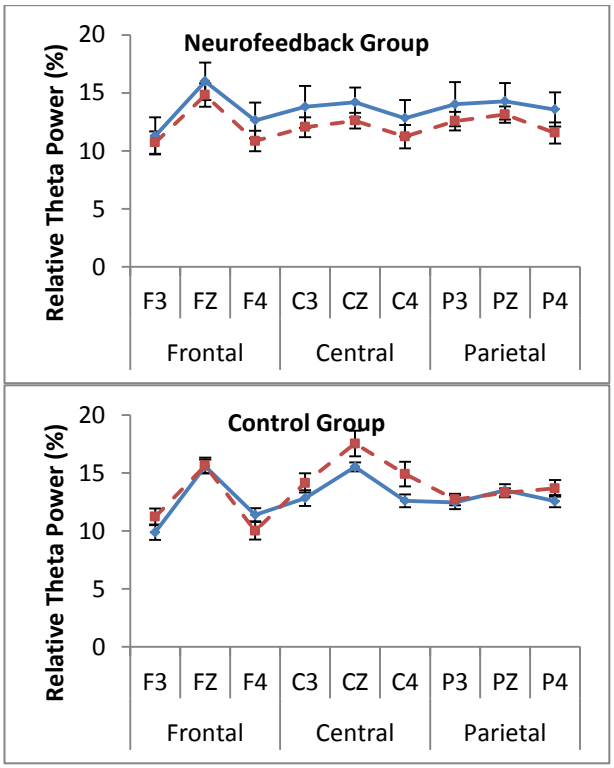


Figure 3.4 **Mean relative theta power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

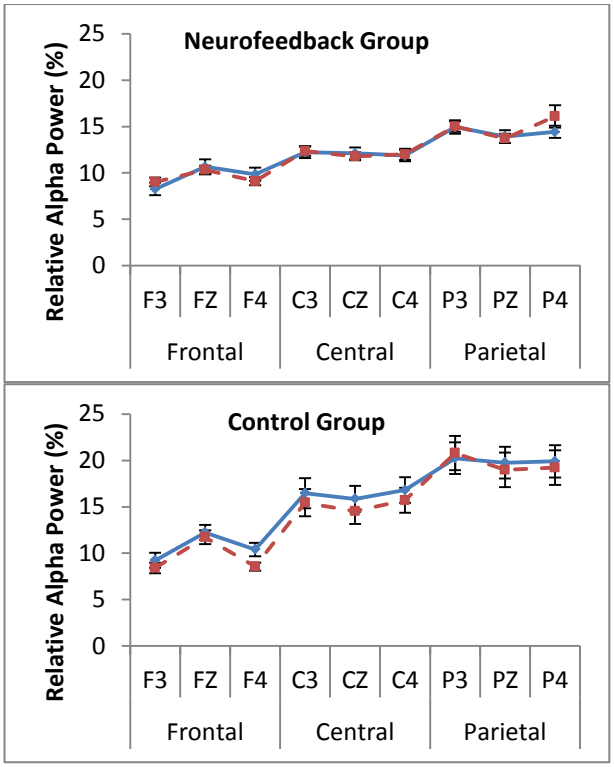


Figure 3.5 **Mean relative alpha power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

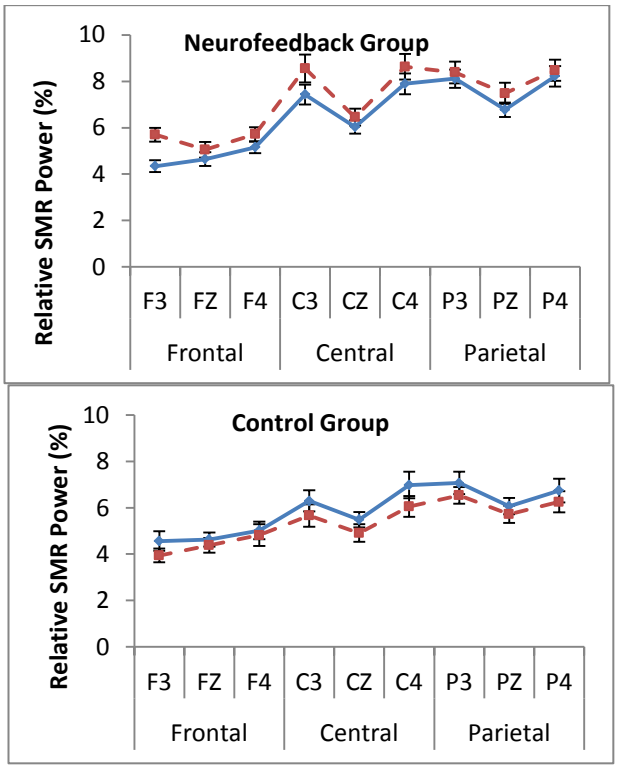


Figure 3.6 **Mean relative SMR power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

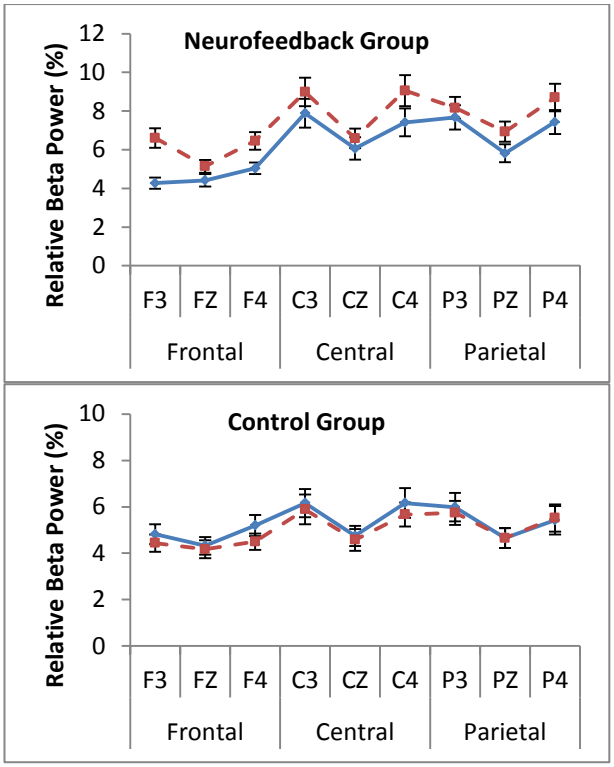


Figure 3.7 **Mean relative beta power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

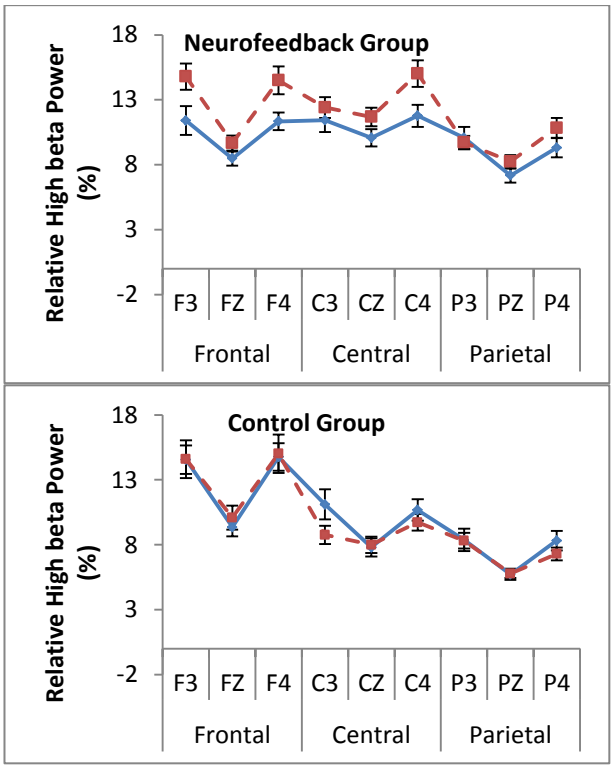


Figure 3.8 **Mean relative *high* beta power in the pre (blue) and post (red dashed) assessments at individual electrode locations for both groups. Error bars depict +/- 0.5 SEM**

The EEG data was normally distributed so did not need to be transformed. As in Experiment I, the following electrodes were included in the analyses, F3, F4, C3, C4, P3, P4. Of particular interest in this study was within group changes in EEG between the pre and post assessment. Therefore, a 3 x 2 x 2 mixed-measures ANOVA was conducted separately for each frequency band with within-subjects factors of Area (frontal, central, parietal) and Hemisphere (left, right). The control group and neurofeedback training group were analysed separately to assess within group changes. Interactions were further analysed by independent t-tests to investigate group interactions at each electrode (*alpha* level adjusted to correct for 6 comparisons at F3, F4, C3, C4, P3, P4) and paired samples t-tests to investigate hemisphere effects within each group (*alpha* level corrected for 3 comparisons (F3-F4, C3-C4, P3-P4).

The statistical findings from the mixed-measures ANOVAs conducted on each frequency are reported in Table 3.1. This revealed significant Assessment x Group interactions for the *SMR* and *beta* frequency bands, the frequency bands which were explicitly targeted during the neurofeedback training. No significant group interactions were revealed for the other frequency bands.

Table 3.1. Summary of 2 x 2 ANOVAs conducted on each frequency band

Frequency	Source	df	F	P	η_p^2
Delta	**Assessment**	**1**	**1.295**	**0.272**	**0.075**
	Group	**1**	**0.001**	**0.975**	**0.000**
	Assessment x Group	**1**	**0.153**	**0.701**	**0.009**
Theta	**Assessment**	**1**	**0.882**	**0.362**	**0.052**
	Group	**1**	**0.011**	**0.917**	**0.001**
	Assessment x Group	**1**	**0.142**	**0.711**	**0.009**
Alpha	**Assessment**	**1**	**0.170**	**0.686**	**0.011**
	Group	**1**	**1.601**	**0.224**	**0.091**
	Assessment x Group	**1**	**0.316**	**0.582**	**0.019**
SMR	**Assessment**	**1**	**0.086**	**0.773**	**0.005**
	Group	**1**	**1.496**	**0.239**	**0.086**
	Assessment x Group	**1**	**5.861**	**0.028***	**0.268**
Beta	**Assessment**	**1**	**2.927**	**0.106**	**0.155**
	Group	**1**	**1.618**	**0.222**	**0.092**
	Assessment x Group	**1**	**7.184**	**0.016***	**0.310**
High Beta	**Assessment**	**1**	**1.218**	**0.286**	**0.071**
	Group	**1**	**0.407**	**0.533**	**0.025**
	Assessment x Group	**1**	**2.689**	**0.121**	**0.144**

Mean values averaged across all 9 electrodes for each frequency in the pre and post assessments are presented in Figure 3.4. The significant interaction in the *SMR* and *beta* frequency bands were investigated further using post hoc paired samples T-Tests conducted on each group to compare pre and post relative power values. This analysis revealed a significant increase in relative *beta* power in the neurofeedback training group between the pre and post assessment ($t(8) = 2.560$, $p= 0.034$) whilst no change was reported in the control group. This statistic was not significant in either group for the relative *SMR* power however.

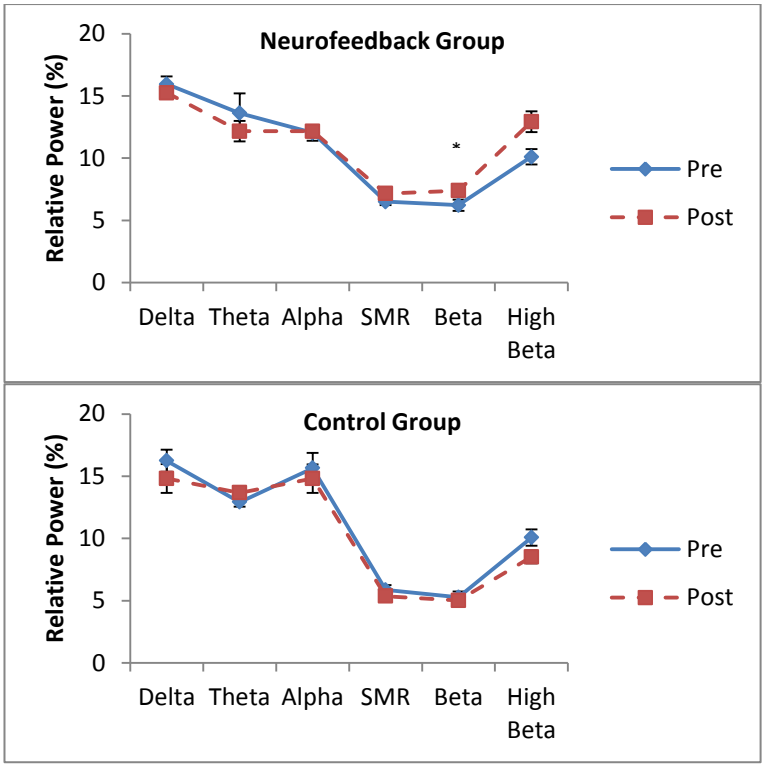


Figure 3.9. **Mean relative power of each frequency in the pre (blue) and post (red dashed) assessments averaged across electrodes for both group. Error bars depict +/- 0.5 SEM**

3.3.2. Behavioural Results

Hypothesis 2) Behavioural Analyses

Performance data in terms of omission and commission accuracy rates were at ceiling for this task with most participants having zero errors. Therefore reaction time (RT) data for GO trials was extracted for analysis. In order to investigate the effect of time-on-task on RTs, the testing session was split into the first and second halves for analysis. A change score was calculated by subtracting the mean RT during the first half from the mean RT during the second half. Therefore, *high*er

change scores would indicate a greater degree of fatigue whereas lower change scores would indicate faster RTs which could be a result of a practice effect.

A mixed-measures ANOVA was conducted with a within-subjects factor of Assessment (pre, post) and a between-subjects factor of Group (neurofeedback, control). No significant main effects or interactions were revealed in this ANOVA. Therefore, this behavioural assessment did not show any beneficial effect of neurofeedback training on sustained attention.

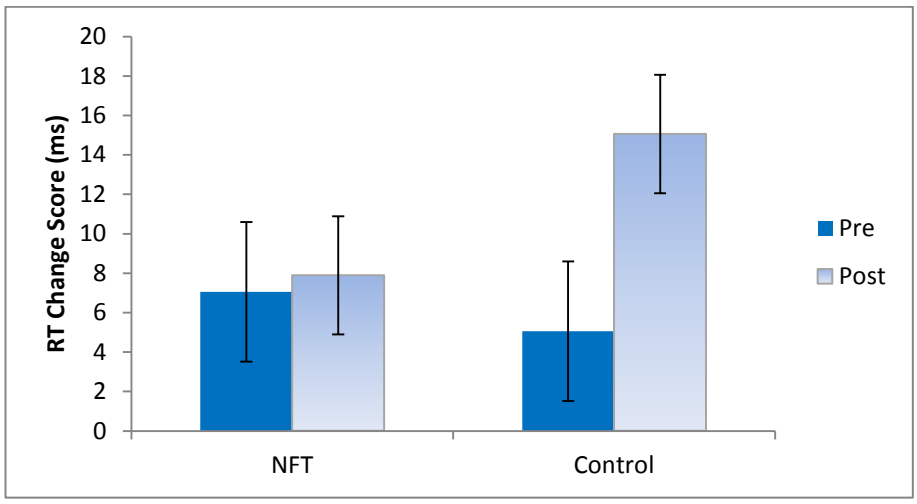


Figure 3.10. **Mean change score in RT (second half minus first half of the task) for the neurofeedback group and control group in the pre and post assessment. Error bars depict +/- 0.5 SEM.**

3.3.3. Neurofeedback Training Analyses

The neurofeedback training data provided two main avenues of interest. Firstly, *within* session data allowed exploration of how EEG is modulated during the training period and whether this modulation is uniform or differs with increased number of sessions. Therefore, within session data was collapsed across the first five sessions and the last five sessions and compared. This investigation also helps to establish whether sessions are an effective length of time or whether there is a trend for learning to tail off before the session is complete. Secondly, analysis of baseline, or tonic, levels of the trained EEG bands *across* sessions provided evidence of how these levels are modulated with increasing number of sessions. A correlation of baseline levels of the reward EEG bands with number of sessions would indicate that the training was effective. Similarly, a plateau of any such learning correlation would indicate that maximum learning had been achieved after a given number of sessions.

3.3.3.1. NFT Analysis – *Beta* Sessions

Mean amplitude values were extracted from the data for each frequency during the 3-min baseline and five 3-min training periods for each of the 10 sessions recorded. Extreme outlier values (more than 3 standard deviations from the mean) were removed from the analyses, this led to less than 1% of values being excluded.

Hypothesis 1) Across Session Analysis – *Beta* Sessions

The aim of this analysis was to investigate whether tonic changes in the EEG frequencies being manipulated by the training protocol were produced. The 3-min baseline at the beginning of each session was used as an index of tonic EEG levels for the relevant EEG frequencies. Correlational analyses were conducted on mean tonic amplitude during the 3-min baseline with increasing number of neurofeedback training sessions.

Pearson correlation analysis revealed a significant increase in tonic *beta* amplitude with number of sessions with a significant linear trend ($r = 0.786$, $R^2 = 0.61$, $F(1,9) = 12.95$, $p = 0.007$). Therefore, as the number of sessions increased, so did the tonic *beta* activity. Since *beta* was the reward frequency throughout the training period of these sessions, it appears that the protocol used was effective in enhancing tonic *beta* levels. Importantly, *theta* ($r = 0.127$, $p = 0.489$) and *high beta* ($r = 0.164$, $p = 0.460$) amplitudes did not significantly correlate in either direction across the 10 sessions, therefore the inhibits put on these bands during the training can be considered effective (see Fig 3.4 for all correlations).

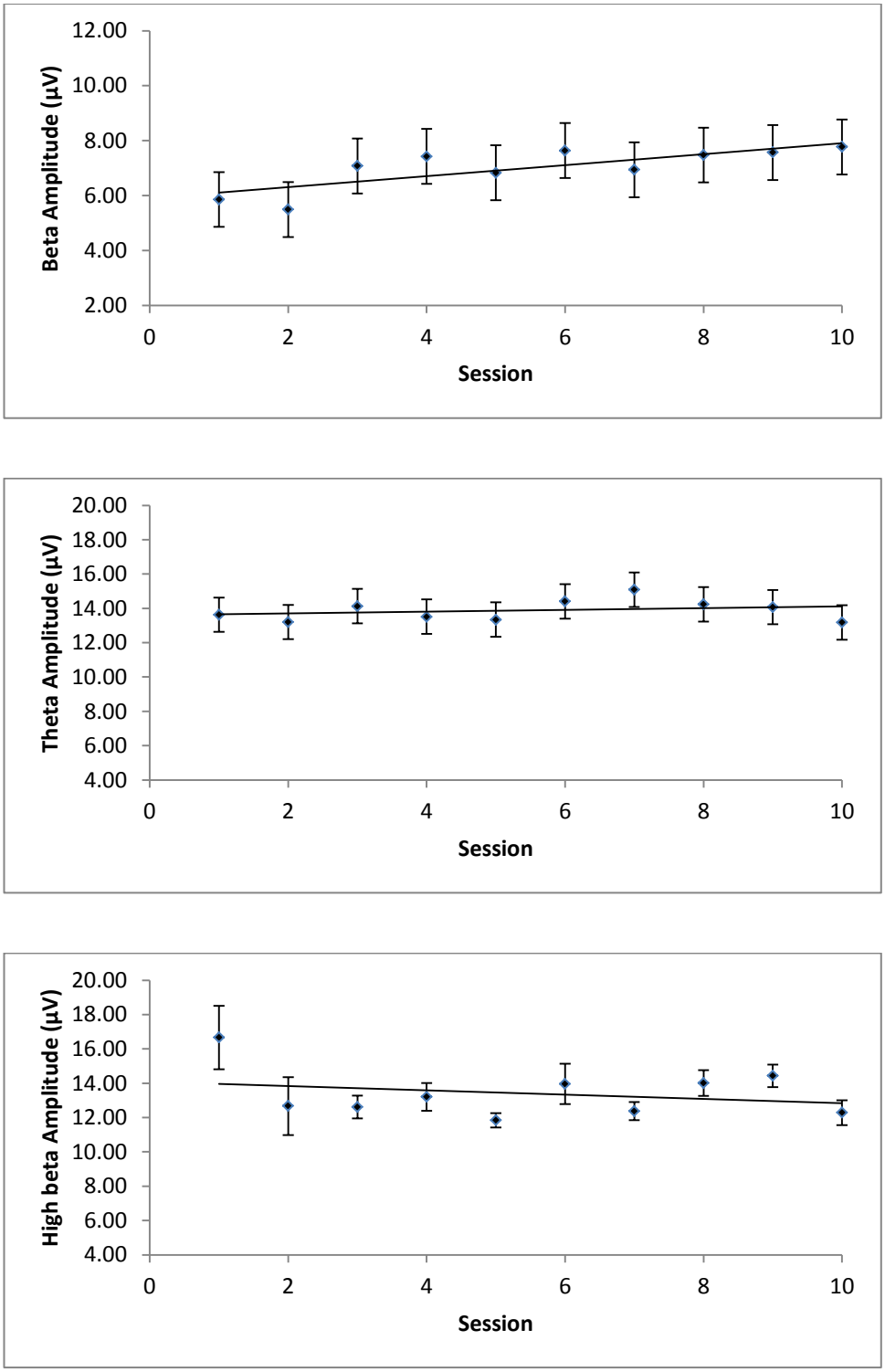


Figure 3.11. Beta NFT sessions - Mean baseline amplitude of beta, theta and high beta as a function of training sessions. Error bars depict +/- 0.5 SEM.

Hypothesis 4) Within Session Analysis– *Beta* Sessions

If neurofeedback training involves consolidation over a successive number of sessions, it would suggest that within session training patterns would change across sessions. To investigate this, within session analysis was broken down into the first 5 sessions (week 1) versus the last 5 sessions (week 2). A repeated-measures ANOVA was conducted for each frequency involved in the training protocol (*beta*, *theta* and *high beta*) with 2 main factors: Session (week 1, week 2) and within session Training Period (1,2,3,4,5), see Figure 3.6.

Beta

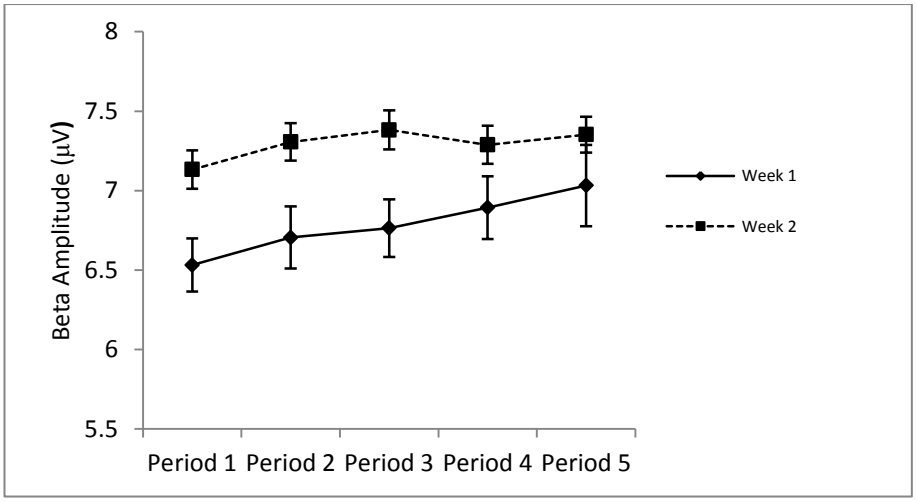
A significant main effect of Session ($F(1,8) = 6.19$, $p = 0.038$, $\mu^2 = 0.436$) revealed a general increase in *beta* activity in week 2 in comparison to week 1. A significant main effect of within session Training Period revealed a general increase in *beta* activity within training session ($F(4,32) = 2.83$, $p = 0.041$, $\mu^2 = 0.261$). There was no significant interaction suggesting within session performance remained constant regardless of early versus late sessions ($F(4,32) = 0.783$, $p = 0.544$, $\mu^2 = 0.089$).

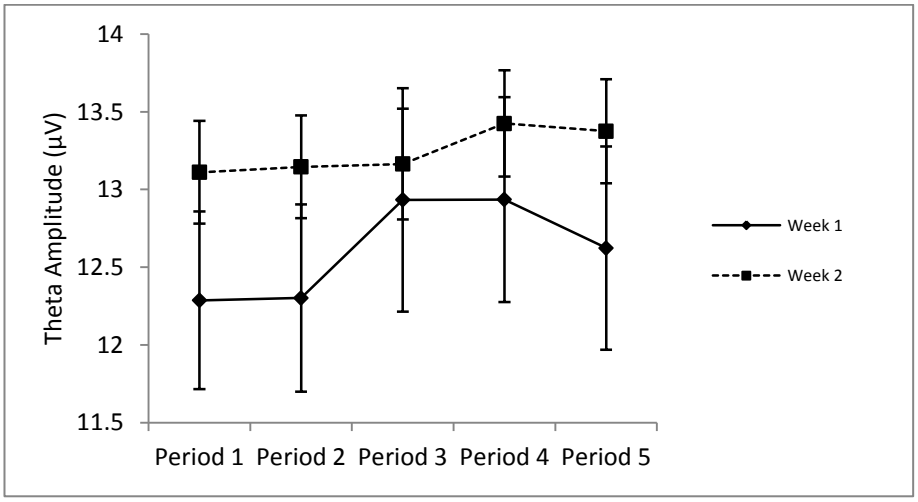
Theta

No significant main effects of Session or within session Training Period or a significant interaction were revealed by the ANOVA.

High Beta

No significant main effects of Session or within session Training Period or a significant interaction were revealed by the ANOVA.





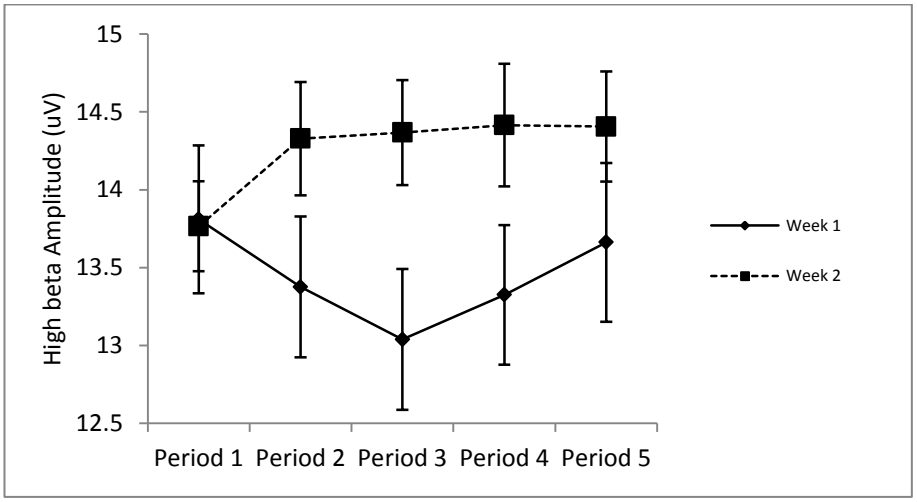


Figure 3.12. Beta NFT Sessions - Mean beta, theta and high beta amplitude for the five training periods collapsed across sessions from week 1 and week 2. Error bars depict +/- 0.5 SEM.

3.3.3.2. NFT Analysis – *SMR* Sessions

Mean amplitude values were extracted from the data for each frequency during the 3-min baseline and five 3-min training periods for each of the 10 sessions recorded. Extreme outlier values (more than 3 standard deviations from the mean) were removed from the analysis.

Hypothesis 3) Across Session Analysis – *SMR* Sessions

The aim of this analysis was to investigate whether tonic changes in the EEG frequencies being manipulated by the training protocol were produced. The 3-min baseline at the beginning of each session was used as an index of tonic EEG levels for the relevant EEG frequencies. Correlational analyses were conducted on a mean tonic amplitude during the 3-min baseline with increasing number of neurofeedback training sessions.

Pearson correlation analysis revealed a significant increase in tonic *SMR* amplitude with number of sessions with a significant linear trend ($r = 0.713$, $R^2 = 0.51$, $F(1,9) = 8.27$, $p = 0.011$). Therefore, as the number of sessions increased, so did the tonic *SMR* activity. Since *SMR* was the reward frequency throughout the training period of these sessions, it appears that the protocol used was effective in enhancing tonic *SMR* levels. Importantly, *theta* ($r = 0.199$, $p = 0.582$) and *high beta* ($r = 0.119$, $p = 0.987$) amplitudes did not significantly correlate in either direction across the 10 sessions, therefore the inhibits put on these bands during the training can be considered effective (see Figure 3.7 for all correlations).

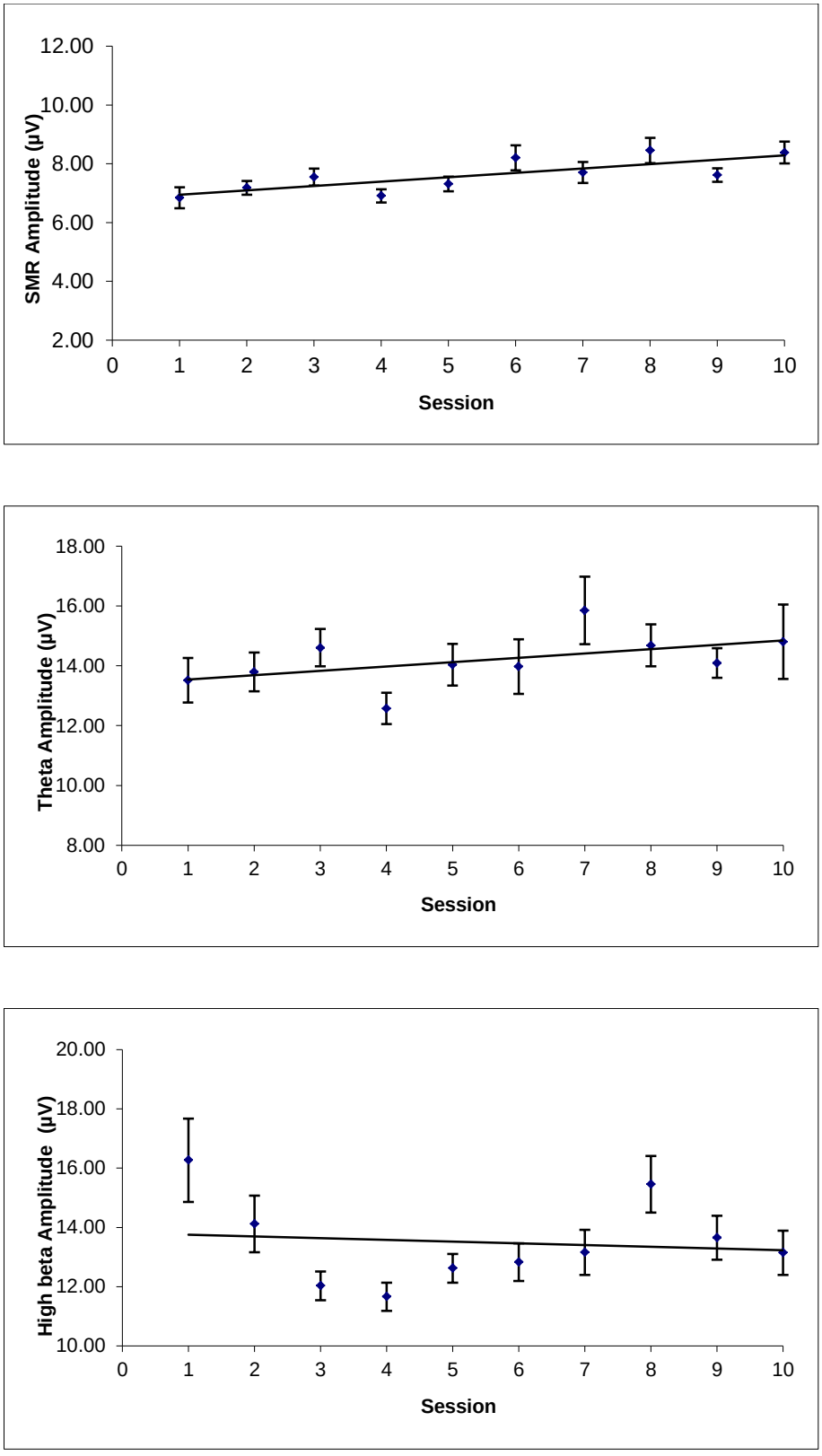


Figure 3.13. SMR NFT sessions - Mean baseline amplitude of beta, theta and high beta as a function of training sessions. Error bars depict +/- 0.5 SEM.

Hypothesis 4) Within Session Analysis– *SMR* Sessions

If neurofeedback training involves consolidation over a successive number of sessions, it would suggest that within session training patterns would change across sessions. To investigate this, within session analysis was broken down into the first 5 sessions versus the last 5 sessions. A repeated-measures ANOVA was conducted for each frequency involved in the training protocol (*SMR, theta, high beta*) with 2 main factors: Session (week 1, week 2) and within session Training Period (1,2,3,4,5), see Fig 3.9 for a breakdown of the data.

SMR

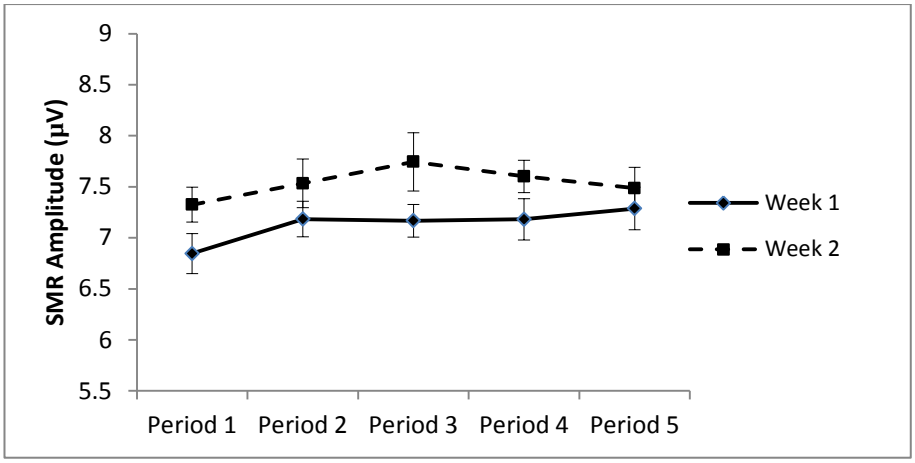
There was no significant main effect of Session ($F(1,8) = 1.61$, $p = 0.241$, $\mu^2 = 0.167$) showing no significant difference in *SMR* activity in week 1 or week 2. A significant main effect of within session Training Period revealed a general increase in *SMR* activity within training session ($F(4,32) = 2.65$, $p = 0.051$, $\mu^2 = 0.249$). There was no significant interaction suggesting within session performance remained constant regardless of early versus late sessions ($F(4,32) = 0.376$, $p = 0.824$, $\mu^2 = 0.450$).

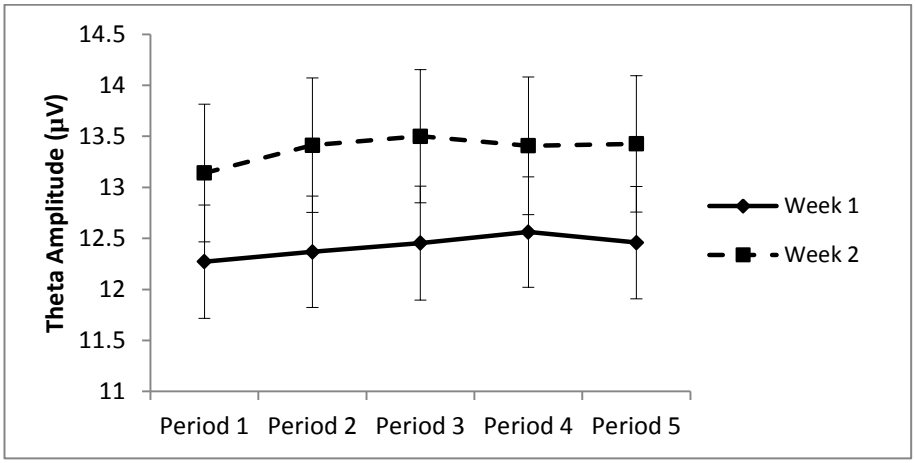
Theta

There was a significant main effect of Session ($F(1,8) = 6.51$, $p = 0.034$, $\mu^2 = 0.450$) with *high*er *theta* power recorded in week 2 than week1. There was no significant main effect of within session Training Period or a significant Session by Training Period interaction.

High Beta

There was no significant main effect of Session ($F(1,8) = 0.64$, $p = 0.806$, $\mu^2 = 0.008$) showing no significant difference in *high beta* activity between week 1 and week 2, in line with the non-significant across session correlation reported earlier. A significant main effect of within session Training Period revealed a general increase in *high beta* activity within training session ($F(4,32) = 5.00$, $p = 0.003$, $\mu^2 = 0.384$). This suggests that during this second neurofeedback training protocol the *high beta* inhibit became increasingly more difficult to maintain towards the end of the 15 min of training. There was no significant Session by Training Period interaction suggesting within session performance remained constant regardless of early versus late sessions ($F(4,32) = 0.276$, $p = 0.891$, $\mu^2 = 0.033$).





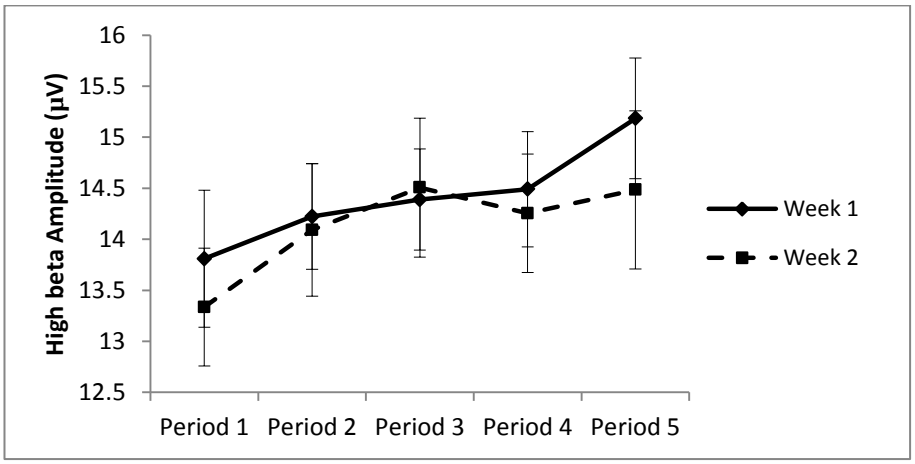


Figure 3.14. SMR NFT Sessions. Mean SMR, theta and high beta ampltude across the five training periods collapsed across sessions from week 1 and week 2. Error bars depict +/- 0.5 SEM.

Hypothesis 5) Training Protocol Comparisons

Key to interpretting this data is to remember that the *SMR* training sessions were carried out immediately after the *beta* training sessions. Both protocols resulted in an increase in the baseline *beta* or *SMR* band relevant to the training protocol without concurrent increases in either the baseline *theta* or *high beta* inhibits. Therefore, at the end of the two week training increased *beta* and *SMR* activity was recorded in the baseline EEGs of participants. This finding implies that the neurofeedback training protocols were successful, especially since the inhibit bands did not increase simultaneously. However, the within session data suggests that participants were starting to become fatigued during the *SMR* sessions. Whilst during the *beta* training sessions, both *theta* and *high beta* inhibits were successfully maintained below threshold (i.e. there were no correlations with within session training period) this was not the case during the *SMR* training sessions. There was a tendency for *theta* and *high beta* to increase with increasing time-on-task, for *theta* activity this was especially pronounced in the late training sessions of week 2. Increased *theta* and increased *high beta* activity suggests participants became increasingly tired and distracted or anxious in this second training protocol.

3.4 Discussion

The quantitative EEG data from the pre and post assessments and the EEG data from the neurofeedback training sessions both indicate that older adults are able to successfully enhance specific EEG bands. This is inline with the findings from healthy younger adults (Vernon et al 2003; Egner & Gruzlier, 2004). The training

protocols implemented required the participant to enhance *beta* and *SMR* power without concurrent rises in *theta* and *high beta* amplitudes. Tonic levels of each of the frequency bands were recorded during the three minute baseline at the beginning of each session: the results showed that tonic levels of both *beta* and *SMR* increased across sessions with both training protocols. Since it is relatively easy simply to increase or decrease the whole EEG spectrum it is important to note that these increases in *beta* and *SMR* were not accompanied by increases in *theta* and *high beta*. This suggests that the inhibits used during both protocols were effective. However, the within sessions analyses *high*lighted a difference between the two protocols. Neurofeedback sessions always began with the *beta* training protocol followed by the *SMR* protocol. Each protocol involved a 3-min baseline followed by 15 min of neurofeedback training. EEG recorded during the *beta* protocol revealed a significant within-session increase in *beta* activity without concurrent increases in *theta* or *high beta* activity. However, participants were less successful in maintaining these inhibits during the *SMR* sessions that followed the *beta*: both *theta* and *high beta* showed increased activity within the *SMR* training period. This indicates that sessions should be kept to a maximum of 15 min to avoid the effects of fatigue and that running two protocols in succession is too demanding. It is likely that this effect would be amplified in a clinical population with attention deficits related to low levels of alertness.

Previous studies on healthy young participants have shown a plateau effect of learning within ten sessions of neurofeedback training (Ros, Moseley, Bloom, Benjamin, Parkinson & Gruzelier, 2009; Gruzelier, Inoue, Smart, Steed & Steffert, 2010). The learning trends reported in this study suggest that older adults had not

reached asymptotic levels within the ten sessions since the linear trend was *high*ly significant. Maximum learning effects were therefore not necessarily achieved after ten session; the implication is that there may be potential for increasing the number of training sessions beyond ten in this age group. Future investigations should directly compare healthy older adults to healthy younger adults on the same protocol. Variations in learning in older adults has implications for interventions related to age-related cognitive decline. This finding fed into the design of Experiment III with an aim to train patients over a considerably increased number of sessions.

The behavioural task failed to elicit supporting evidence for a relationship between EEG modulation of *beta* and *SMR* in accordance with the protocol and improved performance in sustained attention. The lack of significance associated with the RT data could be attributed to the small sample size reducing the statistical power and increasing the probability of failing to reveal a significant effect.

Omission and commission error rates were unfortunately not elicited by the continuous performance task used in this study so could not be used as indices of attention and could not be used to calculate the index of perceptual sensitivity which has been associated with *SMR* and *beta* learning in prior studies. Participants recruited for this study were generally very *high* functioning older adults; whilst this task has previously been used to differentiate ADHD children from controls it appears that this task was not sensitive enough to produce observable improvements in this group. A more appropriate task would be the T.O.V.A in which healthy and clinical populations show omission and commission errors.

Follow-up studies would benefit from employing a between subjects design where participants are allocated to either the *beta* training group or the *SMR* training group in a similar design to Egner and Gruzelier (2004). This design would test whether each specific training protocol exerts specific beneficial effects. When participants have received both protocols it is difficult to disentangle whether one is superior to the other in terms of improving certain aspects of attention. For example, had the behavioural data from the continuous performance task showed an improvement in sustained attention in the neurofeedback group, it would have been impossible to disentangle whether this was a result of the *SMR* training protocol or the *beta* protocol.

Designing a study with a proper control group is one of the major problems faced by neurofeedback studies. It is necessary to have some form of control group to exclude any effects due to repetition of assessments and simple learning effects. Neurofeedback sham studies have been criticised in the past because participant's uncertainty about the intervention they are receiving has caused its own complications. Since neurofeedback training is based on positive reinforcement in response to EEG modulation, a participant in a sham group may become immune to neurofeedback training in the future due to learned-helplessness. Running a sham control group can also prove to be too expensive and time consuming to consider. In this study, the control group simply underwent the pre and post assessments, including the full cap EEG and received no intervention during the intervening time. Therefore, group comparisons bring up the issue of contact time with the experiment and placebo effects. One improvement that could be made would be to have a

control group who had exactly the same contact periods with an experimenter as the intervention group, as suggested by Dempster and Vernon (2009).

To conclude, Experiment II provides evidence that healthy older adults are able to increase *beta* and *SMR* activity over a limited number of neurofeedback training sessions. The significant linear regression suggests that this increase in activity could continue if participants were given more neurofeedback sessions. Whilst the behavioural correlates of this learning remain unclear, there is evidence that increased *beta* and *SMR* activity was associated with an improved ability to sustain attention during a continuous performance task. Given the distorted EEG profile of neglect reported in Experiment I, the protocol employed in Experiment II was extended to this clinical population.

CHAPTER 4)

EXPERIMENT III

4.1. Research Questions and Hypotheses

The aim of Experiment III was to build upon and extend the findings reported in the first two experimental chapters of this thesis. To recap, Experiment I provided supporting evidence for an abnormal EEG profile in neglect. Compared to healthy age-matched controls, neglect was associated with significantly decreased power of fast waves, including *SMR* and *beta*, and significantly increased power of slow *delta* waves. As predicted, this pattern of reduced *SMR* and *beta* power reflects the abnormal EEG profile of ADHD and supports the theory that hemispatial neglect is underpinned by a fundamental disruption to the alertness system. Further support for this theory comes from research correlating increased *beta* activity with improved performance on sustained attention tasks. One technique that has previously been employed as an intervention to normalize EEG in clinical populations with promising results is EEG neurofeedback. It is this intervention that will be explored in this study. However, before proceeding in this investigation, it was first necessary to confirm that an older brain is capable of the same neuroplastic changes as has been reported in the young brain. Experiment II replicated this finding by showing that healthy older adults were able to increase *beta* amplitude over ten sessions of EEG neurofeedback. Both of these experimental findings support the investigation of EEG neurofeedback training as a rehabilitative intervention for hemispatial neglect.

Very few existing rehabilitation interventions for hemispatial neglect have induced long-term beneficial effects in terms of improving the spatial or non-spatial deficits related to the condition or been associated with consistent functional recovery (Luate, Halligan, Rode, Rossetti & Boisson, 2006). There is a distinct lack of trials assessing the efficacy of rehabilitative interventions, with many studies failing to assess patients on functional abilities (rather than simply pen-and-paper tests) or using a follow-up design to determine long-term improvements (Singh-Curry & Husain, 2010). The intervention which has received the most attention in the field is prism adaptation. Whilst post-training improvements have been reported that generalise to functional abilities there is an inconsistency in the literature regarding long-term benefits with studies reporting a range from 24 hr up to five weeks (for a review see Pisella, Rode, Farne, Tilikete & Rossetti, 2006). The recent shift in focus from spatial to non-spatial impairments related to the disorder strongly calls for the same shift in direction for rehabilitative interventions.

As discussed in Chapter 1, neglect patients suffer with deficits related to tonic alertness, with impaired performance in task-related sustained attention (Robertson, Manly, Beschin, Daini, Haeske-Dewick, Homberg et al, 1997; Malhorta et al , 2009). Studies employing phasic alerting techniques have shown promising results. One study employed a training protocol which required verbal prompting from the experimenter to encourage the patient to attend to a sustained attention task (Robertson, Tenger, Tham, Lo, & Nimmo-Smith, 1995). Whilst this study reported improvements in neglect and sustained attention, the follow-up period was only 24

hours so cannot be considered to have long-lasting benefits. The other limitation of this form of training is it requires a degree of awareness from the patient about their neglect-related deficits which reduces its applicability due to the lack of insight most patients have into their condition (Vallar, Bottini & Sterzi, 2004). Sturm, Thimm, Fink, Kust and Karbe (2006) investigated a three-week computerized training task aimed at improving alertness and vigilance in seven neglect patients and reported significant improvements in both of these attentional domains alongside increases in brain activity in regions associated with the VAN, as measured by fMRI. However, when the same assessment was conducted four weeks later, the behavioural improvements had deteriorated and the increased neural activity on fMRI had also diminished. Therefore, the literature to-date suggests that interventions aimed at improving alertness in neglect need to be extensively researched with the aim of finding an effective intervention that generalises to functional abilities as well as spatial attention *and* induces long-term amelioration of deficits.

EEG neurofeedback has many advantages as a rehabilitative intervention. Firstly, it does not require the patient to have any insight into their deficits as it relies on neural as opposed to behavioural learning. Whilst the mechanism by which neurofeedback training produces long-term neuronal changes remains unclear, it has been suggested that neurofeedback works by encouraging the cortex to maintain an efficient oscillatory state during neurofeedback training sessions resulting in an increased likelihood that this state will be elicited by the cortex in more general settings post-training (Cho, Jang, Jeong, Jang, Choi, & Less, 2008). This idea that a rehabilitative intervention could be applied to a clinical group for a limited period of time and produce long-lasting permanent neural changes is very promising.

Experiment I investigated the EEG profile of neglect patients and reported a distorted profile in comparison to age-matched controls. Compared to controls, neglect patients had increased activity at the low end of the spectrum and decreased activity at the *high*er end of the spectrum. This novel finding suggests that neglect is associated with similar EEG abnormalities to ADHD, a condition also linked to deficits in tonic alertness and sustained attention (Monastra et al, 1999; Breshnahan & Barry, 2002). Since EEG neurofeedback training, employing *SMR* and *beta* reward protocols, has proven efficacious in the treatment for ADHD (Lubar et al, 1995; Monstra et al, 2003; Kropotov et al, 2005), it follows that neglect patients may also benefit from this intervention if their greater age does not interfere with learning.

Experiment II confirmed that healthy older adults were capable of modulating their EEG through neurofeedback training. However the significant linear trend of increasing *beta* amplitude with increasing sessions signifies that the asymptote reported in younger participants within ten sessions had not been reached (Gruzelier, Inoue, Smart, Steed & Steffert, 2010; Vernon et al, 2003). This finding therefore supports the application of EEG neurofeedback training to an older clinical population but indicates that more sessions may be needed in order to have a therapeutic effect, an approach previously adopted by clinical populations (Rozelle & Budzynski, 1995; Tinius & Tinius, 2000). Therefore, the aim of Experiment III was to investigate the use of neurofeedback training as an intervention for hemispatial neglect. The goal was to establish whether neglect patients are able to modulate their EEG in the direction of the training protocol, that is, increasing *beta* activity without concurrent rises in *theta* or *high beta* activity. Several neurofeedback

studies have reported that some participants respond well to neurofeedback training by showing EEG changes in the direction of the trained frequency bands whilst other participants showed no changes (Kropotov et al 2005; Ros et al, 2009). Therefore, individual learning profiles were investigated in this study to determine whether individual patients showed EEG learning with increasing number of sessions. Of particular interest for future research are factors that might distinguish patients susceptible to training from those not.

In addition to assessing the therapeutic effects of EEG neurofeedback training, the design of this study permitted a broader, perhaps even more important, line of investigation into the recovery of neglect patients. Each neurofeedback session commenced with a three-minute baseline EEG recording (during which thresholds for the training period were set) meaning a continual dynamic record of resting state EEG would be obtained for each patient across the six-week period. Regardless of whether changes were induced as a result of the training or not, this is the first study to obtain such a detailed account of EEG activity over a prolonged period of time and allow correlations to be made with behavioural measures. Given the distorted EEG profile of neglect patients reported in Experiment I, it was hypothesized that recovery would be associated with a normalization of EEG activity with specific emphasis on an increase in *beta* activity.

Experiment II included both an *SMR* and a *beta* neurofeedback training protocol resulting in a total of 36 min of neurofeedback recording, not accounting for the time required to set-up the equipment and breaks permitted throughout the session.

Within session analyses suggested that fatigue started to impact the second *SMR* session, represented by an increase in *theta* and *high beta* activity across the 15 min training period. These findings were found in a healthy population so it would be predicted that fatigue would set in more quickly and to a greater extent in a clinical population characterised by reduced alertness. Given the reduced alertness presented by neglect patients, only one neurofeedback training protocol was therefore included in this study. Since *beta* training has been associated with improved performance on sustained attention tasks and alertness this protocol was selected over *SMR* training, shown to reduce impulsivity which is not a symptom associated with neglect (Egner & Gruzelier, 2004)

It was predicted that recruitment of patients would be particularly challenging given the demands of the study, requiring 6 weeks of intensive neurofeedback training and a further six week follow-up, the inclusion/exclusion criteria patients needed to fulfil and the prediction that not all patients would want to take part in a research study even if they did meet the recruitment criteria. Therefore all patients received neurofeedback training, rather than allocating patients to an additional control arm. This has obvious implications when it comes to drawing conclusions from the data and means particular care must be taken in assigning any improvements to neurofeedback training as opposed to spontaneous recovery. This study was therefore intended to serve as a preliminary investigation for future studies which would incorporate a control arm.

The issue of spontaneous recovery must be considered when evaluating the efficacy of any rehabilitation intervention, this is especially important in neglect rehabilitation where natural recovery is observed within the acute period post stroke. A range of reliable measures are now available to assess patients on a battery of functional and cognitive aspects in order to monitor a range of improvements over time. Denes, Semenza, Stoppa and Lis (1982) monitored the recovery of 24 left and 24 right hemisphere stroke patients over a 6 month period, with one assessment at time of admission and one six months later. Right hemisphere stroke was associated with significantly less improvement over time on measures of motor impairment and activities of daily living. A sub group of patients presented with neglect on admission, 8 patients with right-sided lesions and 7 with left-sided lesions. At the six month assessment 7 of the 8 patients with right sided lesions still presented with neglect whilst 5 of the 7 patients with left-sided stroke had completely recovered. Over time, patients with right-sided stroke damage showed a lesser degree of independence and social adjustment than those with left-sided stroke with the only distinguishing factor between the two groups being hemispatial neglect. This finding *high*lights the impact neglect has on general activities of daily living.

In a review of stroke recovery, Cramer (2008) summarizes the findings to-date: spontaneous recovery is most likely to occur within the first 3 months after stroke onset, cognitive deficits are more likely to show spontaneous recovery beyond 3 months than motor deficits, recovery is associated with severity of impairments, with mild deficits associated with a quicker rate of recovery and less extended period of time. Hemispatial neglect caused by right-sided lesions usually resolves within 3 months although patients with more severe neglect can continue to improve over a

longer period of time (Levine, Warach, Benowitz & Calvanio, 1986; Cassidy, Lewis & Gray, 1998). It is during this time-window, in the weeks immediately after stroke, that rehabilitative therapies may be most successful, since the brain is primed to initiate repair. This is particularly important for this neurofeedback study which aims to harness the brain when it is most 'plastic' in order to encourage neurophysiological change. During the months, as opposed to weeks, that follow stroke, spontaneous recovery of behavioural deficits appears to plateau (Tombari, Loubinoux, Pariente et al, 2004).

Crucially for this study, it was important to evaluate patients over a prolonged period of time, an element which is often missing in both neurofeedback studies and rehabilitation studies. Assessment sessions were conducted at 3 time points: Time 1 was conducted during the baseline week, immediately following consent, Time 2 was conducted in week 7 after the neurofeedback training period, Time 3 was conducted in week 12. No intervention or contact with the investigator was received by the patient between Time 2 and Time 3.

Due to the demanding and exploratory nature of the study it was predicted that only a small number of patients would meet the inclusion/exclusion criteria, therefore all patients received the neurofeedback training intervention rather than allocating patients to an additional control group. Seven neglect patients completed the full twelve week study, six weeks of neurofeedback training followed by six weeks with no intervention. Given the small sample size and clinical relevance, each patient will be presented as a case study in the first instance. The *beta* training protocol required

patients to increase *beta* activity without simultaneously increasing *theta* or *high beta* activity. To study the effects of EEG modulation several EEG variables will be extracted from the session data: *beta* amplitude during baseline and feedback periods and *theta* and *high beta* activity during baseline and feedback periods. To study any interactions between across-session and within-session changes, early neurofeedback sessions (weeks 1-3) will be compared to late neurofeedback sessions (weeks 4-6).

Based on the outcomes of each case study, patients will then be grouped according to whether or not they showed EEG changes across the training period in the form of an increase in *beta* amplitude, as in Keller (2001) who found increased *beta* after neurofeedback training in a sub group of closed head injury patients. The group analysis will allow investigations into pre-existing factors which may distinguish patients who showed EEG modulation from those who did not. The baseline amplitudes extracted at the beginning of each session will be interpreted as an index of resting state EEG. Therefore, irrespective of whether changes are caused by neurofeedback changes or reflect the natural process of spontaneous recovery, the data will allow conclusions to be drawn about EEG activity and behavioural recovery.

To summarize, this study has two main aims. The first is to present a detailed account of how EEG activity changes across time and whether EEG changes are associated with behavioural improvements. This will be established by investigating whether a significant increase in *beta* activity is associated with an improvement on behavioural assessments. The second aim is to determine whether patients show

evidence of EEG modulation as a direct result of the neurofeedback training intervention. This will be established by investigating whether within-session learning effects were observed in the form of increased *beta* power within the training sessions. Without empirical evidence of within session training, despite an observed across session improvement in *beta* activity, successful neurofeedback training cannot be concluded at this stage. Instead the across session changes in EEG would be put down to spontaneous recovery alone.

The hypotheses listed below will each be addressed in the results section.

Hypothesis 1) Case Studies: Across and Within Session Analysis

Experiment 1 confirmed the hypothesis that neglect patients with right hemisphere lesions have a distorted EEG profile, with increased activity at the low end of the frequency spectrum and reduced activity at the faster end of the spectrum. The principle aim of this experiment was to determine whether patients with clinical neglect are able to modulate their EEG through 6 weeks of neurofeedback training in order to normalize the abnormal EEG profile. The neurofeedback protocol required the patient to increase *beta* activity without concurrent rises in *theta* or *high beta* activity. For each patient, EEG recorded during the 3-min baseline, during which thresholds for the training period were set, of each session will be analysed to assess modulation of EEG across the 6-week training period. Patients will be categorised into those who showed a significant correlation between increased *beta* activity and increased number of sessions (Improver group) and those who did not show any significant change in *beta* activity across sessions (Non-Improver group). For each patient, EEG changes during the neurofeedback training period of each session will

also be analysed and averaged across weeks 1-3 and weeks 4-6. This within session analysis will be used as a marker of neurofeedback learning as opposed to spontaneous recovery. For example, if a patient shows increased activity over the 6 weeks without any sign of within session changes in EEG it would be difficult to claim an effect of neurofeedback training and is more likely to be a result of spontaneous recovery. However, within session changes in *beta* activation would not be expected for any other reason than the reinforcing nature of the neurofeedback training itself. Each case study will also present scores on the behavioural measures from Time 1, Time 2 and Time 3. It is predicted increased *beta* activity across sessions will be associated with improvement on behavioural measures. It is also predicted that a sub-group of patients will show evidence of within session learning as a result of the neurofeedback training whilst others will simply show increased *beta* activity over time as a result of cortical normalization due to spontaneous recovery.

Hypothesis 2) Baseline Group Differences

Analysis of baseline assessment measures will determine whether any factors were significantly different in the patients who were classed as Improvers compared to those who were classed as Non-Improvers. Keller (2001) found patients with closed head injury who showed evidence of neurofeedback learning had more distorted EEG activity than those who did not; specifically they started the training with lower *beta* amplitude than those who did not show EEG changes. Therefore it was predicted that Improvers would have lower *beta* activity at Time 1 than Non-Improvers.

Hypothesis 3) Group Analysis of Outcome Measures

In order to investigate long term effects of EEG normalization, group analysis will compare scores on the behavioural assessments between Time 1 and Time 2 and between Time 2 and Time 3. It is predicted that the group who show enhancement of *beta* activity will show a greater improvement in behavioural scores than patients who showed no change in *beta* activity.

4.2. Method

4.2.1 Participants

Having screened over 60 patients, a total of 16 patients consented to take part in the study having been assessed for neglect and fulfilment of the inclusion criteria. However, not all of these patients were able to complete the study for various reasons including medical complications and an inability to take part in the assessments or neurofeedback sessions. Therefore, seven right hemisphere stroke patients with neglect (5 males and 3 females; mean age = 59.14 yr; S.D = 19.14) were recruited from stroke units in South London and Kent (Kings College Hospital, St Thomas' Hospital, University Hospital Lewisham and William Harvey Hospital). Patients gave informed written consent to participate in the study which was given full ethical approval from East Kent Hospital's Trust along with local approval from each NHS site. All patients met the following criteria;

Inclusion/Exclusion Criteria

In order to be considered for this study patients had to fulfil the following inclusion and exclusion criteria.

Include if yes to all:

1) ≤ 12 weeks since stroke
2) Cortical/sub cortical involvement
3) Clinically assessed spatial neglect
4) Pre-stroke Modified Rankin Score 0,1 or 2

Exclude if yes to any one:

1) Age <18 years
2) Severe communication problems
3) Lack of consent from patient or next of kin
4) Expected survival <12 weeks
5) Visual/spatial deficits pre-date stroke
6) Inability to participate in assessment/training

Patients were all recruited in the acute 12-week post-stroke phase and, in an attempt to ensure any neglect present was chronic, patients were recruited at least 2 weeks post stroke. CT and MRI scans confirmed that all patients had suffered a right hemisphere stroke. Six of these patients were included in Experiment I, RK was only included in this experiment because her Afro-Caribbean hair meant it was not possible to record a QEEG. Table 4.1 displays demographic information for each patient along with the number of neurofeedback sessions completed over the 6 week period.

Table 4.1. Demographic and clinical details of each patient

Patient	Gender	Age (yr)	Stroke	Lesion Location	No. days since stroke	No. of Sessions
HB	M	62	Haemorrhage	Right Fronto-Parietal	62	25
KS	M	50	Infarct	Right MCA	33	22
KH	M	66	Haemorrhage	Right Fronto-Parietal	26	15
JM	F	68	Infarct	Right MCA	29	28
BS	F	72	Infarct	Right MCA	64	23
PS	F	76	Infarct	Right MCA	12	13
RK	F	20	Infarct	Right Parietal	15	15

Note, there were no significant correlations between age, number of days since stroke and number of session of neurofeedback.

4.2.2. Design

Patients were identified as being potentially eligible for the study by members of the clinical teams on each hospital ward. Verbal consent was obtained in order to screen the patient for neglect. Once it had been established that the patient presented with clinical neglect, the study was discussed in detail with the patient, and next of kin when appropriate. Before consenting to take part in the study, all patients took part in a practice session during which the neurofeedback equipment and protocol were explained and demonstrated. Once patients had decided they would be happy to take part in the study, written consent was obtained. Immediately after consent, all patients were assessed at Time 1 on various measures of neglect, stroke-related deficits, mood and functional abilities to conduct Activities of Daily Living (ADLs). Patients then began the 6-week period of neurofeedback training sessions. As many sessions as possible were conducted for each patient but the number varied

considerably due to factors such as illness, availability, working around busy therapy schedules and periods set aside for discharge or transfers to local hospitals. It was considered more important to have a uniform time period between assessments rather than a fixed number of sessions in order to attempt to control for rates of spontaneous recovery. After the 6-week training period, patients were re-assessed on all measures at Time 2. Following this assessment, patients were not seen for a further 6 week period, during which they continued to receive routine therapy but did not have any contact with the investigator. Patients were then re-assessed on all measures at Time 3. Individual patient scores at Time 1, Time 2 and Time 3 on each of the assessment measures are presented in Table 4.2.

4.2.3. Neuropsychological Assessments

Behavioural Inattention Test (BIT)

Visual neglect was assessed by the conventional part of the Behavioural Inattention Test (BIT) (Wilson et al, 1987). This battery consists of three cancellation tasks of varying perceptual difficulty (line, star and letters), a line bisection task, 2 figure copying tasks and a representation drawing task. The accepted cut-off point for clinical neglect is a score of 129/146, with scores less than 129 indicating visual neglect. All patients scored under 129 so were classified as having clinical neglect (see Appendix 1).

National Institute of Health Stroke Scale (NIHSS)

Patients were assessed for general stroke severity by the National Institute of Health Stroke Scale (NIHSS). This scale measures several aspects of brain function

including consciousness, vision, sensation, movement, speech and language. A score greater than 16 is considered to indicate poor prognosis and a *high* probability of severe disability or death. The scoring system used to categorize stroke is: 0 = no stroke, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-42 – severe stroke. All patients recruited scored 5 or more on the NIHSS so were classified as having suffered a moderate or severe stroke (see Appendix 2).

Barthel Index (BI)

The Barthel Index is used to establish the degree of independence from any help on activities of daily living (ADLs). The maximum score on the scale is 20, with lower scores indicating increased dependency and disability. When being used to measure an improvement after rehabilitation, an improvement in scores of 2 or more points reflects a genuine change and change on one item from fully dependent to independent also reflects a reliable improvement (Hsieh, Wang, Wu, Chen, Sheu, Hsieh., 2007) (see Appendix 3).

Nottingham Extended Activities of Daily Living (NEADL)

The Nottingham Extended Activities of Daily Living Scale is another commonly used assessment for independence. The maximum score on the scale is 88, with *high*er scores indicating greater independency. This scale corresponds well with the Barthel Index but provides a more sensitive tool which can be more informative in relation to patients with less severe stroke symptoms (Sarker, Rudd, Douiri & Wolfe, 2012). This scale requires the patients to rate levels of difficulty in performing 22 tasks, including kitchen, domestic and leisure activities. All items are scored on a 4-point scale (0-3) with *high*er scores indicating greater levels of independence. The

NEADL has been recognised as a quick and easy to administer scale with excellent validity and reliability (Harwood & Ebrahim, 2002) (see Appendix 4)

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is commonly used in hospital and clinical settings to determine the levels of anxiety and depression experienced by patients. It is made up of a 14-item scale; 7 items related to anxiety, 7 items related to depression. Each item on the scale is scored between 0-3 meaning that the maximum score for anxiety or depression can lie between 0 and 21, with *high*er scores indicating more severe symptoms. Bjelland, Dahl, Haug and Neckelmann (2002) performed a systematic review based on 747 studies and identified a cut-off point of 8/21 for anxiety and depression (see Appendix 5).

4.2.4. Neurofeedback Training Protocol

The same *beta* training protocol as in Experiment II was used here and followed the same protocol as that used in previous studies whose aim has been to improve alertness. EEG signals were recorded using the Nexus-4 DC-coupled EEG amplifier (MindMedia, the Nethelands) and the NFT was carried out with the Biotrace+ software. The active Ag/Cl scalp electrode was placed at Cz (according to the 10-20 international system) with reference and ground electrodes placed on the mastoids, having used an abrasive gel (NuPrep) to clean the skin and Ten20 conductive gel to act as a glue between the scalp and electrode. The EEG was sampled at 256 Hz and IIR bandpass filtered to extract amplitude values (in µV, peak-peak) for the relevant frequency bands involved in the feedback protocol; *theta*, *SMR*, *beta* and *high beta*. The exported EEG amplitude data was reviewed for artefact rejection. A voltage-

based artefact threshold was implemented to remove eye, muscle and EMG contamination. Fast Fourier Transform (FFT) of the raw data was used to calculate mean amplitudes for each frequency band in terms 3 minute epochs. The first 3-min epoch related to the baseline period and the remaining five 3-min epochs related to the training periods of the feedback, each separated by a short pause.

When possible, neurofeedback sessions took place every week day over a six-week period, either on the stroke ward or at the patient's home if they had been discharged. The total number of sessions varied for each patient. Some patients received many fewer sessions due to periods of illness or difficulties arranging sessions with the families on discharge. Each session consisted of a 15-min protocol which involved enhancement of *beta* power with inhibition of *theta* and *high beta* power. Each session followed a standardized procedure which began with positioning the electrodes and obtaining a clean raw EEG trace. Each session was preceded by a 3-min baseline, from which thresholds for each frequency band were set and during which participants were encouraged to relax. The thresholds were set so that, based on the 3-min baseline, the participant would exceed the reward band threshold (*beta*) 70% of the time, would exceed the inhibit threshold for the *theta* band 20% of the time and the *high beta* band 10 % of the time. After the initial baseline period, the online neurofeedback commenced. Participants were not given any specific instructions on how to control their EEG but were encouraged to maintain an attentive state. The visual and auditory feedback was in the form of a 15-minute video clip from the nature series 'The Blue Planet'. The clip would play continuously when the participant was increasing the reward band (*SMR* or *beta*) above the threshold and when they were keeping the inhibit bands (*theta* and *high*

beta) below threshold. If any of these criteria were not met, the DVD would pause, informing the patient they were not maintaining their target amplitudes. The 15-minute training period was split into five 3-minute blocks to allow the patient to have a short break. If training needed to be paused at any point during the session this was also possible and the session could also be stopped altogether. Often patients were not able to complete the full 15 mins of training due to tiredness and loss of concentration. Patient JM only completed the full 15 minutes of training in 32% of sessions whilst all other patients completed the full training in over 75% of sessions. Headphones were used for patients who were hard of hearing or if the environment was noisy.

	BIT			NIHSS			BI			NEADL			Anxiety			Depression		
Patient	**Time 1**	**Time 2**	**Time 3**	**Time 1**	**Time 2**	**Time 3**	**Time 1**	**Time 2**	**Time 3**	**Time 1**	**Time 2**	**Time 3**	**Time 1**	**Time 2**	**Time 3**	**Time 1**	**Time 2**	**Time 3**
HB	8	19	46	14	11	11	2	8	9	0	2	3	1	1	1	4	2	2
KS	24	41	41	17	16	16	2	5	6	0	4	5	12	9	9	8	5	5
KH	129	134	134	10	10	10	4	10	10	10	13	12	5	5	2	2	2	1
JM	23	65	38	13	13	12	8	8	10	6	7	8	6	12	12	5	3	3
BS	108	130	133	5	3	4	11	13	14	11	25	21	7	8	8	3	1	7
PS	43	124	133	6	1	1	11	17	19	5	37	38	3	3	3	6	7	8
RK	67	132	127	6	1	0	13	20	20	16	46	56	3	3	2	2	3	2

Table 4.2. Individual Patient Scores on Outcome Measures at Time 1, Time 2 and Time 3.

Statistical Analyses

For each case study, the linear multiple regression model was used to determine the relationship between baseline *beta*, *theta* and *high beta* amplitude and session. Figures are presented for each of these regressions apart from *high beta* because less emphasis was placed on this inhibit during the training given the thresholding criteria was not as stringent as for *theta* activity. Given the small sample size, non-parametric Mann Whitney U Tests were used for all analyses at the group level, results are also discussed descriptively.

4.3) Results

4.3.1. Individual Case Study Results

Case study reports are presented for all patients due to the clinical relevance and interest in neurofeedback training at the individual patient level. Please refer to Table 4.2 for individual patient scores on all assessments at Time 1, Time 2 and Time 3. The single case study reports are important because whilst all patients could be categorized as right hemisphere stroke patients with left sided neglect, this still leaves a wide range of individual differences in terms of aetiology and severity of symptoms. Each case study will look at changes on the neglect assessment (BIT), the stroke severity scale (NIHSS), the ADL assessments (BI and NEADL), anxiety scale (extracted from the HADS) and EEG activity. Across session changes in tonic *beta* activity (recorded during the 3-minute baseline proceeding each session) are presented and analysed by linear trend regression. In order to investigate whether within session performance was changing over time, separate correlations were

conducted between within session training block and *beta* amplitude for weeks 1-3 and weeks 4-6. Keller (2001) found that patients who managed to increase their *beta* amplitude across training sessions show improved ability to maintain *beta* above threshold with increasing sessions.

Case Study 1: Patient HB

HB was a 50 yr patient who was admitted to King's College Hospital with a large acute parenchymal haematoma centred on the right frontal parietal region and extending into the temporal lobe with significant mass effect and a contralateral hydrocephalus. He proceeded to a right frontal parieto-temporal craniotomy and evacuation of the right sided haematoma. Post surgery, HB improved rapidly and was transferred to the Frank Cooksey Rehabilitation Unit for intensive therapy approximately 1 month after the initial stroke. At the time of recruitment, 62 days after stoke onset, HB presented with a left hemianopia, left upper motor neuron facial palsy, mild dysarthria and, although he was alert, he was not orientated to time and place. He had complete hemiplegia of the left side of the upper and lower body with reduced sensation on this side.

Figure 4.1 illustrates the severity of neglect this patient presented with at Time 1, this was the most severe neglect of any patient recruited to the study. This neglect did improve linearly throughout the study with increased scores at Time 2 and Time 3. Therefore, even though HB still presented with severe neglect at the end of the 12 week study, this had improved linearly and considerably from baseline with a total

change score of 38 points. Given this patient was assessed at Time 1 approximately 2 months after stroke onset, it would be expected that the level of spontaneous recovery of neglect symptoms would have slowed down by Time 2 and Time 3. However, given the severe neglect HB presented with at Time 3, according to Cassidy et al (1998) his recovery could continue to improve over a longer period of time than patients with mild neglect.

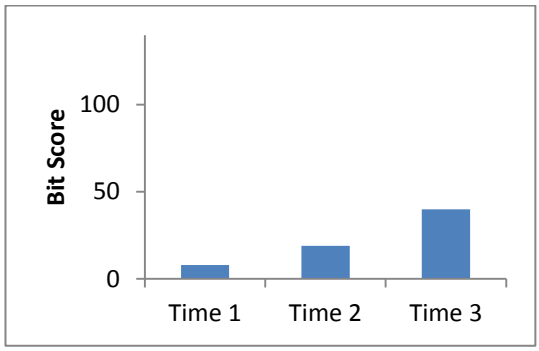


Figure 4.1. *Patient HB. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

The multitude of deficits HB presented with is reflected in his *high* score of 14 on the NIHSS at Time 1 indicating moderate/severe stroke-related deficits. This score improved at Time 2 but remained relatively *high* due to persistent hemiplegia of upper and lower body and the presence of severe neglect. There was no improvement in NIHSS score between Time 2 and Time 3 (see Figure 4.2).

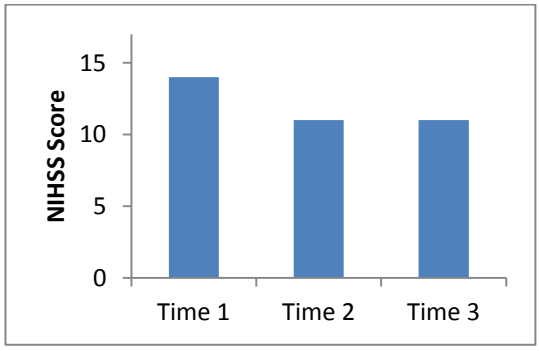
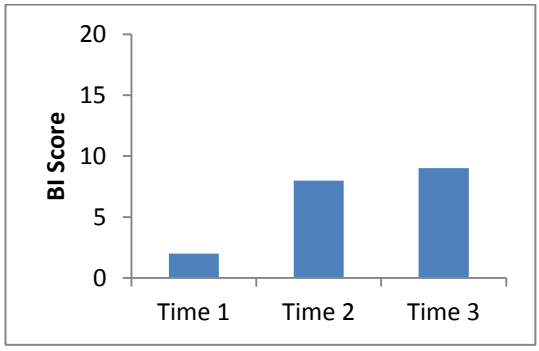


Figure 4.2. *Patient HB. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

HB's initial BI score was very low indicating a reliance upon assistance for most basic ADLs such as washing and toileting. This score increased greatly by 6 points at Time 2 (see Figure 4.3.). Given that an increase of 2 points is considered to reflect a true and significant improvement in basic ADLs, HB made good progress especially considering he was greatly limited by his hemiplegia of upper and lower body. He continued to improve on the BI at Time 3 although to a lesser extent with a 1 point increase. The NEADL, which measures more advanced ADLs, shows that HB completely lacked independence on all advanced ADLs included on this scale at Time 1 (see Figure 4.4). However, improvements were made at Time 2 and Time 3 although remained low, indicative of his hemiplegia which left him wheelchair bound meaning advance ADLs, such as shopping and gardening, were not possible.



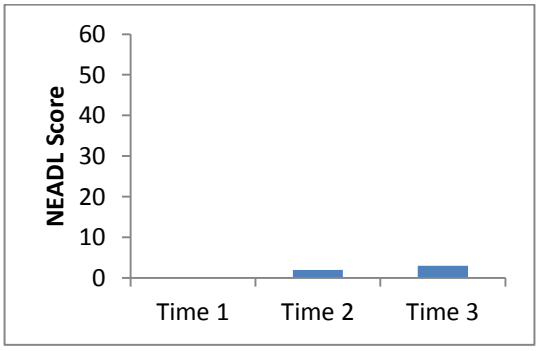


Figure 4.3. *Patient HB. Scores on BI*

Figure 4.4. *Patient HB. Scores on the NEADL*

HB was happy to take part in daily neurofeedback training sessions throughout the study and was particularly keen to maintain the frequency of sessions once he was discharged home. Being a relatively young stroke patient with three children, he was *high*ly motivated to make as many gains through therapy as possible. His anxiety score, extracted from the HADS remained very low throughout the study, indicating this patient did not suffer from anxiety (see Figure 4.5).

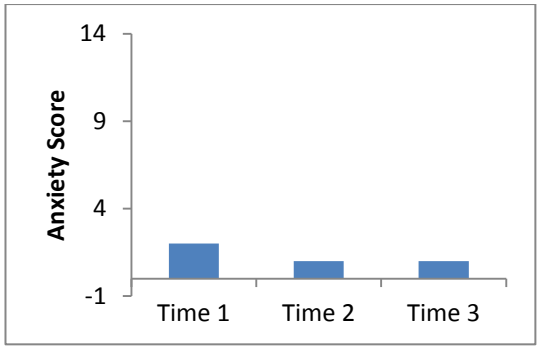


Figure 4.5. *Patient HB. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety.*

HB took part in 25 sessions of neurofeedback training spread evenly over the 6-week period, both on the stroke ward and at home on discharge. Across session linear regression analysis revealed baseline *beta* activity significantly increased across sessions with a significant linear trend (r = 0.396, R^2 = 0.157, $F(1,24)$ = 4.27, p = 0.050, see Figure 4.6).

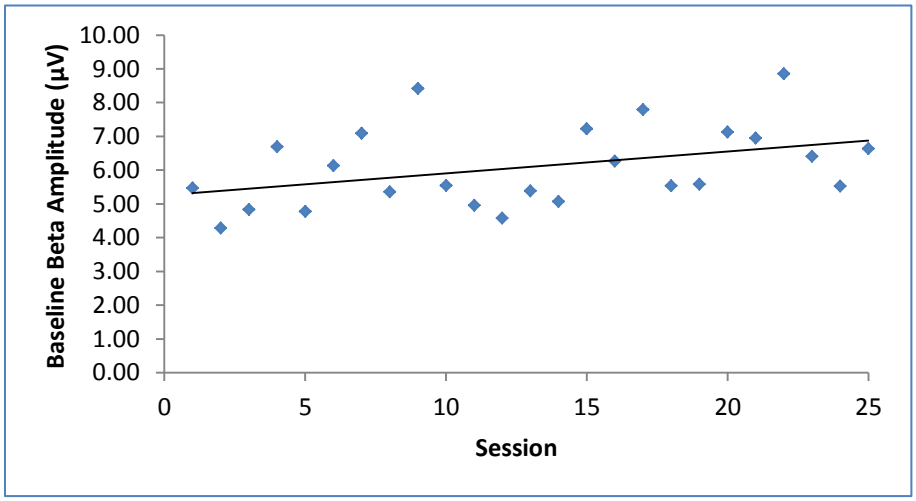


Figure 4.6. *Patient HB. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

This significant relationship was found in the absence of any significant change in the inhibit frequencies of *theta* (see Figure 4.7) and *high beta*.

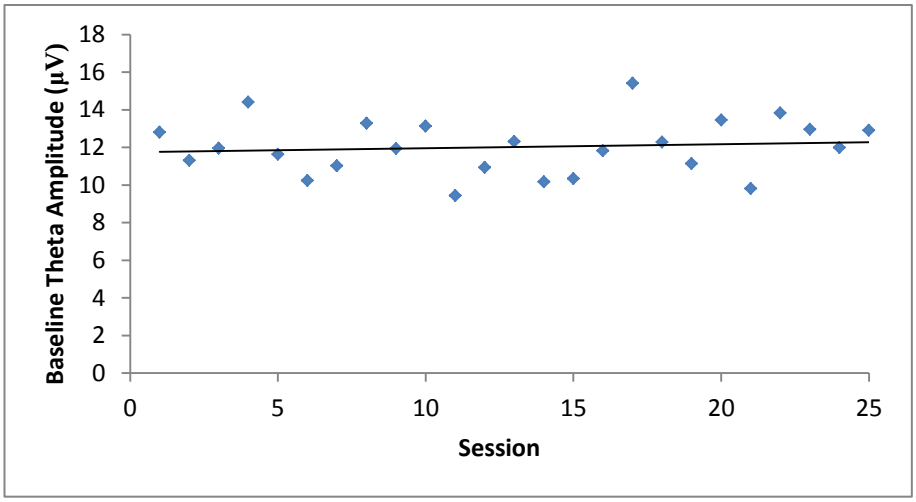


Figure 4.7. *Patient HB. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.8 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of training for the 2 groups of sessions. A positive trend between training period and *beta* amplitude was found for weeks 1-3 ($r = 0.703$, $p = 0.186$) and this correlation increased but remained non-significant for weeks 4-6 ($r = 0.812$, $p = 0.095$). The lack of significant findings however, make it difficult to conclude that neurofeedback learning has been achieved and instead the across session changes are likely to be due to spontaneous recovery.

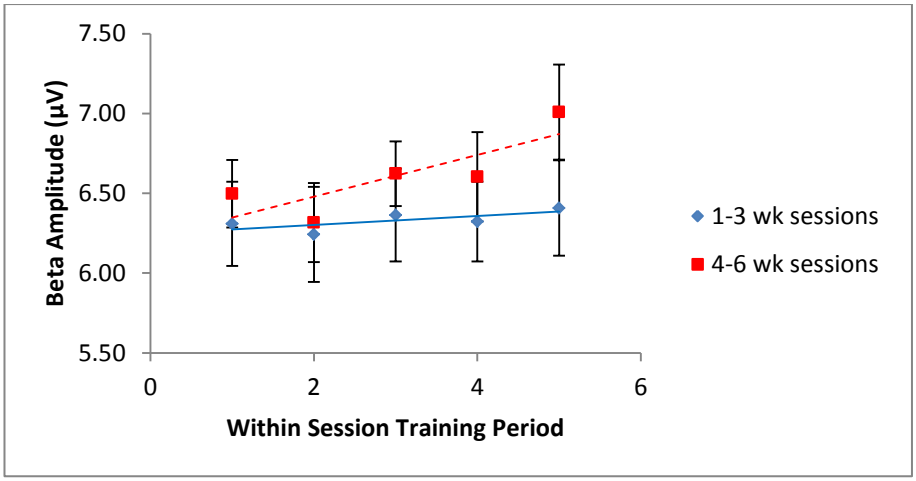


Figure 4.8. *Patient HB Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM.*

In summary, HB was a patient who presented with extremely severe neglect and stroke-related deficits. He was recruited 62 days after stroke onset. HB improved on all behavioural measures from Time 1 to Time 2 and either showed continued improvement in these measures at Time 3 or maintained the improvement, therefore there was no deterioration in behavioural or functional abilities over the 12 week period. Since the fastest rate of spontaneous recovery is usually expected during the first month post stroke, the improvements observed in this patient over the 6-week training period could be a result of the intervention as opposed to spontaneous recovery. Coinciding with improvements on the functional assessments, HB showed significant across session increases in *beta* activity. Therefore, it can be concluded that HB showed an enhancement of *beta* activity, most likely due to spontaneous recovery giving the non-significant within session changes in *beta*, associated with an improvement in stroke-related functional impairments assessed by the NIHSS and the BI. This patient will be allocated to the Improver group for the subsequent group analyses.

Case Study 2: Patient PS

PS was a 76 yr old patient admitted to King's College Hospital with a right MCA territory infarct. The initial CT reported that there was reduced attenuation in the region of the right putamen and mid insula, with possible reduction of grey-white matter differentiation within the posterior frontal lobe. There was also a hyperdense thrombus within the proximal MCA. This patient was thrombolysed with bolus and intra-arterial thrombolysis of the right MCA thrombus. The post-treatment CT revealed an evolving right MCA infarct with some parenchymal and intraventricular haemorrhage. PS consented to take part in the study 12 days post-stroke.

At baseline PS presented with mild left-sided weakness but was able to walk with a stick and required assistance for most ADLs. She was oriented to time and place but was extremely drowsy and had difficulty maintaining concentration during the baseline assessments. Despite cognition being mostly intact, Figure 4.9 illustrates the marked neglect PS presented with at Time 1 with a BIT score of 43. Over the 6 week training period, this marked neglect improved greatly, more than any other patient, and reached an almost non-clinical score of 124/146 (cut off score of 129/146 for non-clinical neglect) and this score increased to non-clinical levels by Time 3.

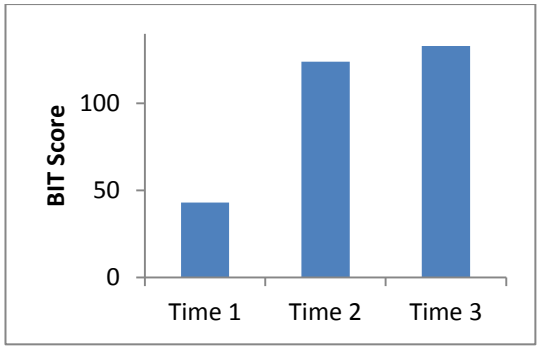


Figure 4.9. *Patient PS. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

PS's NIHSS score at Time 1 indicated a moderate stroke reflecting the initial symptoms she presented with, including left-side weakness, drowsiness and neglect (see Figure 4.10). This score was reduced to 1 at Time 2 and Time 3 meaning her stroke-related deficits were almost negligible, with her only remaining impairment related to the mild neglect at these time points

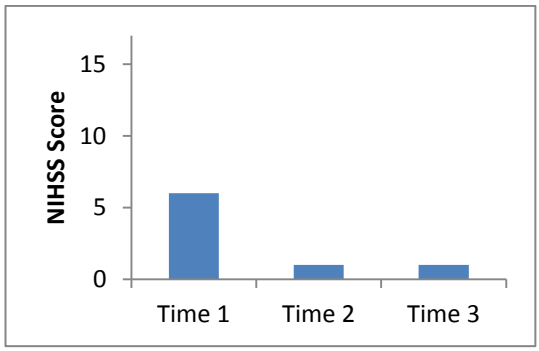


Figure 4.10. *Patient PS. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

PS's initial BI score increased by 6 points at Time 2 (see Figure 4.11), the same extent observed in patient HB. Given that an increase of 2 points is considered to reflect a true and significant improvement in basic ADLs, PS made good progress and became increasingly independent in basic ADLs. She continued to improve on

the BI at Time 3 almost reaching the maximum score for independence on all basic ADLs. The NEADL, which measures more advanced ADLs, shows that PS completely lacked independence on these ADLs mainly due to being hospital bound (see Figure 4.12). By Time 2 and Time 3, this score improved significantly reflecting the ability of the patient to carry out functional tasks such as meal preparation, washing and leaving the house with the support of her husband.

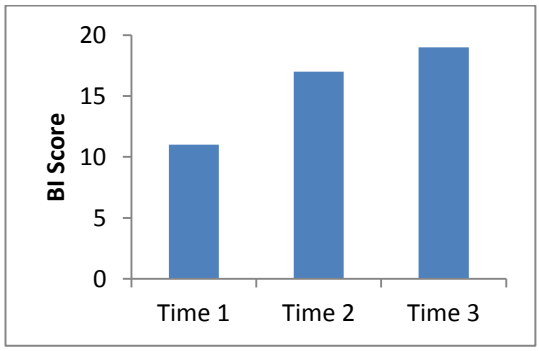


Figure 4.11. *Patient PS. Scores on BI*

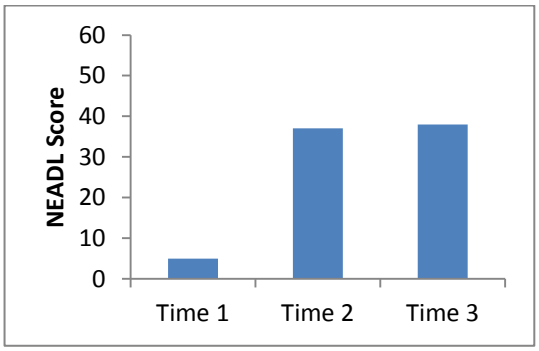


Figure 4.12. *Patient PS. Scores on the NEADL*

PS enjoyed taking part in daily neurofeedback training sessions throughout the study. She was particularly motivated on discharge home due to the lack of continued home therapy. However, it was more difficult to arrange visit times with PS when she was discharged home so the total number of sessions was relatively small. PS did not display signs of anxiety at any point during the study (see Figure 4.13)

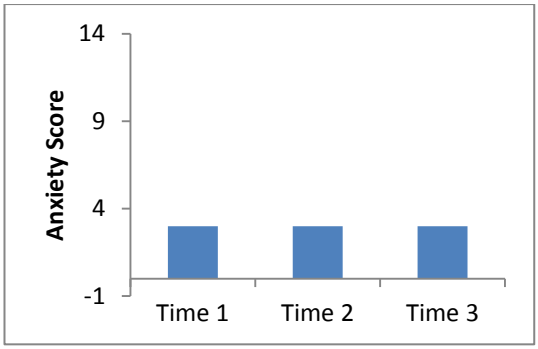


Figure 4.13. *Patient PS. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

PS took part in 13 sessions of neurofeedback training over the 6-week period, both on the stroke ward and at home on discharge. Across session linear regression analysis revealed baseline *beta* activity significantly increased across sessions with a significant linear trend (r = 0.905, R^2 = 0.19, $F(1,12)$ = 49.93, p < 0.001, see Figure 4.14). However, this *beta* increase was associated with a significant increase in *theta* amplitude with a significant linear trend (r = 0.885, R^2 = 0.78, $F(1,12)$ = 39.78, p < 0.001, see Figure 4.15.).

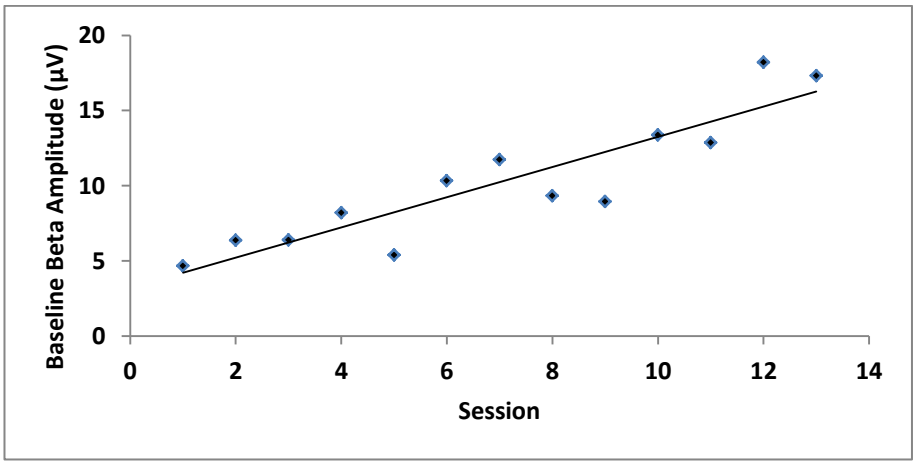


Figure 4.14. *Patient PS. Mean baseline amplitude of beta as a function of training sessions. Error bars depict +/- 0.5 SEM.*

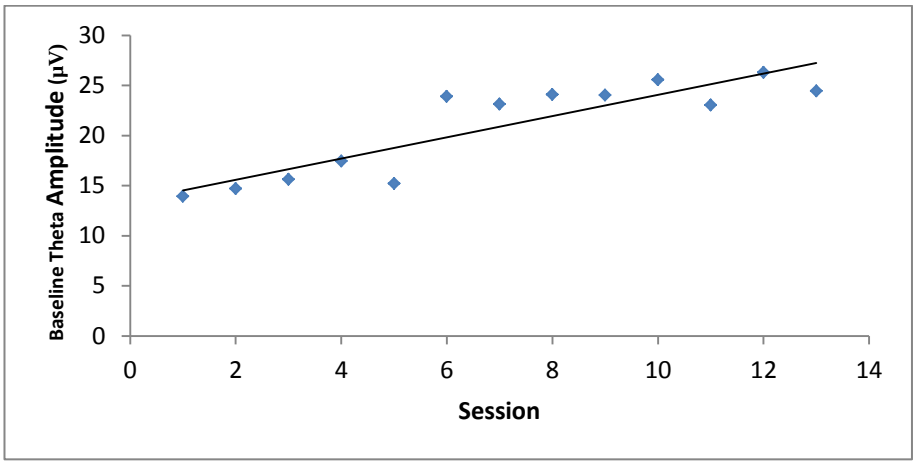


Figure 4.15. *Patient PS. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.16 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of training for the 2 groups of sessions. Although the correlations were not significant, Figure 4.3.18 shows that there was a trend for *beta* amplitude to increase throughout the 15-minute training period in weeks 1-3 ($r = 0.743$, $p = 0.151$) but not in weeks 4-6 ($r = -0.146$, $p = 0.814$). Figure 4.18 also indicates that this patient peaked by the fourth 3-minute block suggesting that 12 minutes might be an optimal training session duration for this patient.

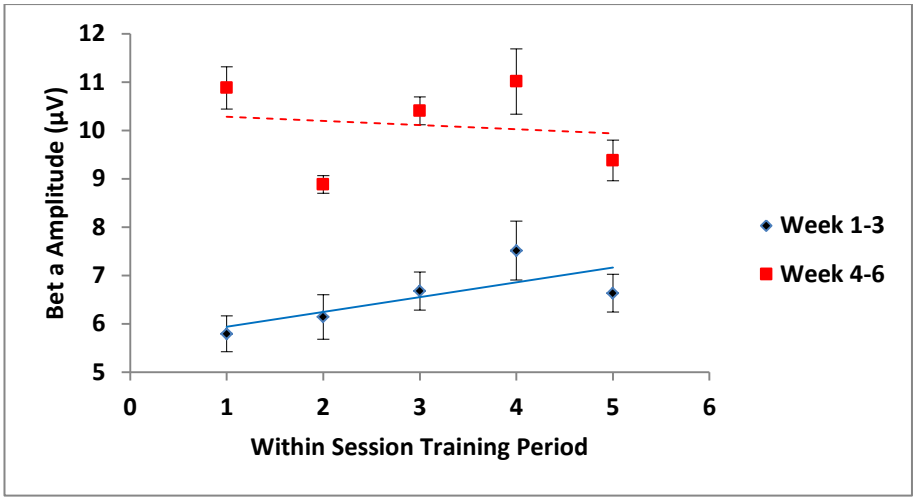


Figure 4.16. *Patient PS. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, PS was a patient who showed vast improvements on all behavioural measures over the course of this study. These improvements were seen from Time 1 to Time 2 and maintained at Time 3. There was little scope to see improvements at Time 3 because PS had reached near maximum scores by Time 2. Since this patient was recruited only 2 days after stroke, it is difficult to disentangle the effects of spontaneous recovery from neurofeedback training since this is the period during which natural recovery rates are fastest. As observed in patient HB, PS showed increased *beta* activity across sessions. Again this points to an association of enhanced *beta* activity with improvements in stroke-related deficits, neglect and independence on ADLs. The lack of significant within session changes in EEG suggests that across session changes in baseline EEG and behavioural symptoms are likely to be a result of spontaneous recovery. This patient will be allocated to the Improver group for the subsequent group analyses.

Case Study 3: Patient RK

This patient was the youngest patient screened at 20 yr. She suffered a right parietal infarct and a small cerebral bleed due to complications with sickle cell disease and pneumonia and was admitted to University Hospital Lewisham. RK was recruited 15 days post-stroke. Due to sickle cell disease she had to undergo blood transfusions during the study so the number of sessions she was able to take part in was limited. Unlike the majority of neglect patients, RK was very aware of her spatial deficit and tried extremely hard to compensate for this when being assessed. At baseline she was mobile around the hospital ward but suffered from drowsiness, left sided weakness and left sided facial palsy.

At Time 1, RK presented with considerable neglect, scoring 67 on the BIT, but this improved greatly by 65 points to non-clinical levels after the neurofeedback training period at Time 2 and remained stable at this level at Time 3 (see Figure 4.17). The slight decrease in score at Time 3 is due to a couple of errors on the non-neglect right side in the star cancellation subtest. This *high*lights the compensatory strategies this patient used due to her acute awareness of the right-sided bias she was prone to present with and an awareness of what the assessment was measuring.

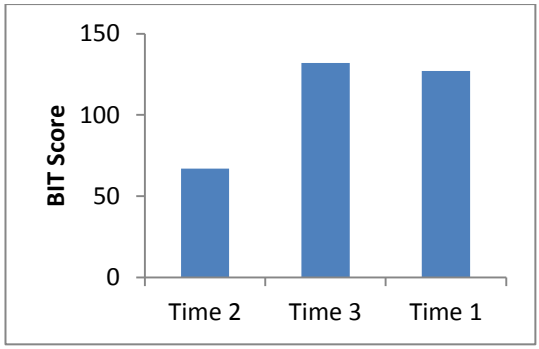


Figure 4.17*. Patient RK. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

RK's NIHSS score at Time 1 indicated a moderate stroke reflecting the initial symptoms she presented with,including left-sided weakness and neglect (see Figure 4.18). This score was reduced to 1 at Time 2 and 0 at Time 3 meaning she made a full recovery from the stroke-related deficits she originally presented with.

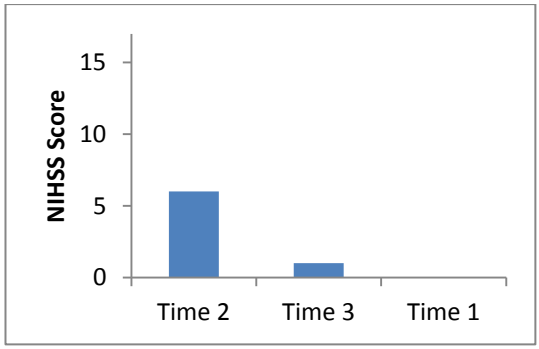


Figure 4.18*. Patient RK. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

RK's initial BI was relatively *high* compared to other patients and continued to improve at Time 2 and Time 3 reaching the maximum score for independence on all basic ADLs (see Figure 4.19). The NEADL, which measures more advanced ADLs, shows that RK lacked independence on most of these ADLs at baseline (see Figure 4.20). By Time 2, having been transferred to the Frank Cooksey Rehabilitation Unit

at King's College Hospital, her score on the NEADL improved greatly reflecting the ability of the patient to carry out functional tasks such as meal preparation, washing and going home on the weekends. Her independence continued to develop as reflected by the further increases in NEADL score at Time 3.

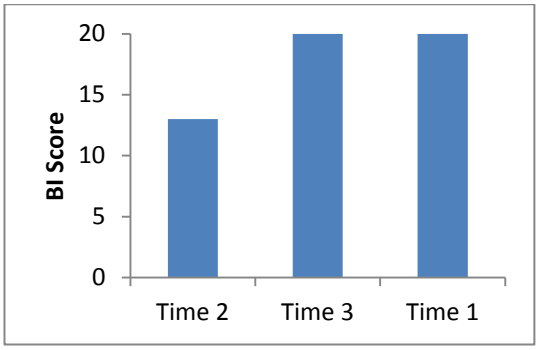


Figure 4.19. *Patient RK. Scores on BI*

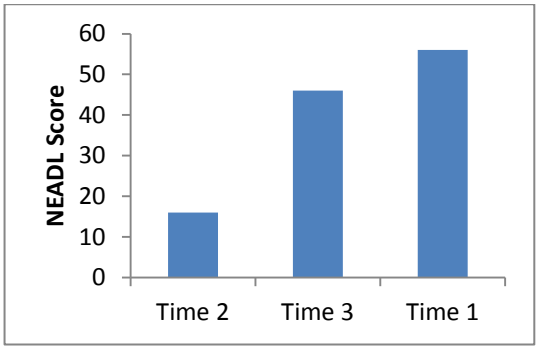


Figure 4.20. *Patient RK. Scores on the NEADL*

RK did not show any signs of suffering from anxiety at any point during the study (see Figure 4.21).

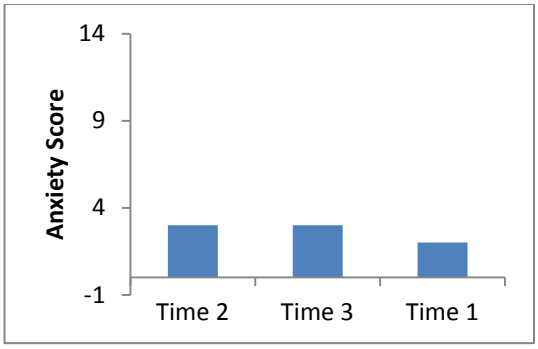


Figure 4.21. *Patient RK. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

RK took part in 15 sessions of neurofeedback training over the 6-week period, both on the acute stroke ward and at the rehabilitation unit. Across session linear regression analysis revealed baseline *beta* activity significantly increased across

sessions with a significant linear trend (r = 0.685, R^2 = 0.469, $F(1,14)$ = 11.47, p = 0.005, see Figure 4.22). This significant relationship was found in the absence of any significant change in the inhibit frequencies of *theta* (see Figure 4.23) and *high beta*.

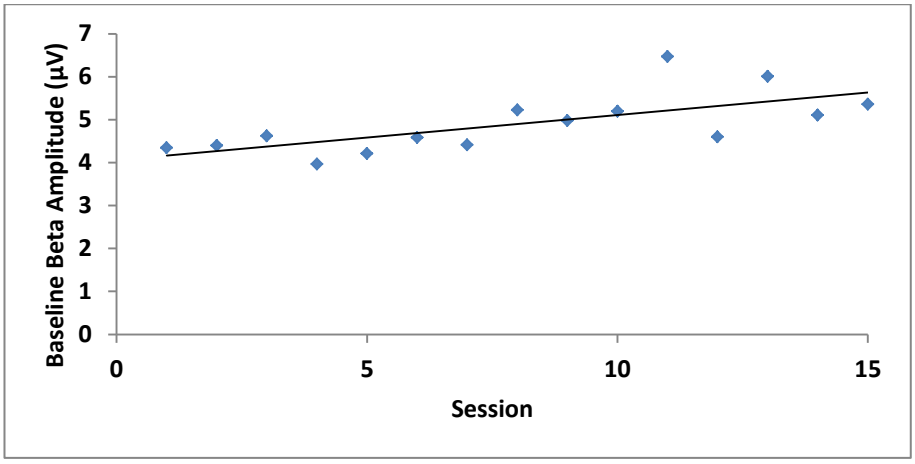


Figure 4.22. *Patient RK. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

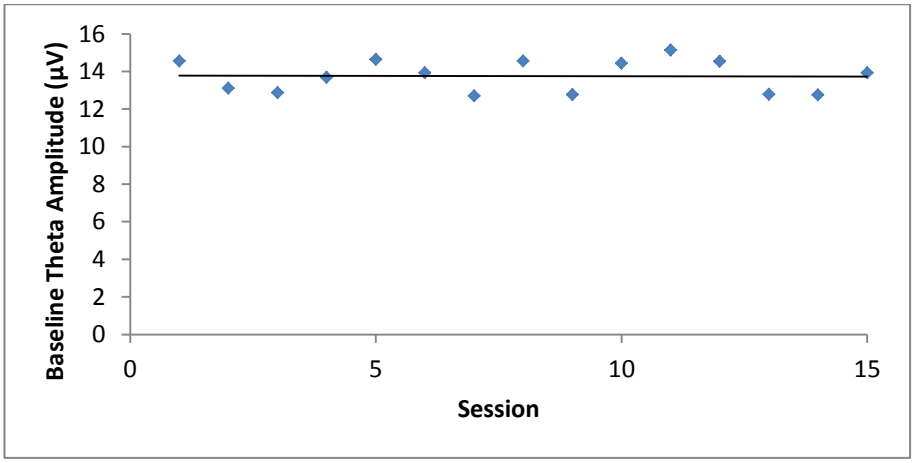


Figure 4.23. *Patient RK Mean baseline theta amplitude ratio as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.24 shows the mean *beta* amplitude for consecutive 3-minute

periods during the 15 minutes of training for the 2 groups of sessions. Figure 4.27 illustrates the significant negative correlation (r = -0.915, p = 0.029) between training period and *beta* activity in the first 3 weeks of the training and the non-significant negative trend in weeks 4-6 (r = -0;675, p = 0.211). This suggests that RK found it increasingly difficult to maintain *beta* activity at the initial level as the session continued. One reason for this effect could be the patient's age. It could be that the feedback (nature video clips) was not as engaging for this 20 year old patient as the older patients. This would affect the learning potential since a lesser sense of reward from the feedback would have been experienced by RK.

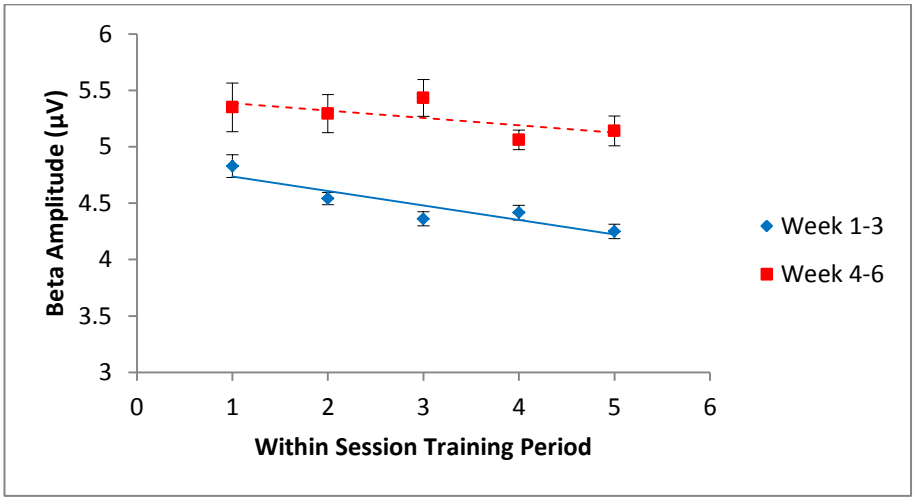


Figure 4.24. *Patient RK. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, this young 20 yr old patient recruited 15 days after stroke presented with relatively severe neglect at Time 1 and moderate stroke-related deficits as measured by the NIHSS, BI and NEADL. RK showed great improvements at Time 2 with her neglect being almost negligible and scores on the NIHSS and BI reaching maximum levels indicating almost complete remediation of her deficits. This left little scope to show any further improvements at Time 3 in comparison to Time 2.

RK showed a steady increase in *beta* activity across sessions but little evidence of within session learning. Due to the lack of within session increase in *beta* activity, it suggests that the improvements in baseline *beta* and behavioural measures were a result of spontaneous recovery and not due to the neurofeedback training. However, this case study supports the data from patients HB and PS that increased *beta* activity across sessions, whether a result of spontaneous recovery or neurofeedback training, is associated with a remediation of deficits. It is also important to note the age of this patient because this could suggest that a quicker rate of neural recovery would be expected in this patient. This patient will be allocated to the Improver group, based on across session improvement in *beta* activity, for the subsequent group analyses.

Case Study 4: Patient KS

KS was a 62 yr old patient who was admitted to King's College Hospital with multiple sub-acute infarcts in the right MCA territory. He was transferred to Frank Cooksey Rehabilitation Unit one month later. He was recruited to the study 33 days post stroke. At the time of recruitment KS presented with severe left sided hemiparesis, extreme drowsiness, double incontinence and had cognitive and communication impairments.

At Time 1 KS had very severe neglect which showed an improvement of 17 points at Time 2 and no further improvement at Time 3 with a final score of 41 (see Figure 4.25). Therefore KS presented with severe neglect throughout the duration of the study with little sign of recovery.

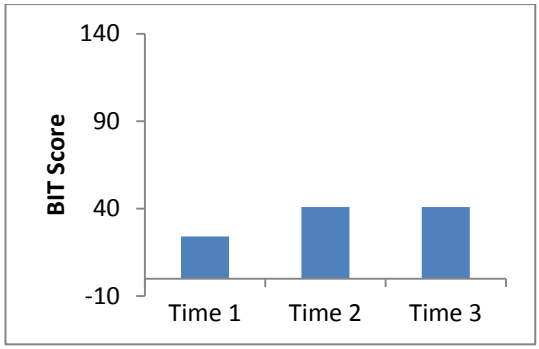


Figure 4.25. *Patient KS. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

Figure 4.26 illustrates KS's *high* NIHSS score at Time 1 indicated a moderate/severe stroke. This score reflects the multitude of stoke-related deficits he presented with, including motor impairments, communication impairments, perceptual impairments and extreme drowsiness. Barely any improvements were observed on these stroke-related measures at Time 1 or Time 2.

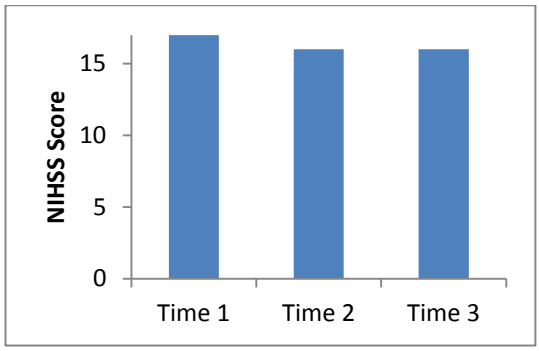


Figure 4.26. *Patient KS. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

KS's initial BI was at the lowest end of the scale reflecting the patient's reliance on maximal assistance for all basic ADLs (see Figure 4.27). This score increased by 3 points at Time 2 showing some improvement and by a further 1 point at Time 3.

However, considering this scale assesses functional ability on only basic ADLs, this patient remained severely disabled at the end of the study. The NEADL, which measures more advanced ADLs, reinforces KS's lack of independence on ADLs by the very low score. This remained persistently low at Time 2 and Time 3 (see Figure 4.28).

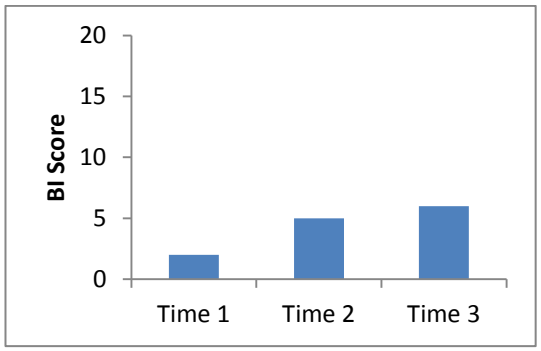


Figure 4.27. *Patient KS. Scores on BI*

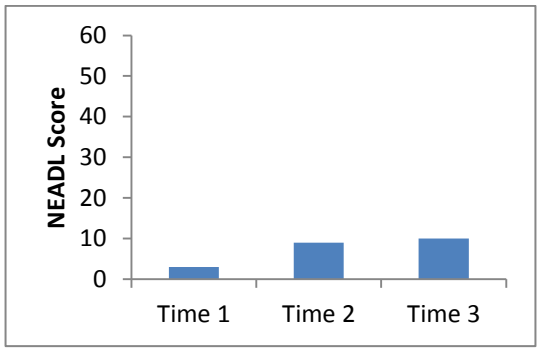


Figure 4.28. *Patient KS. Scores on the NEADL*

Scores above 8 on the anxiety measure extracted from the HADS are considered to reflect clinical anxiety. Figure 4.29 clearly indicates that KS was *high*ly anxious throughout the duration of the study, scoring above 8 at Time 1, Time 2 and Time 3.

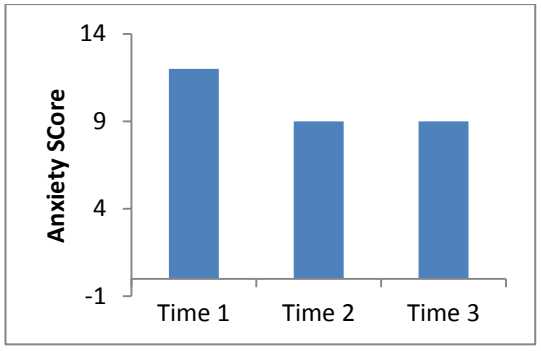


Figure 4.29. *Patient KS. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

KS took part in 22 sessions of neurofeedback training over the 6-week period, both on the acute stroke ward and at the rehabilitation unit. Across session linear regression analysis revealed no changes in baseline *beta* activity across sessions (r = -0.234, R^2 = 0.055, $F(1,14) = 1.16$, p = 0.294, see Figure 4.30). There was also no significant change in the inhibit frequencies of *theta* (see Figure 4.31) and *high beta* .

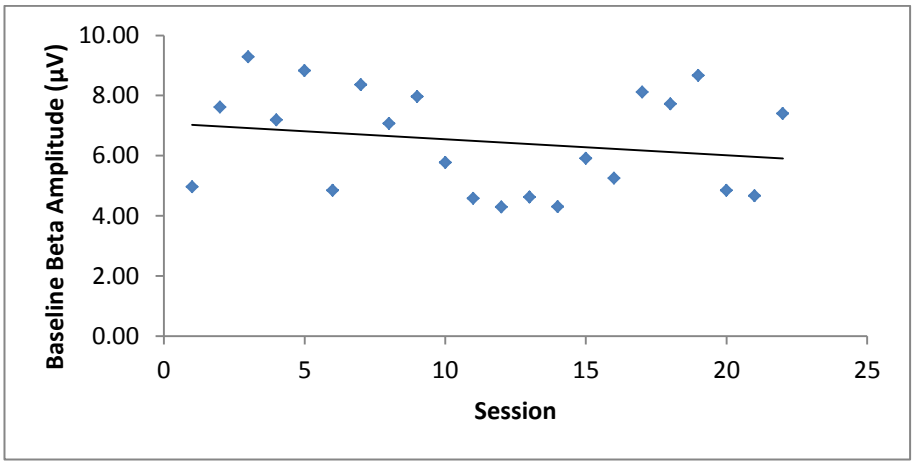


Figure 4.30. *Patient KS. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

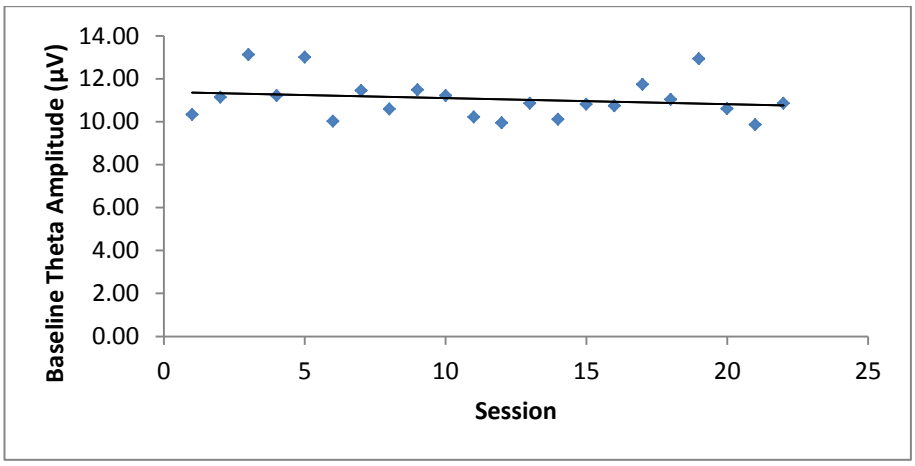


Figure 4.31. *Patient KS. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and

weeks 4-6. Figure 4.32 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of training for the 2 groups of sessions. There was no significant within session change in *beta* in weeks 1-3 (r = 0.536, p = 0.352) or weeks 4-6 (r = -0.678, p = 0.208) but figure 4.36 clearly shows a trend for *beta* activity to decrease within the training sessions in weeks 4-6 compared to weeks 1-3. This supports the negative trend seen in *beta* activity the across session data.

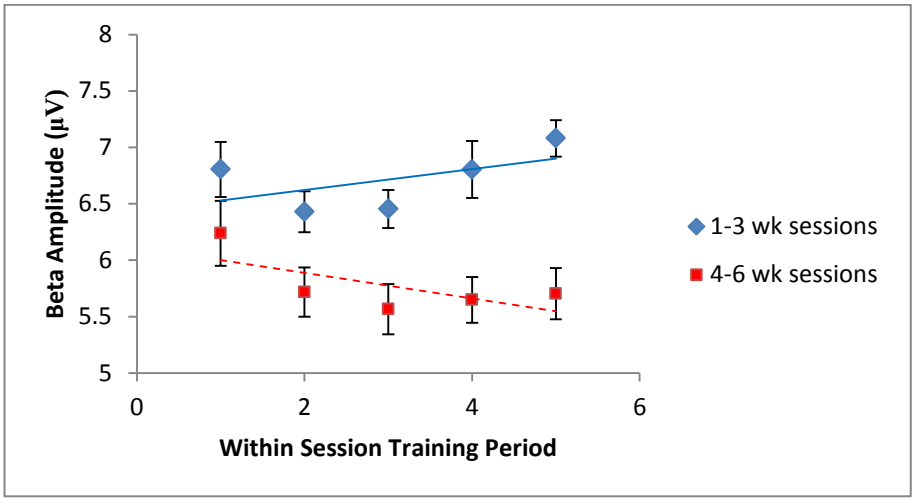


Figure 4.32. *Patient KS. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, this patient recruited, 33 days after stroke, presented with severe neglect at Time 1 and moderate/severe stroke-related deficits as measured by the NIHSS, BI and NEADL. KS required full assistance on most ADLS at Time 1 and continued to be reliant on assistance throughout the 12 weeks with little functional improvement. KS scored *high*ly on the anxiety scale, at a clinical level, at each assessment time. Analyses of across and within session EEG data showed no significant change in *beta* activity. This lack of increased *beta* activity along with the lack of improvement on behavioural and functional measures suggests this

patient did not effectively train during the neurofeedback nor did he experience any significant spontaneous recovery. This patient will be allocated to the Non-Improver group for the subsequent group analyses.

Case Study 5: Patient KH

This 66 yr patient was admitted to William Harvey Hospital with a right frontal parietal intracerebral haemorrhage. He was recruited 26 days after his stroke. At Time 1 KH presented with severe left hemiplegia which left him wheelchair bound throughout the course of the study. He was cognitively unimpaired, other than mild neglect, and enjoyed taking part in the research study.

Despite presenting with quite significant functional neglect on admission, by Time 1 this was only mild, scoring just below the cut-off for clinical neglect (see Figure 4.33). KH's score remained at this mild level throughout the study.

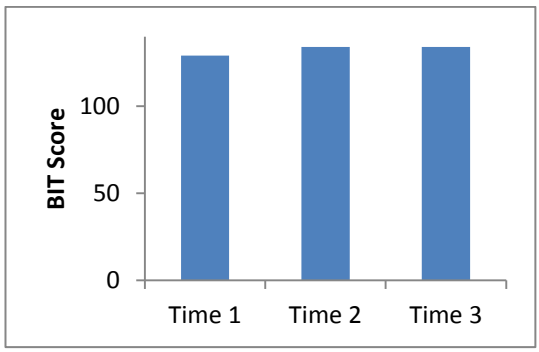


Figure 4.33*. Patient KH. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

According to the NIHSS measure presented in Figure 4.34, KH presented with moderate stroke-related deficits, again a score that showed no improvement at Time 2 or Time 3. This score largely reflects the stroke-related motor impairments KH suffered with which left him wheelchair bound.

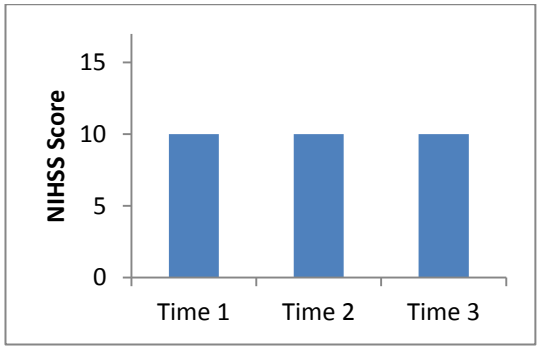


Figure 4.34. *Patient KH. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

KH's low score on the BI reflects the full assistance he required to carry out basic ADLs, largely due to his hemiparesis (see Figure 4.35). This score did show improvements at Time 2, with an increase of 6 points, where it remained at Time 3. Low scores on the NEADL remained unchanged throughout the study, *high*lighting the inability of this patient to carry out advanced ADLs and his reliance on full-time care and assistance (see Figure 4.36).

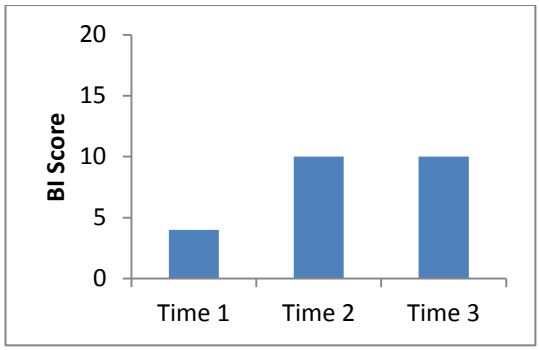


Figure 4.35. *Patient KH. Scores on BI*

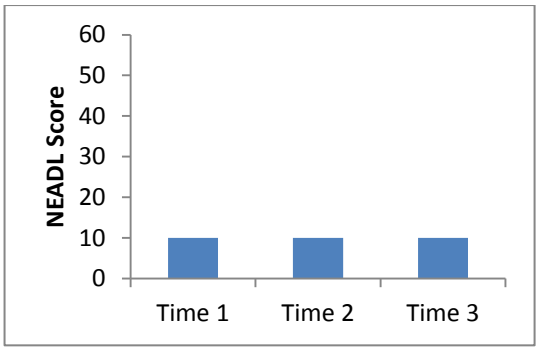


Figure 4.36 *Patient KH. Scores on the NEADL*

Figure 4.37 shows this patient experienced moderate levels of anxiety at Time 1 and Time 2 (in the normal range) with a reduction seen at Time 3.

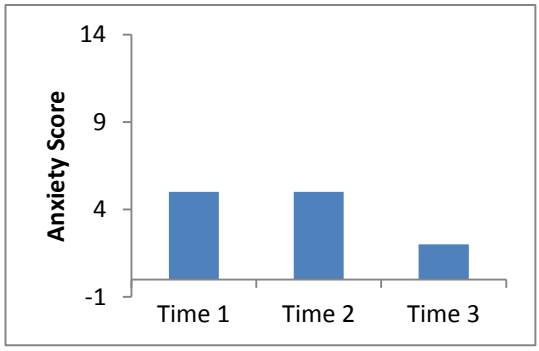


Figure 4.37. *Patient KH. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

KH took part in 15 sessions of neurofeedback training over the 6-week period, both on the acute stroke ward and at the patient's home. Across session linear regression analysis revealed no changes in baseline *beta* activity across sessions (r = 0.056, R^2 = 0.003, $F(1,14)$ = 0.04, p = 0.844, see Figure 4.38). There was also no significant change in the inhibit frequencies of *theta* (see Figure 4.39) and *high beta*.

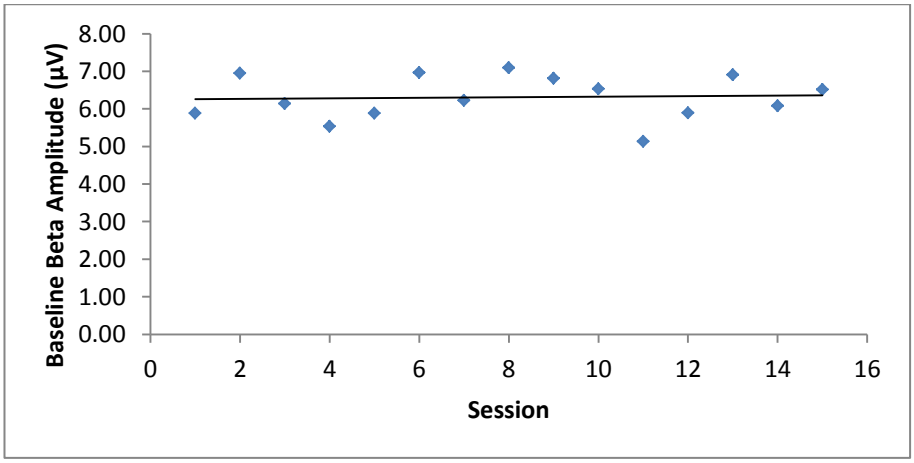


Figure 4.38. *Patient KH. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

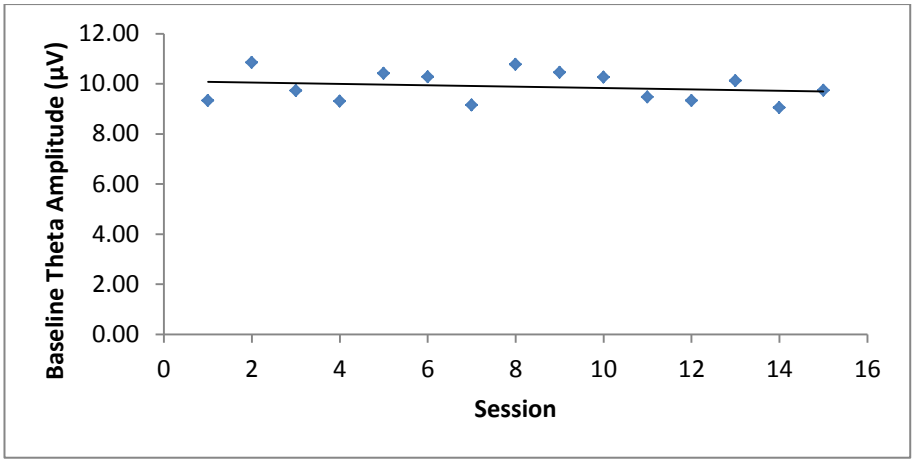


Figure 4.39. *Patient KH. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.40 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of training for the 2 groups of sessions. The data revealed no significant change in *beta* within session in weeks 1-3 (r = 0.861, p = 0.061) or weeks 4-6 (r = -0.719, p = 0.717) suggesting there no significant within session change in EEG.

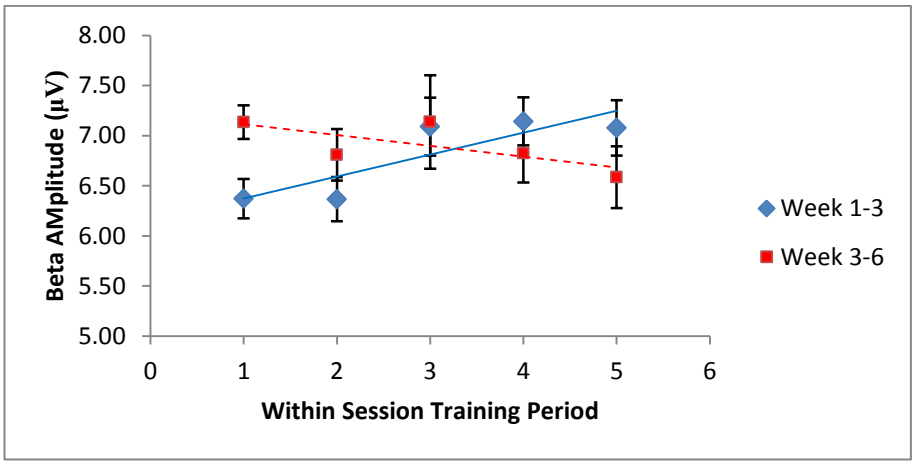


Figure 4.40. *Patient KH. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, KH presented with very mild neglect at the start of the study. Both the severity of his neglect and the extent of impairments on ADLs remained stable over the course of the study with little improvement on any of the measures. Analyses of across and within session EEG data showed no change in *beta* activity. This lack of increased *beta* activity along with the lack of improvement on behavioural and functional measures suggests this patient did not effectively train during the neurofeedback nor did he experience any significant spontaneous recovery. This patient will be allocated to the Non-Improver group for the subsequent group analyses.

Case Study 6: Patient JM

This 68 yr old patient was admitted to William Harvey Hospital with a right middle cerebral artery infarct. She was recruited 29 days post stroke. At the time of recruitment this patient suffered from extreme drowsiness and found it hard to maintain concentration for the duration of the sessions. The patient remained in a wheelchair throughout the study due to severe hemiparesis and presented with cognitive and communication deficits. She had a very supportive and caring husband who was keen for her to take part in any extra form of therapy but JM herself had difficulty engaging during assessment session and neurofeedback training sessions.

At Time 1, JM presented with severe neglect (see Figure 4.41). This did improve at Time 2 but then deteriorated back towards baseline levels at Time 3. Therefore, after the 12 week study duration, JMs neglect showed little improvement.

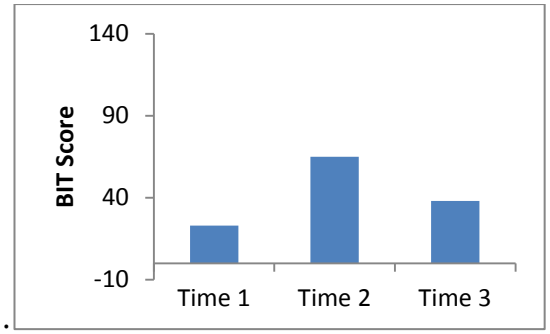


Figure 4.41. *Patient JM. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

JM's *high* NIHSS score at Time 1 (see Figure 4.42) reflected her moderate stroke-related deficits and this score did not change at Time 2 or Time 3. This reflected the lack of improvement this patient experienced in terms of physical, behavioural and cognitive deficits. In line with the lack of improvement in stroke-related deficits, the BI (see Figure 4.43) and NEADL (see Figure 4.44) scores showed no change over time. This patient continued to need full assistance on all ADLs on discharge home and so relied completely on her husband for help with all functional tasks.

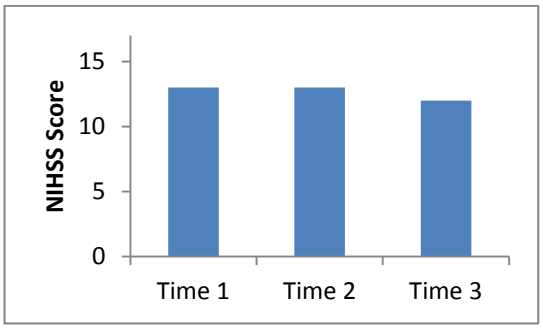


Figure 4.42. *Patient JM. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

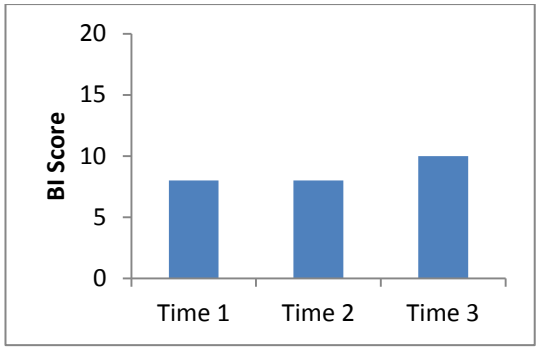


Figure 4.43. *Patient JM. Scores on BI*

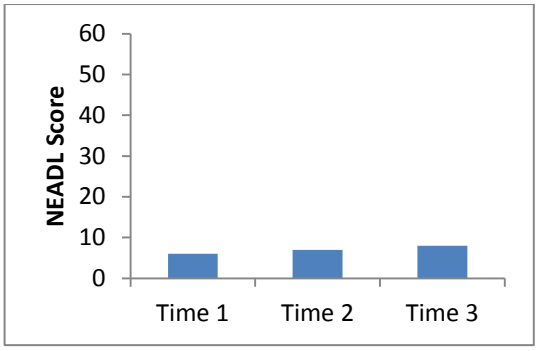


Figure 4.44. *PatientJM. Scores on the NEADL*

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Figure 4.45 illustrates that JM scored *high*ly on the anxiety measure at Time 1 but this was still in the normal range (below 8). However, JM experienced an increase in anxiety levels Time 2 and Time 3 with scores in the clinical range.

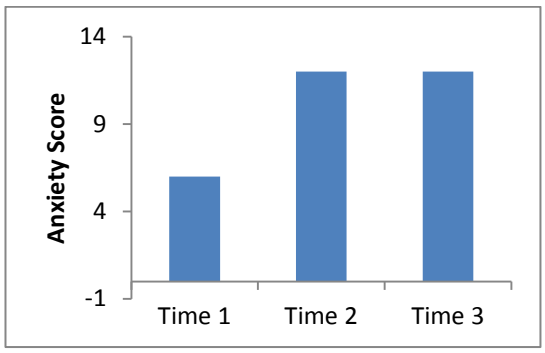


Figure 4.45*. Patient JM. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

JM took part in 27 sessions of neurofeedback training over the 6-week period, both on the acute stroke ward and at the patient's home. Across session linear regression analysis revealed no changes in baseline *beta* activity across sessions (r = 0.096, R^2 = 0.009, $F(1,23)$ = 0.20, p = 0.656, see Figure 4.46). There was a significant increase in *theta* across session however (r = 0.515, p = 0.006, see Figure 4.47). There was no significant change in *high beta* activity.

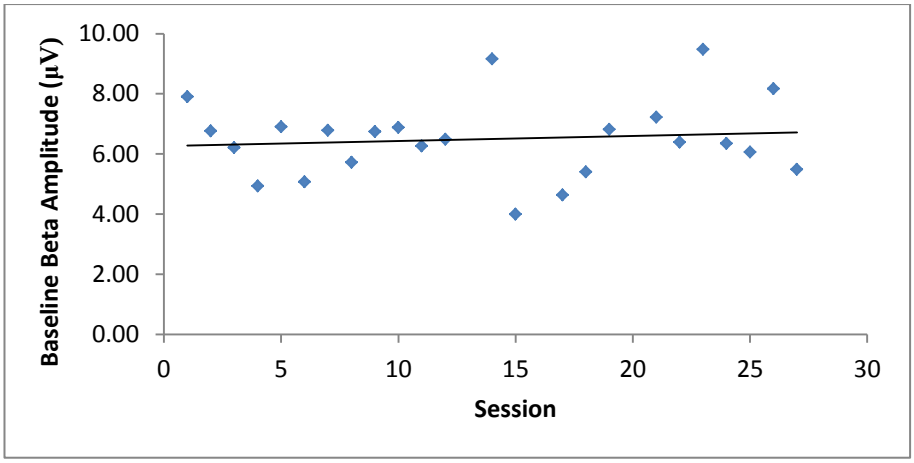


Figure 4.46. *Patient JM. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

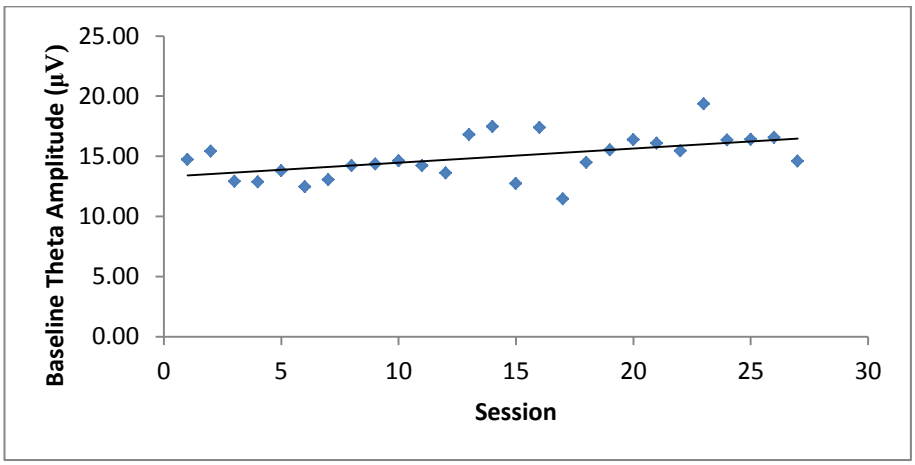


Figure 4.47. *Patient JM. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Of the 27 sessions the patient took part in she only managed to complete the full 15 minutes of training in 5 of them. Therefore the within session analyses will only include four training periods instead of five. Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.48 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of

training for the 2 groups of sessions. The data revealed no significant within session change in *beta* in weeks 1-3 (r = 0.467, p = 0.533) or weeks 4-6 (r = 0.713, p = 0.177) suggesting there was no trend to increase or decrease *beta* activity within a training session.

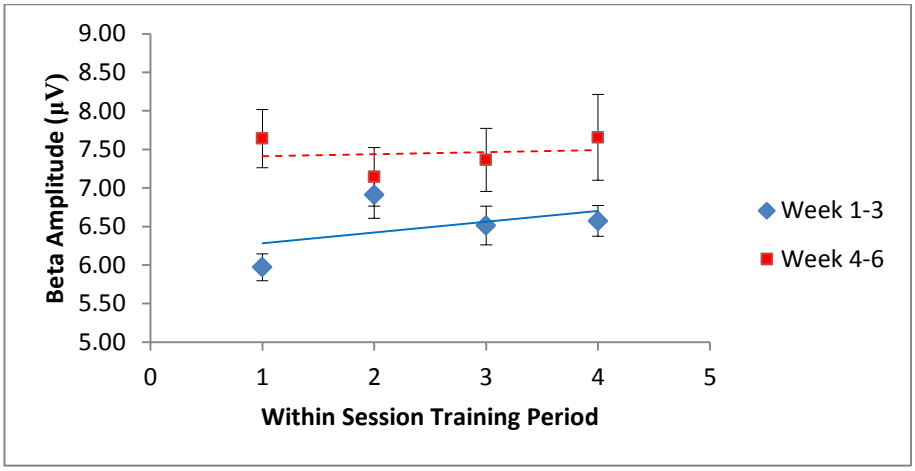


Figure 4.48. *Patient JM. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, JM presented with very severe neglect at the start of the study. Whilst the severity of neglect improved slightly at Time 2, this improvement was not sustained and had worsened by Time 3. The extent of JM's stroke-related deficits and impairments on ADLs remained stable over the course of the study with little improvement on any of the measures. Analyses of across and within session EEG data showed no change in *beta* activity but did show an increase in *theta* activity in the opposite direction of the training. This decreased *beta* activity and increased *theta* activity along with the lack of improvement on behavioural and functional measures suggests this patient did not effectively train during the neurofeedback nor did she experience any significant spontaneous recovery. This patient will be allocated to the Non-Improver group for the subsequent group analyses.

Case Study 7: Patient BS

This 72 yr old patient was admitted to William Harvey Hospital with a right middle cerebral artery infarct. She was recruited 64 days post stroke. At the time of recruitment she presented with relatively mild deficits and was cognitively unimpaired. She was motivated to take part in therapy due to a strong desire to be discharged home where she was cared for by her husband.

BS's *high* BIT score at Time 1 reflects the mild spatial deficit this patient presented with (see Figure 4.49). By Time 2 the BIT score had reached a non-clinical level where it remained at the end of the study at Time 3.

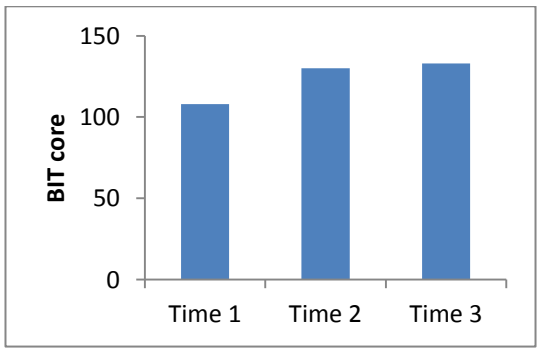


Figure 4.49. *Patient BS. Scores on the BIT. Lower scores indicate more severe neglect. Maximum score = 146, cut-off score for clinical neglect = 129.*

BS's NIHSS scores at Time 1 indicated moderate stroke-related deficits but reduced by 2 points to change the classification to mild deficits at Time 2 (see Figure 4.50). At Time 3, the NIHSS score had slightly increased, suggesting a slight deterioration in deficits.

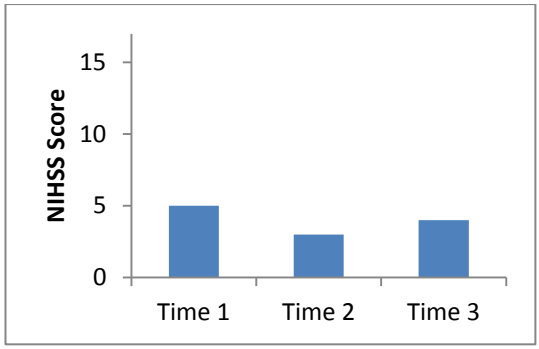


Figure 4.50. *Patient BS. Scores on the NIHSS. Higher scores indicate more severe stroke-related deficits. Classification of stroke : 0 = no stroke, 1-4 =minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, 21-24 = severe stroke*

BS's score on the BI at Time 1 indicated that this patient needed a certain degree of assistance on basic ADLs, largely due to the left-sided weakness she presented with (see Figure 4.51). The BI improved minimally at Time 2 and Time 3. At Time 1, BS had a relatively low score on the NEADL reflecting her reliance on help with advanced ADLs (see Figure 4.52). This score improved at Time 2, with the patient having been discharged home. However, this score slightly worsened at Time 3, inline with the slight worsening of the NIHSS score at Time 3.

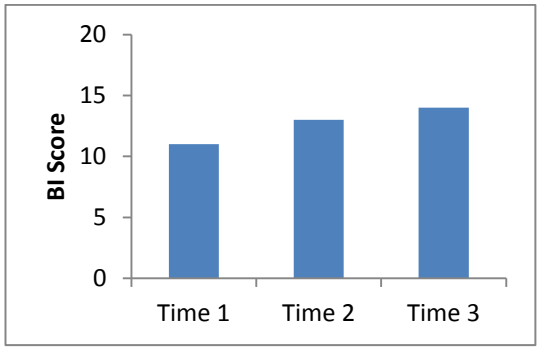


Figure 4.51. *Patient BS. Scores on BI*

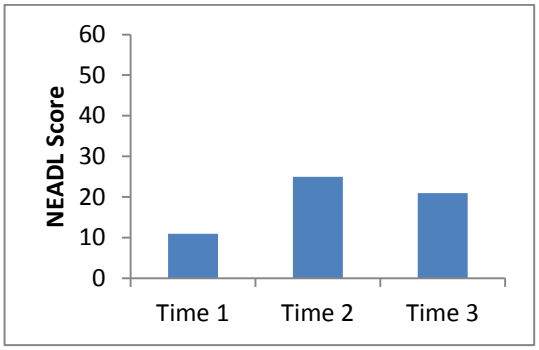


Figure 4.52. *Patient BS. Scores on the NEADL*

BS reported quite *high* level of anxiety at Time 1 which increased slightly at Time 2 and Time 3 (see Fig 4.53) but remained within the normal range (below 8). Prior to

her stroke, BS had been an active member of her local community and she reported being frustrated and embarrassed about her condition when she was discharged home. Her husband was very supportive and took her out on trips but she reported feeling anxious when not in her home environment and worried about issues such as toileting and falling. These factors could explain the small increase in anxiety BS reported at Time 1 and Time 2.

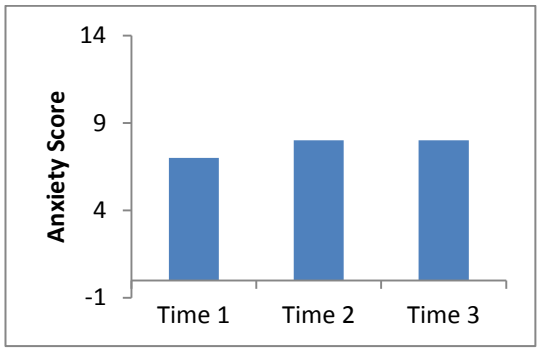


Figure 4.53. *Patient BS. Scores on the Anxiety scale (extracted from the Hospital and Anxiety Scale, HADS). Higher scores indicate higher levels of anxiety. Score > 8 indicates clinical levels of anxiety*

BS took part in 23 sessions of neurofeedback training over the 6-week period, both on the acute stroke ward and at the patient's home. Across session linear regression analysis revealed no changes in baseline *beta* activity across sessions (r = 0.012, R^2 = 0.000, $F(1,22)$ = 0.003, p = 0.957, see Figure 4.54). There was a however a significant increase in *theta* activity with session (r = 0.418, R^2 = 0.18, $F(1,22)$ = 0.047, p = 0.047, see Figure 4.55). There was no significant change in *high beta* activity.

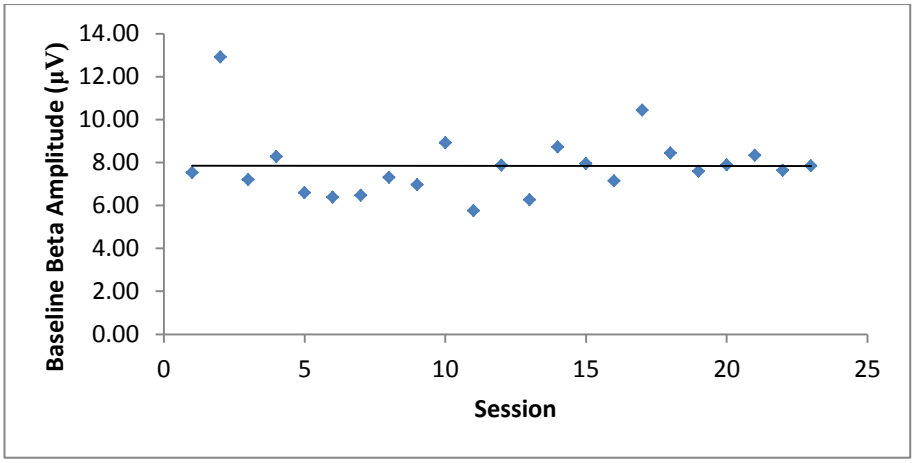


Figure 4.54. *Patient BS. Mean baseline beta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

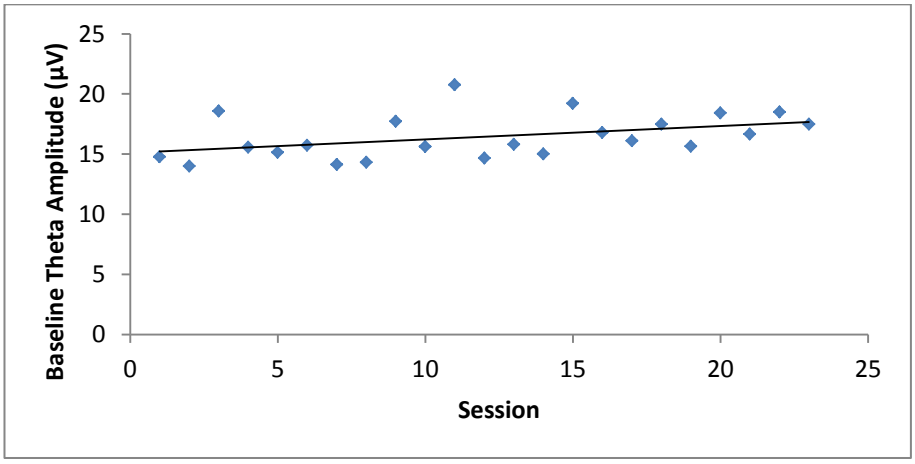


Figure 4.55*. Patient BS. Mean baseline theta amplitude as a function of training sessions. Error bars depict +/- 0.5 SEM.*

Within session data was averaged across weeks 1-3 and weeks 4-6 and correlations were conducted between training period (1-5) and *beta* amplitude for weeks 1-3 and weeks 4-6. Figure 4.56 shows the mean *beta* amplitude for consecutive 3-minute periods during the 15 minutes of training for the 2 groups of sessions. The data revealed no significant within session change in *beta* in weeks 1-3 (r = 0.852, p = 0.067) or weeks 4-6 (r = 0.470, p = 0.424) suggesting there was no trend to increase or decrease *beta* activity within a training session.

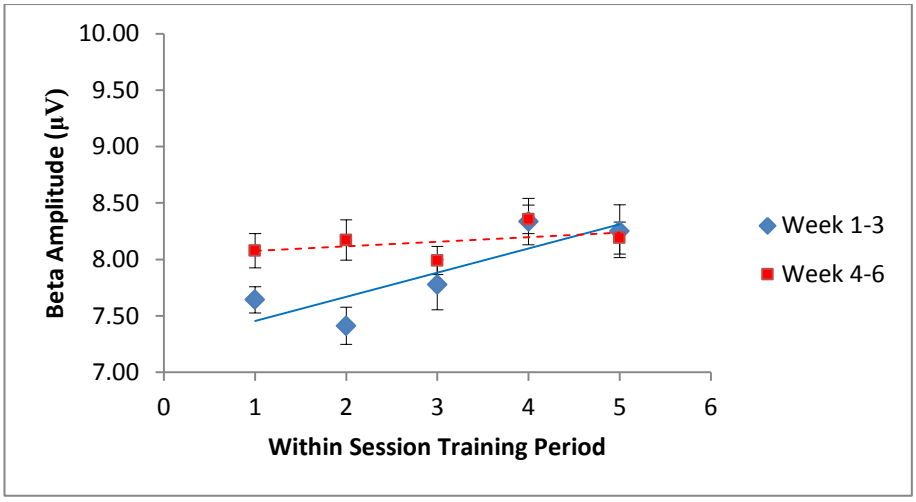


Figure 4.56. *Patient BS. Mean beta amplitude for the five training periods collapsed across weeks 1-3 and weeks 4-6. Error bars depict +/- 0.5 SEM*

In summary, BS initially presented with a mild case of neglect which remediated by Time 2. However, her stroke-related deficits and functional ability on ADLs remained impaired across the study, even showing slight signs of deterioration at Time 3. There was no change in *beta* activity over time but BS did show an increase in *theta* activity with session. Her anxiety levels remained *high*er than most patients at all time points. This patient will be allocated to the Non-Improver group for the subsequent group analyses.

4.3.2. Hypothesis 1) Within session evidence of increased neural excitability

Each training session consisted of five 3-minute training periods during which patients were asked to maintain *beta* amplitude above threshold. In order to ascertain whether patients showed evidence that they were able to modulate *beta* amplitude with increasing success during a session, mean *beta* amplitude for each 3-minute training period were extracted and averaged across all training sessions. Correlations were then conducted to see if there was a relationship between *beta* amplitude and training period, see Table 4.3.

Table 4.3. Correlation coefficients between *beta* amplitude and training period (five 3-min periods) for individual patients averaged across all sessions.

Patient ID	Correlation Coefficient	P value
HB	0.804	0.101
PS	0.224	0.717
RK	-0.984	0.002*
KS	-0.079	0.900
KH	0.615	0.270
JM	0.792	0.110
BS	0.789	0.112

**significant correlation*

Five (HB, PS, KH, JM, BS) of the seven patients showed a trend, defined as a positive correlation coefficient, to increase *beta* amplitude across the five training periods of the sessions, however none of these correlations reached significance. Conversely patients RK and KS showed a negative correlation with a trend to reduce *beta* amplitude across the five training periods. Given the lack of *significant* increases in *beta* amplitude in any of the patients it is not possible to conclude that neurofeedback training has induced neuroplastic changes in these right hemisphere stroke patients in the acute post-stroke phase.

4.3.3. Hypothesis 2) Baseline predictors of improved *beta* amplitude across the study period

Despite the lack of supporting evidence from the within session data that EEG neurofeedback training can have a direct effect on the modulation of specific EEG frequency bands, the second aim of this study was to investigate whether recovery in these patients was associated with an increase in *beta* activity. The case studies presented in the previous section confirm that a sub-group of 3 patients showed an increase in *beta* activity over the 6-week training period, defined by a significant correlation between session and *beta* amplitude, and these were classed as Improvers, whilst the remaining 4 patients showed no improvement, these were classed as Non-Improvers. Since the primary aim of this study was to investigate a relationship between *beta* activity and behavioural and functional abilities, a group analysis was conducted on these two groups. Table 4.4 details patient group allocation along with the correlation coefficient corresponding to the relationship between *beta* amplitude and session.

Table 4.4. Correlation between baseline *beta* amplitude and session for individual patients.

Patient	*Beta* and session correlations	Group
HB	0.396*	Improver
PS	0.905*	Improver
RK	0.685*	Improver
KS	-0.234	Non-Improver
KH	0.056	Non-Improver
JM	0.096	Non-Improver
BS	0.012	Non-Improver
	**significant correlation*	

Table 4.5 summarizes group information. Mann Whitney U Tests did not reveal any statistical differences between groups on age, number of days since stroke or number of neurofeedback sessions.

Table 4.5. Summary of Groups: *Summary of group information based on mean age, mean number of neurofeedback training sessions and mean number of days patients were recruited following stroke (standard deviations in parentheses).*

	Mean Age	**Mean No. of days since stroke**	**Mean No. of Sessions**
Improver Group	48.67	26.33	17.66
(n = 3)	*(29.14)*	*(31.56)*	*(6.50)*
Non-Improver Group	67.00	38.00	19.50
(n=4)	*(4.16)*	*(17.57)*	*(5.35)*

Given the small sample sizes, Mann Whitney U Tests were conducted to investigate whether there were any statistical differences between groups on mean scores for each of the baseline measures: BIT, NIHSS, NEADL, BI, Anxiety (extracted from the HADS) and Depression (extracted from the HADS) (see Figure 4.64 and Figure 4.65 for group mean data and Table 4.4 for individual patient scores on all assessments). The only measure to prove statistically different was Anxiety (U = 12.00, Z = -2.141, p = 0.032) with the Improver group having lower anxiety levels than the Non-Improver group. This finding suggests that initial anxiety level could be a predictor of EEG modulation in the form of increased *beta* activity during the recovery period after stroke. There was no association between group categorisation and neglect severity as measured by the BIT (although the data suggests that the

Improver group had more severe neglect compared to the Non-Improver group), stroke-related deficits or independence on ADLs.

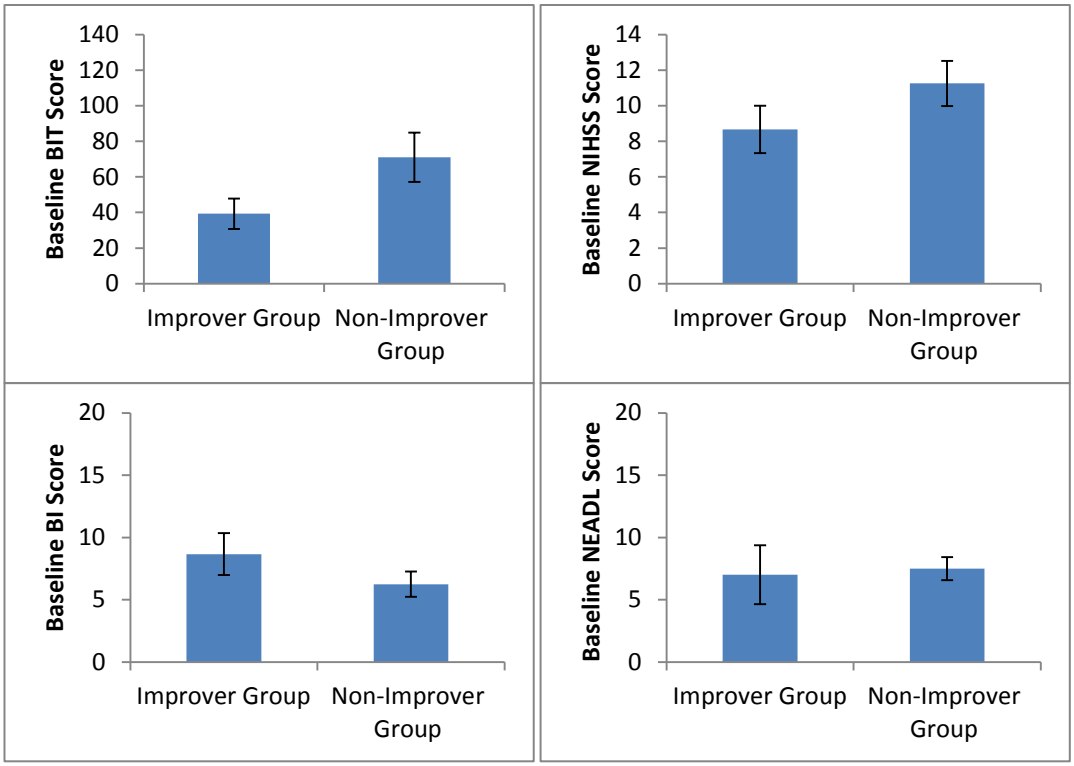


Figure 4.57. *Mean baseline scores for each group on all assessment measures including the BIT, NIHSS, NEADL and BI. Higher scores on the BIT, NEADL and BI indicate less severe deficits whereas lower scores on the NIHSS indicate less severe deficits. Error bars depict +/- 0.5 SEM*

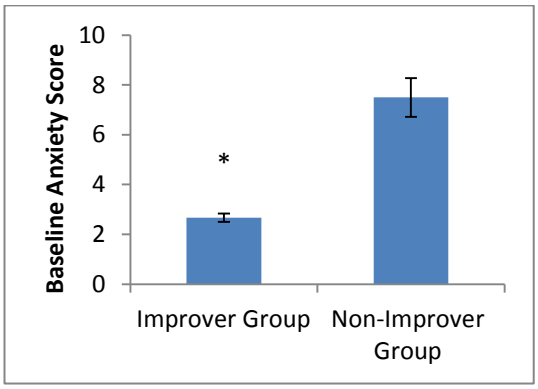


Figure 4.58 *Mean baseline scores for each group on anxiety extracted from the HADS. Higher scores indicate a higher level of anxiety. Error bars depict +/- 0.5 SEM. * denotes significant group difference ($p < 0.05$)*

In order to establish group differences in EEG activity, the mean *beta* amplitude was extracted from the baseline period of session 1, see Figure 4.66. This baseline amplitude therefore corresponds to the baseline assessment measures. Non-parametric Mann Whitney U Tests revealed a non-significant group difference ((*U* = 1.00, Z = -1.77, *p* = 0.077) with the Improver group having a lower *beta* amplitude (M = 4.83, SE = 0.33) compared to the non-Improver group (M = 6.56, SE = 0.73). Experiment I examined EEG abnormalities in neglect patients in comparison to age-matched controls and found increased activity at the lower end of the spectrum with decreased activity at the *high*er end of the spectrum. Given the only significant difference between the groups on behavioural measures was a decreased level of anxiety in the Improver group; this data suggests that an increased *beta* amplitude is compatible with increased levels of anxiety although this group difference was non-significant so must be interpreted with caution. Similarly, given the greater degree of neglect deficits (as measured by BIT, albeit non-significant) in the Improver group compared to the Non- Improver group, the data suggests there could be a trend for this abnormal EEG profile to become more exaggerated with more severe cases of neglect. The data is also compatible with the possibility that patients with more deviant EEG activity are more likely to spontaneously recovery.

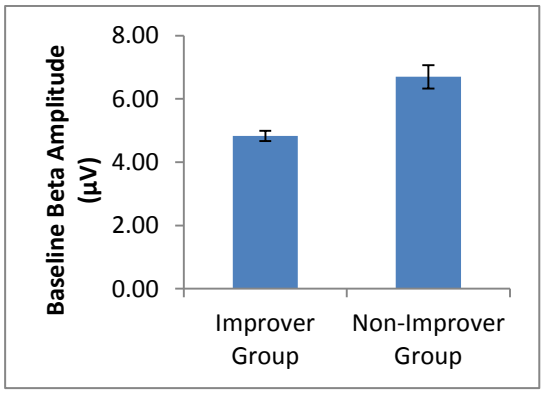


Figure 4.59. *Mean baseline beta amplitude for each group recorded during the first session of neurofeedback training. Error bars depict +/- 0.5 SEM.*

4.3.3. Hypothesis 3) Group Analyses of Outcome Measures

In order to assess improvements in behavioural measures over the 12 week period patients were re-assessed on all baseline measurements at Time 2 (after 6 weeks of neurofeedback training) and Time 3 (after 6 weeks of no training). In order to compare group differences across time, two change scores were calculated: change score 1 was calculated by subtracting the mean on each assessment at Time 1 from Time 2, while change score 2 was calculated by subtracting the mean on each assessment at Time 2 from Time 3. Non-parametric comparison of the means failed to reveal any statistical group differences, other than a significant improvement in NIHSS change score 1 in the Improver group in comparison to the Non-Improver group already reported. Therefore, the data presented below will be discussed descriptively so caution must be taken when interpreting the findings.

BIT

No significant group differences were revealed in the change scores between the two groups. Descriptively, the Improver group showed a reduced change score between Time 2 and Time 3 (during which they did not receive any neurofeedback training) compared to Time 1 and Time 2 (during which they received neurofeedback), see Figure 4.67. Given the non-significant within-session training effects, this finding could represent a variable rate of spontaneous recovery with a faster rate during the first 6 weeks than the last 6 weeks. Since this group showed a significant increase in *beta* activity over the 6-week period corresponding to the greatest improvement in BIT score, there is evidence for a correlation between enhancement of *beta* activity and improvement in neglect severity. The same rate of increase in scores on the BIT

was not observed in the Non-Improver group. Again, supporting evidence for a relationship between *beta* activity and neglect severity. This group showed no signs of *beta* enhancement corresponding to a smaller change in neglect symptoms. The Non- Improver group also showed a negative change score between Time 2 and Time 3 compared to Time 1 and Time 2 showing a slight worsening of symptoms by the end of the study.

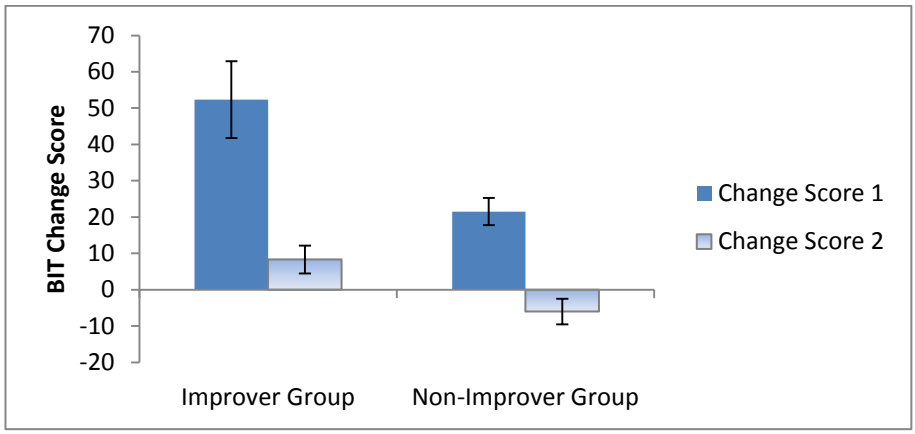


Figure 4.60. *Mean change scores on the BIT. Change score 1 = score at Time 2 minus score at Time 1. Change score 2 = score at Time 3 minus score at Time 3. Error bars depict +/- 0.5 SEM*

NIHSS

In order for all scores on the assessments to correspond with each other, the NIHSS scores were inverted so a positive change score now indicates an improvement in the same way as the BIT, BIT and NEADL. The Mann Whitney U Test comparing change score 1 in both groups revealed a significant difference (U = 3.00, Z = -2.160, p = 0.031), with the Improver group showing a significantly larger improvement in scores after the 6-week neurofeedback training period than the Non-Improver Group. This suggests a correlation between improvements on stroke-related deficits with increased *beta* activity. This improvement was negligible between Time 2 and Time 3, following a similar pattern to the BIT scores. The Non-

Improver group showed very little change across the duration of the study suggesting a lack of improvement of stroke-related deficits corresponding with a lack of change in *beta* activity.

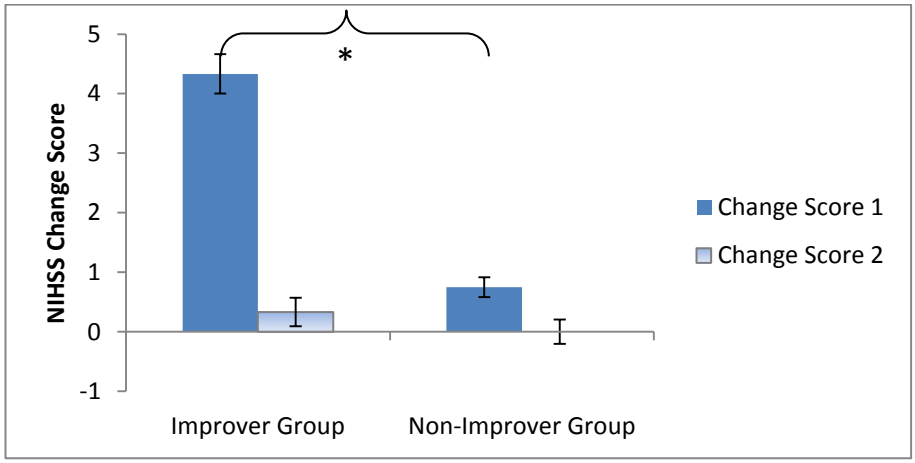


Figure 4.61. *Mean change scores on the NIHSS. Change score 1 = score at Time 2 minus score at Time 1. Change score 2 = score at Time 3 minus score at Time 3. Error bars depict +/- 0.5 SEM. * denotes significant group difference ($p < .05$)*

BI and NEADL

No significant group differences were revealed in the change scores between the two groups on either the BI or the NEADL. The BI and NEADL both represent measures of independence in ADLs and the change scores in Figure 4.69 show a similar pattern for both as would be expected. The Improver group showed a much greater improvement on both scales during the first 6 weeks compared to the Non-Improver group. This trend corresponds with the faster rate of improvement in both neglect deficits and stroke-related deficits in this group over the neurofeedback training period. This rate of improvement was greatly reduced between Time 2 and Time 3, a similar pattern reported on the BIT and the NIHSS. The improvement in scores in

the Non- Improver group was not as notable as the Improver group during the first six weeks and also showed little change between Time 2 and Time 3.

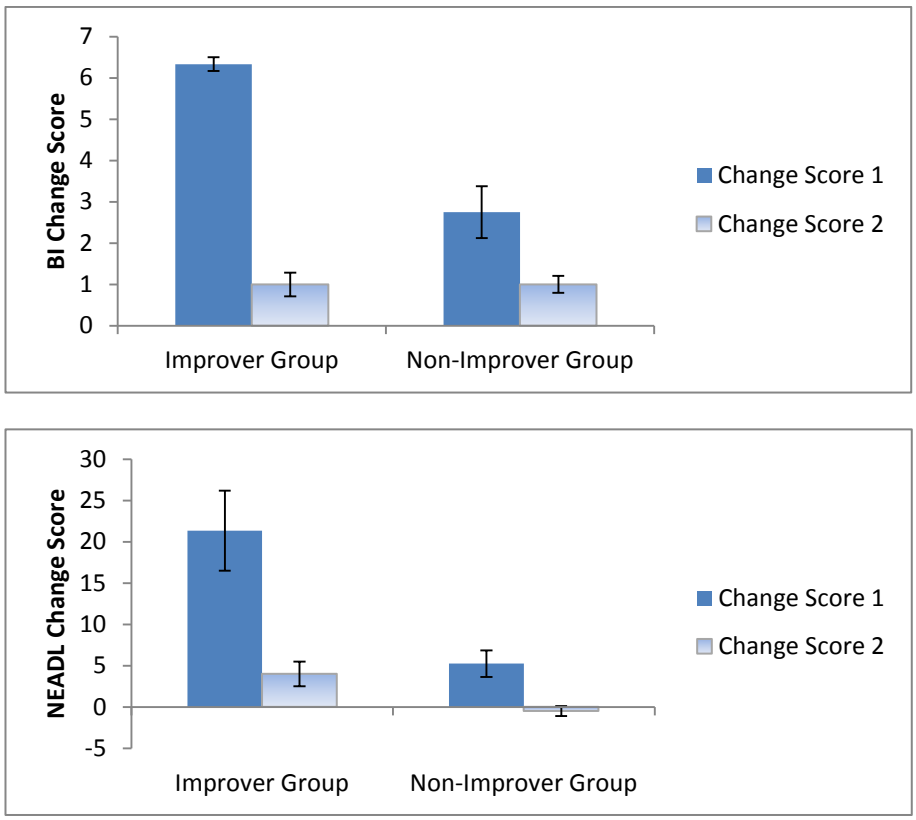
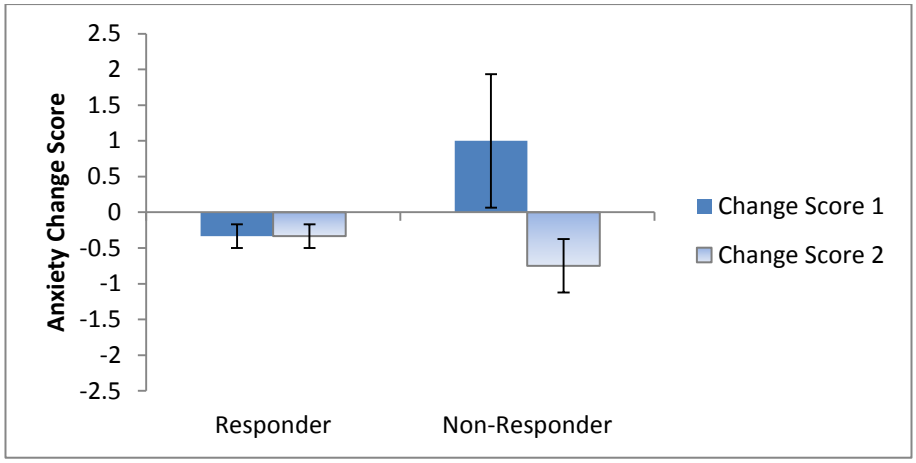


Figure 4.62. *Mean change scores on the BI and NEADL. Change score 1 = score at Time 2 minus score at Time 1. Change score 2 = score at Time 3 minus score at Time 3. Error bars depict +/- 0.5 SEM*

Anxiety

No significant group differences in anxiety were revealed in the change scores between the two groups. The anxiety change scores in general were negligible (less than 1) so can be interpreted as being stable throughout the 12 week study, see Figure 4.70.



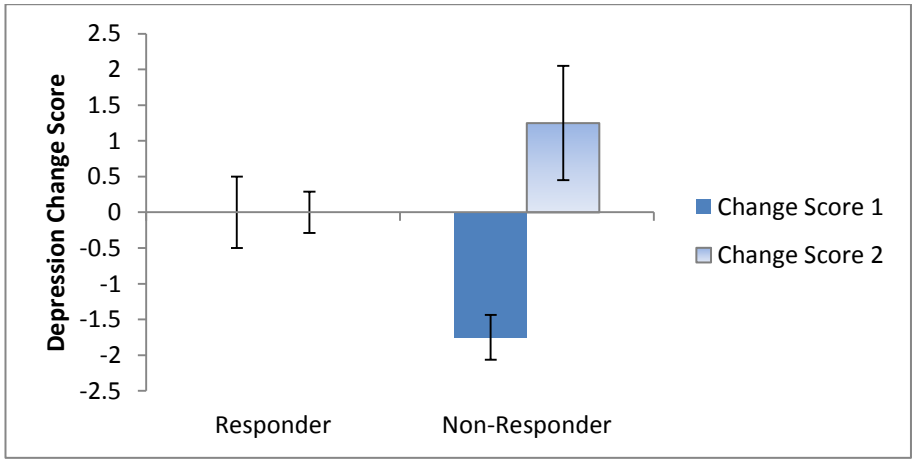


Figure 4.63. *Mean change scores in Anxiety (top table) and Depression (bottom table), extracted from the HADS. Change score 1 = score at Time 2 minus score at Time 1. Change score 2 = score at Time 3 minus score at Time 3. Error bars depict +/- 0.5 SEM*

4.3. Discussion

The primary aim of this study was to investigate how EEG activity corresponds to recovery in patients with hemispatial neglect. Since *beta* activity has been linked to tonic alertness (Valentino et al, 1993; Arruda et al, 2007) and tonic alertness has been shown to be severely impaired in neglect patients (Malhorta et al, 2009; Lazaar et al, 2002; Buxbaum et al, 2004; Samuelsson, 1998), one goal of this study was to determine whether there was indeed a link between *beta* activation and severity of impairments. This is the first study known to provide a detailed account of how

EEG activity changes after stroke through the continual monitoring of baseline EEG across a six-week period.

Experiment I provided supporting evidence for an abnormal EEG profile in hemispatial neglect through a comparison of resting state EEG with age-matched controls. One of the significant findings from Experiment I was that *beta* activity was greatly reduced in neglect patients. This abnormal EEG activity supports previous suggestions that a deficit in tonic alertness is a major contributing component in the manifestation of neglect. Therefore, it follows that normalization of EEG, specifically of *beta* activity, should correspond to a reduction of neglect symptoms. Experiment III provides supporting evidence for this hypothesis by reporting that patients who showed an increase in tonic *beta* activity over a 6-week period, i.e. the Improver group, also showed a corresponding significant improvement in NIHSS scores in comparison with patients who failed to show a change in *beta* activity. If *beta* activity is considered to be a measure of alertness, the findings of this study suggest that an improvement in alertness is associated with a general improvement in stroke-related deficits in neglect patients.

In order to determine whether there were any factors distinguishing patients who showed increased *beta* activity from those who did not, baseline EEG and behavioural measures were compared across groups. Interestingly, anxiety proved to produce the only significant difference, with low anxiety corresponding to patients who showed an increase in *beta* activity over time. This finding suggests that anxiety could be a predictor of EEG normalization and behavioural recovery. This

deserves further investigation in future studies as it has implications for rehabilitation studies. The second distinguishing group factor was baseline EEG activity. The initial *beta* activity was lower (but not significantly) in patients who went on to show increased *beta* over time. This finding is inline with Keller (2001) who reported increased *beta* activity across sessions in a sub-group of patients who had significantly lower baseline levels of *beta* activity. Both findings suggest a relationship between baseline EEG deviations and potential for normalization, with more extreme deviations in EEG associated with a *high*er rate of change over time.

There was a trend for patients who showed increased *beta* activity across sessions to have more severe neglect, as measured by the BIT, although this was not significant. This tentative conclusion points to a relationship between neglect severity and EEG modulation. If patients are able to modulate their EEG despite having more severe neglect deficits this has significant implications for future therapy. The trend for reduced *beta* amplitude at baseline to be associated with more severe neglect corroborates the findings of Experiment I which reported a significant relationship between neglect and a distorted EEG profile characterised by decreased *beta* activity.

Since all patients received neurofeedback training, the second goal of Experiment III was to attempt to establish whether EEG changes were a result of spontaneous recovery or the neurofeedback training itself. Of the seven patients recruited to the study, only three showed evidence of increased *beta* activity over the six week period of recording. Therefore, it can be concluded that these patients experienced

EEG normalization either as a result of spontaneous recovery or in response to the neurofeedback training. The changes in baseline tonic *beta* levels alone do not permit for a training effect to be attributed. However the within session results provide more insight. Since the training protocol required patients to increase *beta* activity in order to receive positive feedback, an increase in *beta* activity during the training period would indicate improved performance and a learning effect over the course of a 15 minute period with no feedback. None of the patients showed a significant correlation between *beta* activity and within session training period so it is not possible to attribute any improvements in baseline EEG or behavioural sympotoms to the neurofeedbacktraining. It is more likely that the change in tonic *beta* activity reported in the three patients in the Improver Group (HB, PS and RK) across sessions were a consequence of EEG normalization due to spontaneous recovery. However, given that five of the seven patients showed non-significant positive correlations between baseline *beta* activity and within session training period, there could still be grounds to further investigate the effectiveness of neuorfeedback training in this patient population. If anything, one would expect *beta* activity to decrease within the training session as patients found it increasingly more difficult to sustain their attention. Keller (2001) suggests that an improved ability to maintain *beta* activity at a *high* level within session is an indicator of an improved ability to sustain attention.

When making the distinction between spontaneous recovery and training effects it is also important to note that RK, who showed a significant negative correlation between *beta* activity and within session training period, was a young 20 year old patient. The lack of within session training effect related to RK could be due to an

age-related response to the feedback itself. Perhaps the reward in the form of the continual playing of the nature video was not as motivating for this patient as it was for the older patients. This *high*lights the need to carefully consider the form of feedback employed by a study and to tailor this to the audience. Given RK was extremely motivated she may have benefited from a more competitive form of feedback. For example, a continual performance-based score may have been more effective and engaging as a form of feedback for this patient. Several neurofeedback studies with children have used a game-based feedback similar to that of a computer game, such as rocket races and Pac Man, in an attempt to engage the children (Beauregard and Levesque, 2006; Fuchs et al, 2003). The type of feedback presented to these patients was given a lot of consideration with emphasis placed on feedback that would hold the attention of these severely under-aroused patients. The nature videos used in this study were chosen for specific reasons. Firstly, videos which relied on heavy dialogue were avoided because the continual pausing would have disrupted the flow of the story which would have been very frustrating for the viewer. Secondly, videos which would elicit a strong emotional response were avoided as this could have impacted on the EEG activity in an unknown way. Thirdly, since the video paused for an undetermined amount of time throughout the fifteen minute training period, the patient would not watch the entire video clip for each session. Therefore, the first minute of the video seen in the following training session would not immediately follow from the end of the video clip from the preceding session. The nature videos were advantageous in this respect because they did not require the patient to follow a story per se and were entities in themselves. In general, patients enjoyed the feedback selected for this protocol, finding the content engaging and interesting. Therefore future healthy and clinically-based studies

should consider a similar form of feedback. Further research should also seek to investigate the impact of different forms of feedback with particular attention to age-related and symptom-related groups.

When considering an intervention for any condition, there are two major factors that must be addressed. Firstly, any beneficial effects should translate into behavioural and functional abilities that will improve the standard of living of the patients. Secondly, an intervention should have long-term beneficial effects rather than a transient remediation of symptoms. Prism adaptation is one form of rehabilitation that has received a great amount of attention. Studies have shown that this intervention results not only in a reduced spatial bias as measured on paper-and-pencil tasks but also in improvements on a variety of behavioural aspects, including wheelchair navigation and postural balance. However, these improvements have not been proven to be permanent with several studies reporting only very short-term effects (see Ladavas et al, 2011 for review).

The findings of this study would have been complemented by the addition of a quantitative EEG measure included alongside the behavioural assessments. This would allow for a more detailed inspection of EEG dynamics across hemisphere and resting-state recordings in both the eyes-open and eyes-closed conditions. This study had originally intended to include this assessment but, upon piloting this with patients, it was not a suitable assessment for such an acute and severely impaired cohort of patients. The baseline recording obtained from the single electrode neurofeedback sessions was a much more convenient and less time-consuming

measure that could be recorded regularly and which was able to be consistently recorded in every patient.

This study recruited acute neglect patients in order to maximise the chances of being able to manipulate EEG changes through the training since it is during this period post-stoke that the brain is most plastic. Recruiting acute patients is also easier than trying to find chronic neglect patients, as all patients admitted to hospital can be screened on admission and followed up throughout their recovery on the hospital wards. However, in order to disentangle spontaneous recovery from intervention effects, recruiting patients with chronic neglect may provide more insightful results.

CHAPTER 5: GENREAL DISCUSSION

5.1. Thesis Rationale

The motivation for this thesis was born out of the extensive literature pertaining to non-spatial deficits of hemispatial neglect. Tonic alertness is a factor that has been implicated in spatial attention, both in the healthy population and clinical populations of ADHD and neglect. Given that EEG studies have found correlates between specific EEG frequency bands and levels of tonic alertness, this thesis explored the EEG profile of neglect. The primary goal was to ascertain whether the EEG profile of neglect was abnormal in comparison to age-matched healthy control with the prediction that it would be similar to that of ADHD, with increased activity of slow wave frequencies and decreased activity of fast wave frequencies. If this proved to be the case, it would lay the foundations for the use of an alertness-based intervention for neglect, namely EEG neurofeedback.

5.2. Evaluation of Results and Implications for Future Research

Is hemispatial neglect associated with an abnormal EEG profile?

The first aim of this thesis was to determine the EEG profile of hemispatial neglect. Only a handful of studies have recorded quantitative EEG in neglect patients and each of these studies has focussed on the lower end of the frequency spectrum, reporting increased *delta* and *theta* activity (Watson et al, 1977; Demeurisse et al, 1998; Colson et al, 2001). It is unclear why these studies did not report EEG data from fast frequency bands such as *beta*, although this could be because this

frequency range is more likely to be contaminated by muscle artefact (Finnigan et al, 2007). There is strong evidence to suggest a relationship between stroke-induced brain injury and increased *delta* activity and this was evident in the findings of Experiment I. However, the frequency bands which proved to be consistently and significantly reduced in patients compared to age-matched controls, in both the eyes-open and eyes-closed conditions, were *SMR* and *beta*. The predicted increase in *theta* activity in neglect patients compared to healthy controls was not found. The ADHD literature has reported increased *theta* at frontal and central sites (Mann et al, 1992, Monastra et al, 1999, Lubar et al 1996). Since the analysis in Experiment I averaged over central and parietal sites only, this could explain the different results.

Experiment 1 also reported significantly reduced *alpha* power over the injured right hemisphere and a non-significant reduction over the left hemisphere compared to age-matched controls. This is inline with the reduced *alpha* power that has been reported in ADHD (Loo et al, 2009); evidence that seems to contradict previous suggestions that decreased *alpha* power is associated with increased arousal. In an attempt to unravel these dissociations between *alpha* activity, *beta* activity and arousal, the findings of Experiment I could be extended to include a direct measure of arousal, such as skin conductance level. Barry et al (2004) found no correlation between *beta* activity and skin conductance and suggest that *beta* represents a measure of task-related alertness rather than arousal. Since it is this task-related alertness which is critical in neglect patients, *beta* activation is the better target for an intervention study.

Experiment I also reported that neglect was associated with a significantly reduced peak *alpha* frequency. Since previous studies have reported a relationship between decreased alertness and decreased peak *alpha* frequency (Newman et al, 1992; Knott, 1988) this finding provides further support for a hypoarousal model of neglect. This finding also corroborated Juhasz et al's (1997) finding that large parietal lesions are associated with a reduced peak *alpha* frequency over both hemispheres. Peak *alpha* frequency would be more reliable as an index than power or amplitude values because frequency is more immune from pre-processing and artefact methodologies and more consistent across different experimental studies (Bazanova, 2012). Therefore, future studies should aim to corroborate this finding and determine whether peak *alpha* frequency is a reliable index for alertness. When considering neurofeedback protocols, peak *alpha* frequency training could also prove beneficial to this group of patients given the statistically reduced frequency reported here. Angelakis et al (2007) reported preliminary evidence from six healthy elderly participants, three of whom were allocated to a neurofeedback protocol to increase peak *alpha* frequency, two of whom were allocated to a neurofeedback protocol in increase *alpha* power and one of whom was allocated to a sham feedback group. Both experimental groups successfully managed to increase the peak *alpha* frequency or peak *alpha* power relevant to the training protocol. Interestingly, each protocol was associated with different cognitive improvements. The *alpha* peak frequency group was associated with a general improvement in speed of processing and executive function and the *alpha* power group was associated with improved memory. This pilot data suggest differential cognitive effects of frequency and power training and supports the findings of Experiment II that older adults are capable of showing EEG modulation through neurofeedback training. This line of

research should be further explored in the healthy population and extended into clinical conditions with associated deficits of alertness such as neglect.

The additional finding of a hemisphere asymmetry within the neglect patient group provokes further ideas for rehabilitation. Experiment I reported reduced power at the *high*er end of the spectrum in the damaged hemisphere in comparison to the undamaged hemisphere. The age-matched controls confirmed symmetrical activity in a healthy brain. Therefore, future therapies could direct their attention to reducing this hemispheric asymmetry using a neurofeedback training protocol to specifically reward increased activity over the damaged hemisphere in order to normalize the imbalance.

Whilst this study had a relatively small patient group, the differences reported here comparing patients to age-matched controls did reach significance and therefore can be regarded as reliable indicators of the true EEG profile of neglect. All of the neglect patients recruited to this study were within the 3 month post-stroke phase and considered to be acute neglect patients. Therefore, whilst patients are likely to have experienced some form of spontaneous recovery since stroke onset, it is hoped that this EEG reflects acute electro-dynamic abnormalities before permanent functional compensation and reorganisation has taken place. Future research should aim to investigate EEG patterns in a larger sample of patients. Of particular interest would be to compare right-sided stroke patients with neglect with right-sided stroke patients without neglect. This comparison could further our understanding of

electrophysiological markers specific to hemispatial neglect and even allow early identification of patients who are likely to be affected by the syndrome.

When considering how to extend the work of Experiment I it is important to consider the challenges this study faced. Quantitative EEG acquisition is fraught with practical issues and would be unfeasible in many clinical settings. Firstly, recording quantitative EEG in acute patients is often not possible due to the patient being bed-bound, medically unstable and too drowsy. Neglect patients often have extremely poor sitting balance, often leaning to the right, which means they are unable to sit comfortably in a chair. Not only does this have implications for setting up the recording equipment but also prevents the experimenter being able to position themselves appropriately in order to fit the cap and gel the electrodes. Therefore, the less dense the electrode array needed, the more feasible quantitative EEG recording becomes. Experiment III used the EEG recorded during the baseline of the neurofeedback sessions to extract baseline EEG measures for all frequency bands. This method requires only one active scalp electrode but can also be done using a bipolar set-up with two electrodes. This could provide a quicker, more comfortable way of acquiring EEG data from severely impaired patients, including those who are bed-bound.

Are older adults able to modulate their EEG through neurofeedback training?

The motivation behind Experiment II was to determine whether older adults are able to modulate their EEG through ten session of neurofeedback training, as has

previously been shown in studies with younger adults. This is the first study known to the author to explore the effectiveness in healthy older adults of neurofeedback training protocols based on enhancement of *SMR* and *beta* activity. The two protocols implemented in this study rewarded participants when they elevated *SMR* or *beta* activity without concurrent rises in *theta* or *high beta* activity. Both protocols have been associated with improvements in attention so both were used to maximise the chance of eliciting a behavioural effect alongside any EEG changes. When reviewing the neurofeedback literature, a major problem in drawing conclusions from the data arises because EEG data from the neurofeedback sessions themselves is not reported. Instead, several studies simply use pre and post assessment measures to determine whether neurofeedback training has resulted in behavioural changes. This means our understanding of the mechanisms involved in neurofeedback training are still relatively unknown, an issue *high*lighted by Vernon (2005). Therefore, it was of utmost importance that Experiment II investigated EEG variables both within and across training sessions, in addition to analysing pre and post quantitative EEG and behavioural measures.

In this study, the within session data showed significant improvements in *SMR* or *beta* within the 15 minute training protocol without increased *beta* or *high beta* activity. The within session data is supported by the across session baseline changes in EEG. The across session analyses revealed a significant increase in baseline *SMR* and *beta* activity without significant changes in *theta* or *high beta* activity. One explanation for across session changes is that they reflect a result of familiarity with the experimenter and procedure, resulting in reduced stress and anxiety and therefore more focussed performance. However, at the start of each training session,

participants were asked to rate how anxious, tired, calm and lively they were on a scale and there were no correlations in these measures with training session, suggesting there was no significant change in their mood over the two-week period. Therefore, since this was a healthy high-functioning population, the most plausible explanation for the observed increased baseline *beta* and *SMR* activity is that it reflects an effect of neurofeedback training with maintenance of within session training effects carrying over to the next day. This finding supports the idea that the process of enhancing *SMR* or *beta* activity during neurofeedback sessions results in a residual increase in *SMR* or *beta* activity that is evident for periods over 24 hrs after these training sessions. Since this increase was seen linearly across the two weeks of training, which incorporated at least one full weekend break, it supports the long-lasting effect of neurofeedback training sessions (Cho et al, 2008). The significant linear increase in *beta* and *SMR* across sessions also implies that older adults had not plateaued in their learning within the ten sessions. Instead, it suggests that, had the training sessions continued, even greater EEG changes could have been produced. This is contrary to the literature on healthy young adults which has shown a trend for across session learning to plateau within ten sessions (Gruzelier et al, 2010; Ros et al, 2009).

Another index of learning which was considered when designing the analysis procedure was a 'training efficiency' index incorporating a comparison of training amplitude with baseline amplitude in the form of a training amplitude/baseline amplitude ratio. An increase in this ratio would reflect *high*er amplitudes during the training period than during the baseline period and suggest an improvement in learning. However, given the increase in baseline *beta* amplitude across session, this

ratio actually decreased with increasing sessions. This relationship simply reflects increased difficulty in raising *beta* activity during the training period above baseline activity as amplitudes increase and is therefore not particularly insightful.

Additional support for this is presented in the post assessment quantitative EEG. In comparison to the control group, who received no intervention and showed no changes in EEG, the neurofeedback group showed significant enhancement of *SMR* and *beta* activity. Unlike Egner and Gruzelier (2004) who reported behavioural improvements after *SMR* and *beta* training without concurrent changes in quantitative EEG, the data presented here suggests that neurofeedback training promotes tonic changes in trained frequency bands and therefore any behavioural improvements could be attributed to these changes. Indeed, the reaction time data from the pre and post assessment sessions point to a post-training improvement in sustained attention in the neurofeedback group (although this must be interpreted with caution due to the non-significant effect). With hindsight, the behavioural task employed in Experiment II was not appropriate as a tool to measure improvements in the healthy population. This visual continuous performance task did not elicit measurable omission or commission errors in this older adult group meaning it was not possible to extract the variables of attention, such as impulsivity and sustained attention, that have previously been shown to change as a function of neurofeedback training (Egner & Gruzelier, 2004). The visual continuous performance task was chosen due to the lateral element incorporated within it with the aim to use this as a comparable assessment tool for neglect patients in Experiment III. Unfortunately when this was piloted on neglect patients (after Experiment II had been conducted) it was found to be inappropriate. Therefore, the findings of Experiment II are limited

in the conclusions that can be drawn with regards to the effect of *beta* and *SMR* enhancement on cognitive improvement.

Does EEG activity correlate with behavioural recovery in right hemisphere stroke patients with hemispatial neglect?

Having already established an abnormal EEG profile in neglect in Experiment I, Experiment III provided the opportunity to correlate *beta* activity with behavioural recovery over a six-week period. The three patients assigned to the Improver group showed significantly increased *beta* activity over the six-week period, at this stage no assumptions are made as to whether this increase was caused by training or spontaneous recovery. The four patients allocated to the Non-Improver group showed no change in *beta* activity, with two of these patients showing increased *theta* activity. The change scores presented between Time 1 and Time 2 reflect improved scores on the behavioural measures, with bigger change scores indicating a greater extent of recovery. The group analysis revealed that the Improver group improved to a greater extent on all behavioural measures, spatial and non-spatial, than the Non-Improver group, although this group difference was only significant for the National Institute of Health Stroke Scale. Nevertheless, this trend suggests that increased *beta* activity is associated with a reduction of deficits across a range of behavioural measures, including neglect, general stroke-related impairments and independence on activities of daily living. Given the association of *beta* activity with alertness, it can tentatively be assumed that increased alertness in neglect patients correlates with a reduction in spatial and non-spatial impairments. This

finding suggests that *beta* activity could be used as an index of recovery in neglect patients with respects to the effectiveness of rehabilitative interventions.

Disentangling Spontaneous Recovery from EEG neurofeedback learning

In addition to investigating a link between *beta* activity and behavioural recovery, Experiment III aimed to investigate the suitability and effectiveness of neurofeedback as a rehabilitative intervention for hemispatial neglect. The motivation for using a *beta*-enhancing protocol came from research linking task-related alertness, spatial attention and *beta* activity. Due to the predicted small number of patients that would be recruited to the study, all patients received neurofeedback training sessions. The major challenge faced by this study was disentangling effects of spontaneous recovery from neurofeedback training. There is very little research into how EEG changes with spontaneous recovery after stroke although Giaquinto et al (1994) report the biggest change occurs in the first three months in the form of decreased *delta* and increased *theta* and *alpha* over the injured hemisphere. In this study, there was no significant change in EEG in the 3-6 month period post stroke. The time course of spontaneous recovery suggests the greatest behavioural improvements are seen in the first few weeks after stroke and reach a plateau after which little natural recovery would be expected (Tombari et al, 2004). Therefore, as already discussed in relation to neurofeedback learning indices in Experiment II, across session changes in EEG cannot be equated to effectiveness of neurofeedback training. This is even more pertinent when concerning neglect patients in the acute phase after stroke. The across session increases in *beta* baseline amplitude observed in three of the patients (HB, PS and RK) could simply reflect

spontaneous recovery. Additional analysis of the within session data, enabled inferences about spontaneous recovery and training to be made. None of the patients had a significant correlation of *beta* amplitude with within session training period. It was therefore postulated that the enhanced *beta* activity seen in these three patients was unlikely to be a result of neurofeedback training and was more likely to reflect spontaneous recovery.

Patient HB provides a particularly interesting case study. Since he was recruited to the study 62 days after stroke onset, it is likely that most of the spontaneous recovery he experienced would have tailed off by the time neurofeedback training commenced. Despite this, HB showed a significant linear increase in *beta* activity over the six weeks of training alongside a linear improvement in his neglect deficit. He was the only patient to show a marked improvement in neglect between Time 1 and Time 2 *and* Time 2 and Time 3. If the increased *beta* activity is attributed to the neurofeedback training as opposed to spontaneous recovery it suggests an improvement which out-lives the training period, as suggested by Cho et al (2008). Patient PS made such a remarkable recovery of neglect deficits by Time 2 that she had already reached non-clinical levels meaning it is therefore not possible to draw the same conclusions. This finding that patients with extremely severe neglect are able to benefit from EEG neurofeedback training provides a solid platform on which to develop the training protocol, with particular emphasis on extending the training period until the linear training pattern of EEG activity plateaus.

There are many factors which can influence recovery and these should be considered in relation to the case studies reported in Chapter 4. Firstly, the physical and social environment can greatly impact on recovery with more enriched environments and increased social interaction having been associated with improved behavioural outcome (Kolb & Gibb, 1991; Craft, Glasper, McCullough et al, 2005). In all cases included in this study, patients came from supportive family households, with immediate family members providing full-time care and company to each patient. Because of the nature of the study, which required a great deal of cooperation from the main care-giver in order to coordinate sessions, this was essentially a prerequisite for participation in the study. Therefore, whilst there was some variation in environment, it is unlikely that these factors significantly impacted on the recovery of these patients. However, anxiety proved to be the only distinguishing factor between the Improvers and Non-Improvers. Patients who showed increased baseline *beta* had much lower anxiety scores than patients who showed no change in *beta* over time. *High* anxiety levels could hinder the ability of a patient to engage with the neurofeedback training or could interfere with the process of natural recovery. Either way, anxiety levels could be an informative assessment to identify those patients who are most likely to recover or respond to therapeutic intervention.

Experiment I reported a reduced peak *alpha* frequency in neglect patients compared to healthy age-matched controls. An extension of the findings of Experiment III would be to include a pre and post quantitative EEG measure recorded during an eyes-open and eyes-closed condition. In addition to extracting power values of individual frequency bands, this would allow the extraction of peak *alpha* frequencies for each patient from the eyes-closed condition. An increase in peak

alpha frequency would be predicted as a function of recovery and would provide a much more robust and more easily extracted marker of neglect.

Is neurofeedback a viable intervention for neglect?

Long standing behavioural intervention strategies for neglect are hampered by the lack of awareness the patient has about their deficits. Attempting to compensate for a behaviour they do not feel is a problem presents a significant challenge for such methods. EEG neurofeedback does not present this challenge however. Whilst it does require a certain amount of engagement from the patient in order that they are able to attend to the feedback presented for the duration of the session, it does not require them to have an awareness of their spatial deficits. With technology advancing at such a fast rate, the equipment needed for neurofeedback training is likely to improve and become more suitable for severely impaired clinical groups. Several manufacturers have already developed EEG headsets with dry electrodes, eliminating the need to abrade the skin and use electroconductive paste. Technological improvements such as these will make neurofeedback an increasingly appealing intervention for a range of clinical disorders.

The initial aim of this thesis had been to recruit acute patients within the first few months post stroke in order to target the brain during a period of increased plasticity. However, with hindsight, recruiting patients at a more chronic and stable phase would have been better for several reasons. Firstly, as already discussed, this would have made it easier to draw conclusions that improved performance was a result of

the neurofeedback training rather than spontaneous recovery. Secondly, research into several other techniques aimed at increasing neural excitability, such as TMS and TDCS, have recruited patients from a few weeks to a few years post stroke and demonstrated significant improvements in all patients (Nyffeler, Cazzoli, Hess and Muri, 2009; Sparing, Thimm, Hesse, Kust, Karbe and Fink, 2009). Therefore, future neurofeedback studies should widen the recruitment criteria to include chronic patients rather than limiting the inclusion criteria to 2 months post stroke. The neurofeedback training may also be more applicable to patients in a more stabilised condition, especially given that engaging with the treatment is an important part of this intervention. Rather than recruiting patients from acute stroke wards, recruitment could focus on specialized residential rehabilitation units where patients with particularly severe deficits will often be referred. These units focus on rehabilitation interventions and are more appropriately set-up for regular training sessions with timetables quiet rooms than busy acute stroke wards.

The inclusion of chronic neglect patients with stabilised deficits would also allow for a more controlled design. For example, Gorgoraptis, Mah, Machner, Singh-Curry, Malhorta, Hadji-Michael, et al (2012) implemented a complex double-blind, randomized, placebo-controlled design in the investigation of rotigotine as a treatment for neglect. This design allowed them to maximise the small patient group recruited because each patient receives both the treatement and control conditions. A similar design could be used in a neurofeedback study in chronic neglect patients who demonstrate stabile neglect deficits. If assessment measures, both behavioural and electrophysiological, are first recorded over an initial six week period and show no change but then show a change in a proceeding six week period during which

they have received neurofeedback training, reliable conclusions can be drawn regarding the effectiveness of the intervention.

Research assessing the effectiveness of an intervention should ensure that appropriate assessments are used, The BIT was chosen as the assessment for spatial neglect because it includes a range of different tests (cancellation, line bisection, figure copying, drawing) and has been reported to be highly correlated to functional performance on everyday tasks (Hartman-Maeir and Katz, 1994). However, whilst the BIT is able to detect a range of clinical presentations of neglect, it does have limitations. For example, the BIT is limited to assessing neglect in peripersonal space only, rather than personal or extrapersonal space. Also, all sub-tests require visual search and manual exploration, meaning it is difficult to disentangle sensory neglect from motor neglect and hemiplegia. Therefore, the BIT is not the most sensitive of tests. Azouvi et al (2002) compared the sensitivity of a variety of neglect assessments and found that the most sensitive tests were the Bells Test (Gauthier, Dehaut & Joanette, 1989) and the Reading Test (Van Eeckhout, Sabadel, Signoret et al, 1982). The analyses also showed that rather than the number of omissions, the spatial location of the starting point on cancellation tests, such as the Bells Test, was a more sensitive measure. The sensitivity of neglect assessments in future studies should be considered thoroughly given the extent of the improvements that patients can make within a relatively short period of time. Whilst severe neglect is very obvious on paper and pencil tests, milder neglect is more difficult to detect but may still exist. A more sensitive measure of mild neglect that could be used is the Stimulus Onset Asynchrony Task (SOA) (Robertson, Mattingley, ROrden and Driver, 1998).

A fundamental aspect that is missing from this study is that there is no measure of non-spatial attention, especially given that the neurofeedback intervention is targeting this aspect of attention. The VCPT used in Experiment II was intended to act as a measure of sustained attention in the patient group. Unfortunately however, this task proved to be too difficult for the patients so could not be used. An extension of this study would be to include a non-spatial assessment to investigate whether the protocol implemented in this study could impact on both spatial and non-spatial deficits. This is also pertinent given that non-spatial deficits can often persist when spatial deficits have resolved.

Limitations of Conducting Longitudinal Research

The issue of spontaneous recovery of neglect and more general stroke-related deficits requires further investigation. However, few studies have involved continual monitoring of cognitive and functional impairments in neglect or stroke patients over a prolonged period of time. Denes et al's (1982) study, which only included two assessments over a six month period, initially recruited a total of 90 stroke patients but had a drop-out rate of almost 50%. Reasons for drop-out included death, unwillingness to cooperate, moving to another town and suffering from subsequent stroke. Wade, Wood and Hewer (1988) attempted to design a more rigorous evaluation of stroke recovery by assessing patients at weekly intervals over a 13 week period. Of the 117 patients recruited to this study, 40 died before 3 months, 12 were 'lost' to follow-up and 3 were found to have tumours. This resulted in a 47% drop out rate, similar to that reported by Denes et al (1982). This *high*lights the difficulties which longitudinal studies with stroke patients are forced to contend with.

The selection criteria for neglect patients also deserve consideration. Over 60 patients were screened for this study after referral from occupational therapists and physiotherapists who noted behavioural neglect on functional assessments. Despite this overt neglect-type behaviour, a spatial bias was often not observed on the paper-and-pencil subtests of the BIT. This suggests that a more sensitive measure of neglect may help in the identification of patients with mild or functional neglect. Bonato (2012) addresses this issue in his review and argues that commonly used paper-and-pencil tests are not demanding enough and allow patients to employ attentional resources to overcome the spatial bias. More attentionally demanding computer-based assessments have proven to be more sensitive measures of neglect especially in the chronic phase by which time patients have learnt compensatory strategies to correct for a spatial bias which is nevertheless still present (van Kessel, van Nes, Brouwer, Geurts & Fasotti, 2010; Bonato, Priftis, Umilta & Zorzi, 2012; Rengachary, d'Avossa, Sapir, Shulman & Corbette, 2009). The other limiting factor of the use of the BIT as a measure of neglect is it only considers visual neglect. Reliable and measurable assessments for auditory and sensory neglect have not been established but should be considered in both the identification and the recovery of neglect.

One of the limitations of these experiments is the small number of neglect patients recruited. Every effort was made to recruit as many neglect patients as possible but several issues made recruitment very difficult. Firstly, patients were screened as soon as they had been identified by the clinical team. However, due to the demands for beds on acute stroke wards, by the time a patient was suitable for screening they

had often been discharged home or transferred to their local hospital where the study did not have approval for recruitment. Several patients who fulfilled all the inclusion criteria did not want to volunteer for the study, the concept of EEG recording being particularly unfamiliar. Since stroke research is receiving ever-increasing attention, patients had often already been recruited to acute research trials before being appropriate to be approached about participating in this study. At Kings College Hospital for example, there are over 20 active stroke trials all recruiting from the same ward. It was vital patients were medically stable enough to withstand the EEG recording procedure which could take up to an hour to complete. One patient who consented to the study collapsed during the EEG procedure due to a vasovagal syncope (fainting episode), *high*lighting the vulnerability of these patients. Whilst a large proportion of right-sided parietal stroke patients do present with neglect, the introduction of thrombolysis as a very effective form of treatment for acute stroke has meant that there is a reduction in the number of patients left with the debilitating effects of neglect in comparison to previous years when thrombolysis was not routinely used.

Throughout the course of this study several attempts were made to increase recruitment rates, with every change having to be approved by the ethics committee of the lead NHS site. For example, initially the inclusion criteria was that the stroke for which the patient had been admitted had to be their first ever stroke. This immediately meant a *high* proportion of patients were excluded due to previous stroke. Therefore, the inclusion was changed to include patients with previous stroke providing the neglect was new-onset and not a pre-existing condition related to a previous stroke. Another initial requirement was that the stroke had to be right-sided

with accompanying left-sided neglect. This criteria was changed also to include left-sided stroke patients with right-sided neglect. However, this failed to increase recruitment because most patients with left-sided stroke had associated language deficits which meant communication was greatly impaired and right-sided neglect is simply not as common and generally remits within the first few days post-stroke.

5.3. Closing Remarks

The rehabilitation of hemispatial neglect continues to present a challenge, largely due to the complex nature of the syndrome and lack of insight into the core components underlying the disorder. There is evidence to suggest that interventions targeting alertness could be effective in the rehabilitation of hemispatial neglect. Alertness correlates in the EEG with decreased *theta* and increased *beta* activity and Experiment I showed that neglect patients had significantly reduced *beta* activity compared to age-matched controls. This finding is consistent with an alertness deficit underpinning neglect and suggestive that the symptoms of neglect could be ameliorated by *beta*-enhancement through neurofeedback training. Experiment II established for the first time that healthy older adults were able to modulate their *beta* activity, inspiring confidence that the greater age of stroke patients should in itself not interfere with their learning. Experiment III extended the intervention to neglect patients and supported two novel conclusions. Firstly, the training involved extensive monitoring of EEG over a six-week period and revealed that the extent of the recovery was linked to the extent of normalization of tonic *beta* activity; recovery and normalization of EEG was however less apparent in patients with *high*er levels of anxiety. Secondly, within session training analyses helped to

distinguish training benefits from spontaneous recovery and supported the conclusion that patients who showed evidence of training-induced increases in *beta* activity showed a greater extent of improvement on outcome measures. Both findings deserve further exploration and possible exploitation in developing lasting interventions for hemispatial neglect.

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APPENDIX 1

Scoring Sheet for Behavioural Inattention Test (BIT)

SUB-TEST	SCORES	TOTAL SCORE
Line Crossing -score the total number of lines crossed (do not include the central column)	_ _ _ _ _ _ 6 6 6 6 6 6	_ 36
Letter Cancellation -score the total number of E's and R's cancelled in each column	_ _ _ _ 10 10 10 10	_ 40
Star Cancellation -score the total number of small stars cancelled in each column (do not include the two small stars immediately above the centralizing arrow)	_ _ _ _ _ _ 8 8 11 11 8 8	_ 54
Figure and shape copying **a)Figure Copying** -score one for each figure drawn complete **b)Shape Copying** -score one if all the shapes are drawn complete	a) Star: /1 Cube: /1 Daisy: /1 b) /1	_ 3 _ 1
Line Bisection -score each line according to the amount of deviation shown on the scoring template	Left line: /3 Centre line: /3 Right line: /3	_ 9
Representational Drawing -score one for each drawing completed.	Clock face: /1 Man: /1 Butterfly: /1	_ 3
	Total Conventional Score	_ **146**

APPENDIX 2

National Institute of Health Stroke Scale (NIHSS)

		Score	Time 1	Time 2	Time 3
1a. Level of Consciousness	Alert Drowsy Stuporous Coma	0 1 2 3			
1b. LOC Questions	Answers both correctly Answers one correctly Both incorrect	0 1 2			
1c. LOC Commands	Obeys both correctly Obeys one correctly Both incorrect	0 1 2			
2. Best Gaze	Normal Partial gaze palsy Forced deviation	0 1 2			
3. Visual	No visual loss Partial hemianopia Complete hemianopia Bilateral hemianopia	0 1 2 3			
4. Facial Palsy	Normal Minor Partial Complete	0 1 2 3			
5a. Motor Arm left	No drift Drift Can't resist gravity No effort against gravity No movement	0 1 2 3 4			
5b. Motor Arm right	No drift Drift Can't resist gravity No effort against gravity No movement	0 1 2 3 4			
6a. Motor leg left	No drift Drift Can't resist gravity No effort against gravity No movement	0 1 2 3 4			
6.b Motor leg right	No drift Drift Can't resist gravity No effort against gravity No movement	0 1 2 3 4			
7. Limb Ataxia	Absent Present in one limb Present in two limbs	0 1 2			
8. Sensory	Normal Partial Loss Severe Loss	0 1 2			
9. Best Language	No aphasia Mild to Moderate Severe Mute	0 1 2 3			
10. Dysarthria	Normal Articulation Mild to Moderate Near to intelligible Intubated or other barrier	0 1 2 3			
11. Extinction and Inattention	No neglect Partial Neglect Complete Neglect	0 1 2			

APPENDIX 3

Barthel Index (BI)

		Time 1	Time 2	Time 3
Date				
Bowels::				
incontinent (or needs to be given enema)	0			
occasional accident (once/week)	1			
Continent	2			
Bladder:				
incontinent, or catheterized and unable to manage	0			
occasional accident (max once per 24 hours)	1			
continent (for over 7 days)	2			
Grooming:				
needs to help with personal care	0			
independent face/hair/teeth/shaving (implements provided)	1			
Toilet use:				
Dependent	0			
needs help, but can do something alone	1			
independent (on and off, dressing, wiping)	2			
Feeding:				
Unable	0			
needs help cutting, spreading butter etc.	1			
independent (food provided in reach)	2			
Transfers				
Unable - no sitting balance	0			
major help (one or two people, physical), can sit	1			
minor help (verbal or physical)	2			
Independent	3			
Mobility:				
immobile	0			
wheelchair independent, including corners etc.	1			
walks with help of one person (verbal or physical)	2			
independent (but may use any aid e.g. stick)	3			
Dressing:				
dependent	0			
needs help but can do about half unaided	1			
Independent (including buttons/zip/laces)	2			
Stairs:				
Unable	0			
needs help (verbal, physical, carrying aid)	1			
independent up and down	2			
Bathing:				
Dependent	0			
independent (or in shower)	1			
Total:				

APPENDIX 4

Nottingham Extended Activities of Daily Living

DO YOU….. 0 = Not at all 1 = With help 2 = Alone with difficulty 3 = Alone easily	**Time 1**	**Time 2**	**Time 3**
DATE			
MOBILITY			
walk around outside?			
climb stairs?			
get in and out of the car?			
walk over uneven ground?			
cross roads?			
travel on public transport?			
IN THE KITCHEN			
manage to feed yourself?			
make yourself a hot drink?			
take hot drinks from one room to another?			
do the washing up?			
make yourself a hot snack?			
DOMESTIC TASKS			
manage your own money when out?			
wash small items of clothing?			
do your own shopping?			
do a full clothes wash?			
LEISURE ACTIVITES			
read newspapers and books?			
use the telephone? write letters?			
go out socially?			
manage your own garden?			
drive a car?			
TOTAL			

APPENDIX 5

Hospital Anxiety and Depression Scale (HADS) – Page 1 of 2

	Baseline		6 WKS		12 WKS	
	A	**D**	**A**	**D**	**A**	**D**
I feel tense or 'wound up' most of the time						
Most of the time	**3**		**3**		**3**	
A lot of the time	**2**		**2**		**2**	
Occasionally	**1**		**1**		**1**	
Not at all	**0**		**0**		**0**	
I still enjoy the things I used to enjoy						
Definitely as much		**0**		**0**		**0**
Not quite so much		**1**		**1**		**1**
Only a little		**2**		**2**		**2**
Hardly at all		**3**		**3**		**3**
I get a sort of frightened feeling as if something awful is about to happen						
Very definitely and quite badly	**3**		**3**		**3**	
Yes but not too badly	**2**		**2**		**2**	
A little, but it doesn't worry me	**1**		**1**		**1**	
Not at all	**0**		**0**		**0**	
I can laugh and see the funny side of things						
As much as always		**0**		**0**		**0**
Not quite so much now		**1**		**1**		**1**
Definitely not so much now		**2**		**2**		**2**
Not at all		**3**		**3**		**3**
Worrying thoughts go through my mind						
A great deal of the time	**3**		**3**		**3**	
A lot of the time	**2**		**2**		**2**	
Not too often	**1**		**1**		**1**	
Very little	**0**		**0**		**0**	
I feel cheerful						
Never		**3**		**3**		**3**
Not often		**2**		**2**		**2**
Sometime		**1**		**1**		**1**
Most of the time		**0**		**0**		**0**
I can sit at ease and feel relaxed						
Definitely	**0**		**0**		**0**	
Usually	**1**		**1**		**1**	
Not often	**2**		**2**		**2**	
Not at all	**3**		**3**		**3**	
I feel as if I am slowed down						
Nearly all the time		**3**		**3**		**3**
Very often		**2**		**2**		**2**
Sometimes		**1**		**1**		**1**
Not at all		**0**		**0**		**0**

**Note – this assessment continues to the next page*

Hospital Anxiety and Depression Scale (HADS) – Page 2 of 2

	Baseline		6 WKS		12 WKS	
	A	**D**	**A**	**D**	**A**	**D**
I get a sort of frightened feeling like 'butterflies' in the stomach						
Not at all	**0**		**0**		**0**	
Occasionally	**1**		**1**		**1**	
Quite Often	**2**		**2**		**2**	
Very Often	**3**		**3**		**3**	
I have lost interest in my appearance						
Definitely		**3**		**3**		**3**
I don't take as much care as I should		**2**		**2**		**2**
I may not take as much care		**1**		**1**		**1**
I take just as much care as ever		**0**		**0**		**0**
I feel restless as if I have to be on the move						
Very much indeed	**3**		**3**			**3**
Quite a lot	**2**		**2**			**2**
Not very much	**1**		**1**			**1**
Not at all	**0**		**0**			**0**
I look forward to enjoyment to things						
As much as I ever did		**0**		**0**		**0**
Rather less than I used to		**1**		**1**		**1**
Definitely less than I used to		**2**		**2**		**2**
Hardly at all		**3**		**3**		**3**
I get sudden feelings of panic						
Very often indeed	**3**		**3**		**3**	
Quite often	**2**		**2**		**2**	
Not very often	**1**		**1**		**1**	
Not at all	**0**		**0**		**0**	
I can enjoy a good book or radio or TV programme						
Often		**0**		**0**		**0**
Sometimes		**1**		**1**		**1**
Not often		**2**		**2**		**2**
Very Seldom		**3**		**3**		**3**
TOTAL						