EEG Biofeedback for Memory

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A thesis submitted for the degree of
Doctor of Philosophy
at the Dunedin School of Medicine, University of Otago,
New Zealand

December 2017

Abstract

The brain has an ordered structure of functional connections within brain networks, but this order becomes disrupted in Alzheimer's disease (AD). The default mode network (DMN) and its central hub, the Posterior Cingulate Cortex (PCC) are particularly affected. Disruption to the functional relationships results in AD memory symptoms. Electroencephalography (EEG) biofeedback analyses a subject's EEG, and displays an aspect of that signal back to them. That subject can then take control over that aspect of their EEG signal. Biofeedback can be used to alter the functional relationships in brain networks and could restore the abnormal functional connectivity relationships seen in AD, and in doing so improve memory symptoms. The aim of this thesis is to examine whether source-localised EEG biofeedback of the PCC could alter functional connectivity in the earliest stages of AD and improve memory outcomes.

First, a pilot study in 10 people with amnestic type Mild Cognitive Impairment (aMCI) was conducted. The protocol was designed to up-train the power of theta and alpha, source localised to the PCC (broadband feedback). Participants completed 15 sessions of 40 minutes of biofeedback training. Their memory was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which has two forms (A and B). Participants were tested using form A prior to training, and form B after training to reduce repeated testing effects. There was a significant improvement in both the RBANS Immediate Memory index (mean improvement 12.4 points, p=0.011) and the Delayed Memory index (mean improvement 7.0 points, p=0.016).

Following on from the pilot study, a three armed randomised controlled trial was designed to:

1) Assess alpha band only source localised feedback (narrowband) against broadband feedback
2) Assess both biofeedback paradigms against a placebo control
3) Test biofeedback training in a more general population of adults with memory deficits

Volunteers were screened using the RBANS. Those who scored below 90 on the immediate memory index were randomised to receive 15 sessions of either broadband feedback, narrowband feedback or placebo feedback. Memory was assessed using the RBANS.

53 people completed all 15 sessions of biofeedback training and were included in the analysis. No effect on memory was found (Randomisation*Time interaction = 1.162, p=0.388). A significant increase in the power of the alpha band in the narrowband feedback group was identified (β=0.0323, p=0.003), indicating that the training had an effect on the targeted frequency in this group; however no change in the targeted frequency in the broadband feedback group was detected. No significant impact on DMN connectivity was found. A significant difference was found in the difficulty of tasks in the RBANS immediate memory index, form A was more difficult than form B.

This particular kind of source localised biofeedback training does not appear to be effective at improving memory outcomes in the short term. In addition, a significant form effect was discovered for the RBANS, which entirely explained the result of the pilot study. Future studies of biofeedback should use a counterbalanced design when using alternate forms of neuropsychological tests.

Acknowledgements

I would like to acknowledge the LF Hall foundation for providing me a scholarship to work on the pilot study conducted in 2015.

I would also like to thank the Brain Research New Zealand Centre of Research Excellence for awarding me the PhD MBChB scholarship to continue working on this project and carry out the randomised controlled trial in 2016. I also thank the Helen Rosa Thacker trust for awarding me the Helen Rosa Thacker PhD scholarship for the same purpose.

I would also like to thank the Department of Medicine administrative staff for helping me to run what turned out to be a very intensive trial. I particularly would like to thank Claire Ashford for her assistance with booking rooms and participant vouchers. Also, Andrew Grey provided a lot of good advice about the statistics I was using

I am indebted to each of my supervisors. I thank Associate Professor Patrick Manning for his practical assistance and advice in running the randomised trial. Professor Dirk de Ridder is an endless source on knowledge and I am grateful for all the ideas about what to do next when I didn't know. But I am mostly indebted to Dr Nick Cutfield who brought my paper-thin knowledge of medical science through to where it is today. I am grateful for him supporting the tenuous idea I had for the controlled trial in August of 2015, and developing that idea into something that would actually work.

I am also very thankful for the volunteers in the Dunedin community who volunteered to take part in this project. The willingness to contribute is outstanding, which is shown by the large number of people who volunteered for screening. I asked far too much of these people, and yet they gave anyway, and they deserve much credit for what they have done.

And finally, to everyone who listened to me complaining about this project, thanks must go to you too.

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List of Abbreviations

Alzheimer's Disease	AD
Amnestic type Mild Cognitive Impairment	aMCI
Apolipoprotein E genotype	APO E
Attention Deficit Hyperactivity Disorder	ADHD
Blood Oxygen Level Dependant imaging	BOLD
Cerebral Spinal Fluid	CSF
Computed Tomography	CT
Default Mode Network	DMN
Electroencephalogram	EEG
Exact Low Resolution Electromagnetic Tomography	eLORETA
Function Magnetic Resonance Imaging	fMRI
Independent Component Neurofeedback (Computer Program	ICoN
Low Resolution Electromagnetic Tomography	LORETA
Magnetic Resonance Imaging	MRI
Magnetoencephalogram	MEG
Medial Temporal Lobe	MTL
Mild Cognitive Impairment	MCI
Mini Mental State Examination	MMSE
Montreal Neurological Institute	MNI
National Institute of Mental Health and Neuroscience	NIMHANS
National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association	NINCDS-ARDRA

Peak Alpha Frequency	PAF
Posterior Cingulate Cortex	PCC
Quantitative Electroencephalogram	qEEG
Repeatable Battery for the Assessment of Neuropsychological Status	RBANS
Rey Auditory Verbal Learning Task	RAVLT
Standard Deviation	SD
Sensorimotor Rhythm	SMR
Standardised Low Resolution Electromagnetic Tomography	sLORETA
Subjective Memory Decline	SMD
Supplementary Motor Area	SMA
Traumatic Brain Injury	TBI
Weschler Adult Intelligence Scale III	WAIS III
Weschler Memory Scale	WMS

Chapter 1 Introduction

Alzheimer's Disease

Disease Progression

Alzheimer's Disease (AD) is a form of progressive dementia that primarily affects older people (1). People who present with Alzheimer's disease generally first present with loss of memory (2). At early stages memory loss is restricted to recent declarative memory, that is memory of recent events and facts (3). Older memories, although impaired, are affected to a lesser extent initially (4). When this memory impairment reaches a level that causes impairment of social or occupational activities, or activities of daily living, a diagnosis of dementia is typically met (2). Executive function is also affected early on in the disease progression. This affects the person's ability to make decisions, and may underlie an inability to perform tasks of daily living early on in the disease (5). Language function is also affected in early stages of Alzheimer's disease, and tends to deteriorate along with memory function (6).

Clinically, there is progressive deterioration in the ability to access memories, which can affect other cognitive domains (3). Memory deteriorates progressively, leading to patient's appearing to 'live in the past' as the ability to retain new information is lost completely (7). Implicit memory such as learning motor skills are preserved well into the illness progression (8). The ability to interpret visuospatial information is often affected in intermediate stage of Alzheimer's disease (9). Significant loss of language function can occur, with patients becoming mute at severe stages of the disease (3). Patients with Alzheimer's disease often experience neuropsychiatric symptoms as well, the most common of which is apathy (10).

At diagnosis, the life expectancy of the person is reduced by one third. Severe Alzheimer's disease is characterised by complete loss of memory function and complete loss of ability to communicate (3).

Pathology

Alzheimer's disease (AD) is characterised by the accumulation of pathological amyloid beta plaques and neurofibrillary tangles in the brain (1). Post mortem examination of patients with Alzheimer's disease reveals a large number of beta amyloid plaques, also called neuritic plaques. These are also found in the brains of non-demented individuals; however the amount of plaques is much greater in those with Alzheimer's disease (11). These plaques contain an accumulation of protein derived peptides called amyloid beta (Aβ) (1) This protein is derived from the proteolytic cleavage of amyloid precursor peptide by beta and gamma secretase (12). Amyloid precursor peptide is a transmembrane protein found particularly in neurons (1),. The amyloid hypothesis for the pathogenesis of Alzheimer's disease suggests that the deposition of amyloid beta by beta and gamma secretase is the antecedent of Alzheimer's pathological and clinical outcomes (13).

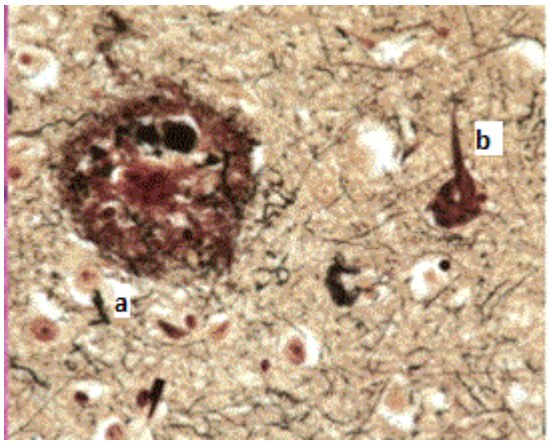


Figure 1-1 A silver stain of a histological section from an Alzheimer's affected brain. The letter a indicates the position of a beta amyloid plaque. The letter b indicates the position of a neurofibrillary tangle. Adapted from Figure 1 Serrano-Pozo, A., et al. (2011). "Neuropathological Alterations in Alzheimer Disease." Cold Spring Harbor Perspectives in Medicine 1(1).

Deposition of Aβ plaques starts a biochemical cascade which leads to the alteration proteins called tau within axons (14). Tau proteins are structural elements within axons which become hyper-phosphorylated and form neurofibrillary tangles (15). These neurofibrillary tangles disrupt axons and may ultimately lead to the death of those neurons, particularly in the hippocampus (16). Loss of neurons, and loss of synapses between neurons is strongly correlated with cognitive decline, more strongly correlated than the density of plaques and tangles alone (17). Gradual accumulation of pathology results in neuronal loss, which causes progressive cognitive decline (18). Loss of

connection and loss of neurons results in inefficient communication of brain networks, which may be responsible for symptoms seen in AD (19).

Epidemiology

Alzheimer's disease is both a costly and prevalent disease. The prevalence of AD rises sharply with age. Surveys in European countries find the prevalence rises from 0.8% of ages 65 to 69 years olds to 18% of individuals older than 90 (20). There appears to be lower rates in the Chinese community (21). In 2011, more than 48,000 New Zealanders had dementia, most of which was due to Alzheimer's pathology. It is estimated that by 2050, nearly 150,000 New Zealanders will have dementia (22). Likewise, incidence also increases with age (23), and incidence is lower in Asian communities (24). Rates of Alzheimer's disease are higher in women, although this seems to be a reflection of the fact women live longer than men, rather than a true association (23). In 2011 4% of those with Alzheimer's disease identified as Maori, and this proportion is expected to rise to 5.7%, due to an increasing life expectancy of Maori. It is estimated that dementia cost New Zealand a total of 954.8 million dollars in 2011 (22).

Amnestic type Mild Cognitive Impairment

Amnestic type mild cognitive impairment (aMCI) is a condition that describes otherwise cognitively normal adults who have isolated memory impairment, but without functional difficulties (25). Amnestic mild cognitive impairment is a subset of mild cognitive impairment (MCI) , a condition characterised by cognitive or memory impairment beyond normal aging, without the functional decline of dementia (26). People with MCI are at increased risk of developing AD and also at an increased risk of death (27). Amnestic mild cognitive impairment , and mild cognitive impairment in multiple domains with memory impairment are regarded as often representing prodromal forms of AD, and are therefore targets for early intervention in AD (26). However, researchers have found that MCI is an unstable diagnosis (28), that is when followed over a period of time, people with mild cognitive impairment either progress onto dementia or sometimes recover normal function. Although some studies have reported that up to 38% of people meeting criteria for MCI convert back

to normal cognition (29), other studies which required people to be consistently impaired found that this group did show significant cognitive deterioration compared to controls (28).

Amnestic mild cognitive impairment is diagnosed using clinical criteria proposed by National Institute of Aging – Alzheimer's Association work group criteria (30). These criteria are as follows:

1. The person has a subjective memory complaint
2. Normal activities of daily living,
3. The person has otherwise normal cognitive function for their age,
4. Abnormal memory on testing,
5. Not demented
6. Where possible, other aetiologies, such as vascular disease, have been ruled out.

The annual rate of conversion from MCI to AD is about 10-15%, compared to an annual rate of conversion of healthy older adults to AD of about 1% (25). Amnestic mild cognitive impairment is a diagnosis that results in a heterogeneous group of patients, which is diagnosed on the basis of clinical criteria and not pathology, which means it contains people who will not progress onto AD. Therefore caution must be used when interpreting the results of intervention in this group (29).

Considerable effort has been put into trying to find ways to predict which people with aMCI will go on to develop AD. This has resulted in the development of biomarkers for Alzheimer's pathology, a few of which are cerebral spinal fluid (CSF) amyloid beta 42 (Aβ-42), CSF phosphorylated tau (31), hippocampal volume and apolipoprotein E (APO E) genotype (32). Cohorts characterised as being likely to have AD pathology by these kinds of tests have higher rates of conversion to dementia than those characterised by clinical criteria alone. This is useful in order to target clinical research to those who are at high risk of developing AD (31-33).

However, MCI patients do have demonstrable memory impairment and higher risk of developing AD (25), which clearly suggests that aMCI is a condition worth intervening in, to try and improve

memory outcomes, reduce the conversion rate to dementia, and delay conversion to dementia. It is estimated that a five year delay in conversion to dementia could reduce the projected prevalence by one third (34). The recent Lancet Commission on Dementia prevention, intervention and care (35) suggested that up to 35% of dementia might be prevented, by addressing modifiable risk factors such as hypertension, midlife hearing loss and social isolation. However the commission also showed that interventional trials to prevent the onset of dementia in both healthy adults and those with aMCI have often failed to show any benefit.

General Memory Function

Alzheimer's pathology clearly has a significant effect on memory function early on, and therefore it is important to understand how normal memory function works and the impact of pathology on this. Normal memory is divided in different subsystems, which are sub-served by different parts of the brain. Memory is split into explicit and implicit memory (36). Explicit (or declarative) memory is divided into episodic memory, memory of events, and semantic memory, memory of facts and ideas (37). As Alzheimer's disease particularly affects declarative memory (3), so this discussion of memory will be restricted to processes of declarative memory.

Memory is initially stored in the working memory system. The working memory system is a theoretical model of how the brain holds information temporarily for further processing, permitting reasoning, decision making and initiating goal directed behaviour. With regard to declarative memory, the working memory can hold a restricted number of items for a short period of time (38). These items can be actively manipulated while in this system (39). The working memory system is generally considered to consist of three subsystems, a phonological loop for processing and temporarily storing verbal material, a visuospatial loop for processing and temporarily storing visual material, and an executive control system which mediates attention and control over the other two systems (38). Functional neuroimaging studies such as Positron Emission Tomography suggests that the phonological loop is contained in high level verbal areas, such as Broca's area the lateral frontal lobe (40). The visuospatial system is sub served by some prefrontal and some occipital areas (40,

41). The executive control, which determines what details are attended to and are stored in the working memory, is located in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (40, 42). This part of memory is relatively preserved early in Alzheimer's disease (3).

Memory retrieval of larger lists of items, over periods of time longer than a few seconds, or after a distraction has occurred requires the integrity of the medial temporal lobe storage and retrieval system (39). Damage to the medial temporal lobe system demonstrates just how crucial the system is to memory storage and retrieval (43, 44). Famous examples include historic patients H.M and R.B who each suffered damage to their hippocampus bilaterally, and were subsequently unable to store and retrieve new episodic memory (43-45).

Information to be remembered about an event converges on the medial temporal lobe structures such as the parahippocampal cortex and the entorhinal cortex, and which processes the stimuli and stores an 'index' in the hippocampus. This 'index' can then be used to retrieve that information in a top down manner, thus retrieving a memory (46, 47). There is functional imaging evidence that the medial temporal lobe system is important for both episodic memory and semantic memory over the course of a life time (48). The integrity of the medial temporal lobe system is therefore vital to the functioning of memory. The parahippocampal gyrus, the PCC and the approximate position of the hippocampus are shown in Figure 1-2.

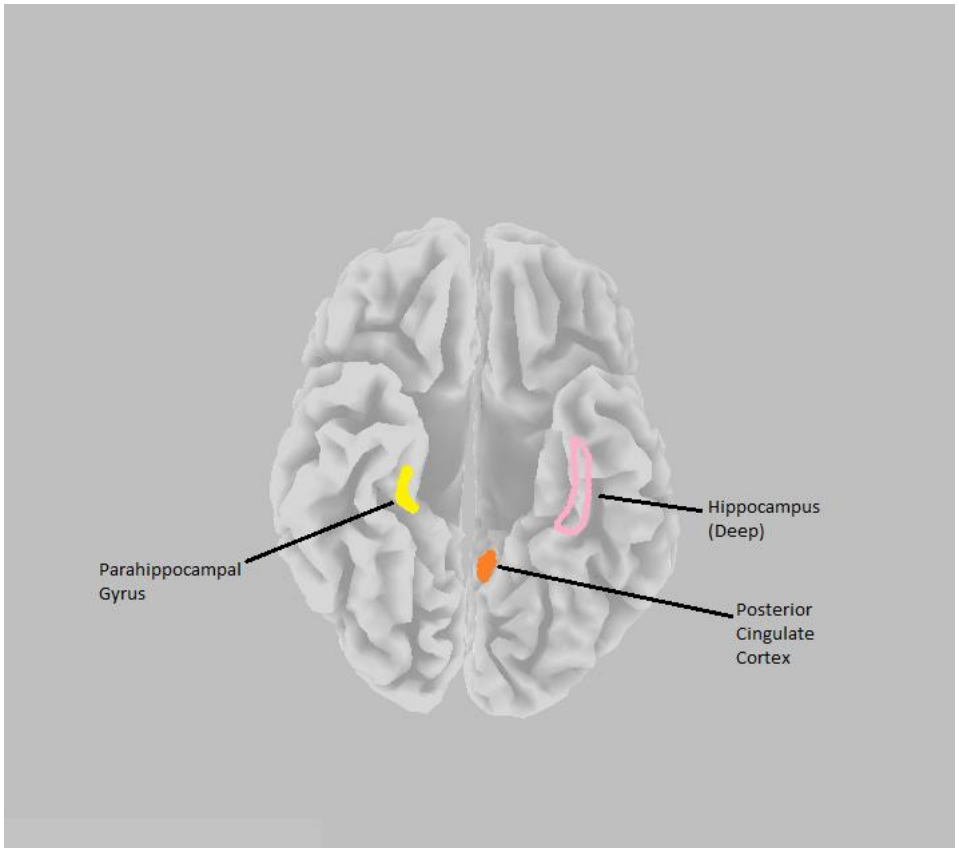


Figure 1-2: Inferior view of the brain. The approximate positions of the PCC, parahippocampal gyrus and the hippocampus are shown. The hippocampus is not a cortical structure, but is located deep to the parahippocampal gyrus.

Default Mode Network, Memory and Alzheimer's Disease

The Default Mode Network and Posterior Cingulate Cortex

The brain can be considered as a functional network with a 'small world topology'. This means it is made up of connected groups of neurons, of which most have few connections and a few have a large number of connections. Highly connected regions are known as hubs (49). Small world architecture results in a modular structure, where hub connect local modules together, as is seen in Figure 1-3. Clusters of neurons doing related tasks are often located close together. This allows for the segregation of information. Hub regions connect the modules of related neurons together, forming long range connections between the modules of related neurons. This allows for information processed by different modules to be integrated. This system of hubs and modules separates the brain into different functional networks, which have distinct functional roles (50). These networks are connected together through the highly connected hubs (51). One of the best characterised network is the Default Mode Network (DMN) (52).

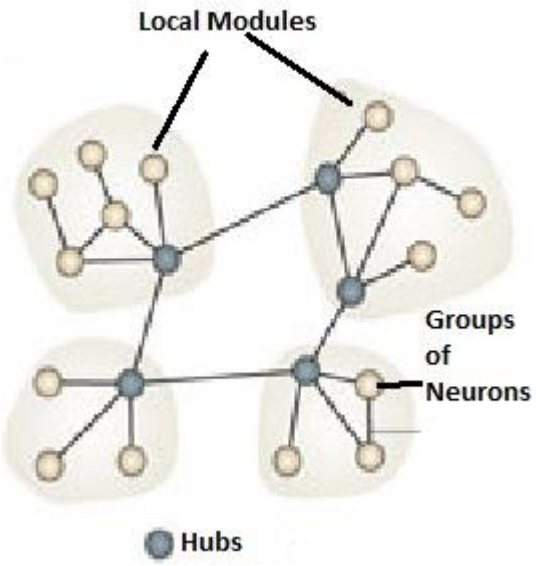


Figure 1-3: A Network with small world topology. Clusters of Neurons form a local module, which is connected to other modules by highly linked nodes. Adapted from Box 3 Bullmore, E. and O. Sporns (2012). "The economy of brain network organization." Nat Rev Neurosci 13(5): 336-349.

The Default Mode Network was hypothesised to exist when it was noticed that certain areas of the brain were noted to deactivate simultaneously during a cognitive task (53). Functional imaging studies, using functional magnetic resonance imaging (fMRI), identified areas of the brain that were active during particular tasks, by comparing images to brain activity when the participant wasn't engaged in a particular task, the 'resting state'. When goal directed activity occurred, specific regions of the brain showed a coordinated increase in activity, whereas other parts showed decreases in activity (53). These deactivated areas define the default mode network, which is shown in Figure 1-4 below. These regions are highly active in the resting state and are less active when the brain is engaged in directed activity (53). The network consists of the Posterior Cingulate Cortex (PCC), Medial Prefrontal Cortex, the Parahippocampal Gyrus, Anterior Cingulate Gyrus, Inferior Temporal Cortex, orbitofrontal cortex and inferior parietal cortex (52). Another network, which is activated during sensory tasks, is the salience network. It is active when the default mode network is inactive, and during the resting state when the default mode network is active, the salience network is deactivated. These two networks are said to be anti-correlated. (54).

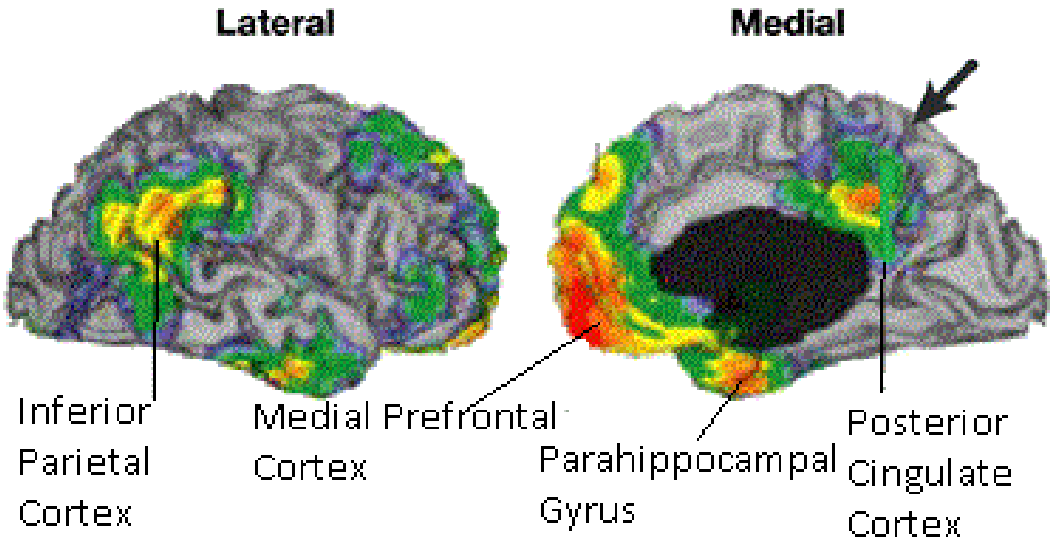


Figure 1-4. The anatomical location of the major parts of the Default Mode Network. Adapted from Figure 1 Debra, A. G. and E. R. Marcus (2001). "Searching for a baseline: Functional imaging and the resting human brain." Nature Reviews Neuroscience 2(10): 685.

The Posterior Cingulate Cortex is both highly connected (55), and highly active (53). The PCC is thought to be involved in the evaluation of environmental information to determine whether a behavioural switch is necessary (55). It is also highly connected anatomically to the parahippocampal gyrus and medial temporal lobe structures (56), suggesting that it has a significant role in memory encoding and retrieval (57). Due to its highly connected nature, and its pivotal role in memory circuits, the PCC is considered the hub of the DMN (58). It then follows that any pathology that affects the PCC is likely to have a significant effect on the connectivity of the DMN and memory (49).

Memory Retrieval and the Default Mode Network

Memory retrieval also depends on the anatomical components of the default mode network, such as the PCC (59). The integrity of the anatomical white matter tracts that connects the nodes of the DMN determines the functional connectivity of the network (60, 61). The integrity of the functional connectivity of the DMN is important to the successful retrieval of memory (62). A full discussion of functional connectivity can be found in the section below. Additional evidence to suggest the importance of the DMN to memory retrieval is that selective damage to the posterior cingulate cortex and surrounding area results in a phenomenon called retrosplenial amnesia, which is similar

to the kind of amnesia experienced by the historic patients mentioned above with damaged hippocampi (63).

Alzheimer's disease profoundly affects the medial temporal memory system (16, 64). Loss of neurons in the hippocampus is strongly associated with decreased memory (16). Neurofibrillary tangles tend to accumulate in the medial temporal lobes and affect its connections to other areas of the brain, such as the posterior cingulate cortex (64).

AD also strongly affects the default mode network (65). Beta amyloid deposition in vivo can be located and measured using the Pittsburgh compound B contrast Positron Emission Tomography scanning. The Pittsburgh Compound B is a radioactive ligand that binds to beta amyloid in vivo (66). A PET scan using the Pittsburgh compound in a person with Alzheimer's Disease is demonstrated in Figure 1-5 below. The pattern of deposition of beta amyloid plaque, measured by Positron Emission Tomography using the Pittsburgh compound, is similar to the anatomical location of the default mode network (65). In addition, early metabolic reductions are seen in the PCC area, and throughout the DMN (67). This suggests that the default mode network is prominently affected by Alzheimer's pathology.

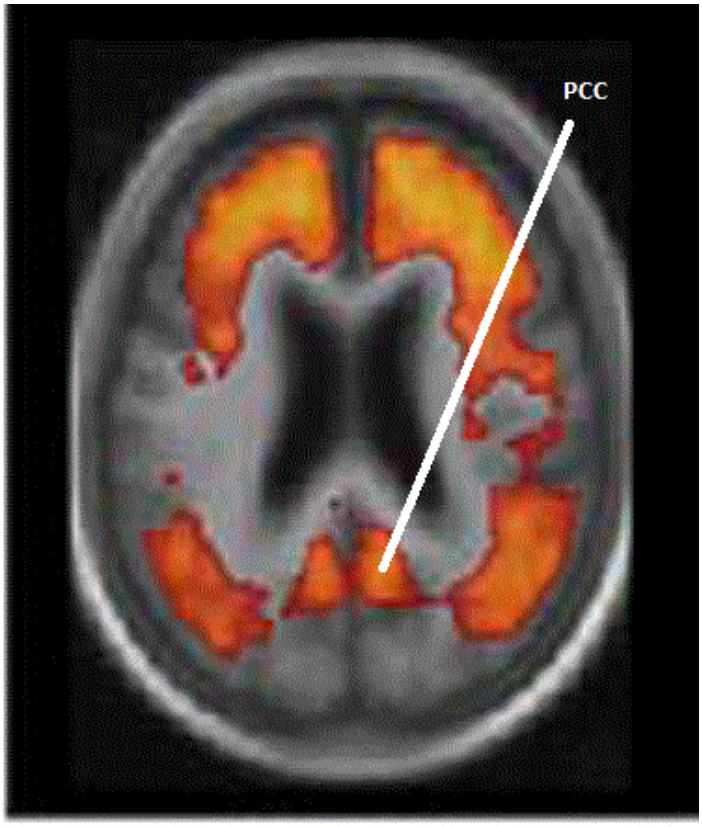


Figure 1-5: PET scan of a person with Alzheimer's disease, using the radioactive ligand Pittsburgh Compound B to label the deposition of beta amyloid. The PCC has been labelled. Note the similarity to the distribution of the default mode network. Adapted from Figure 2 Buckner, R. L., et al. (2005). "Molecular, Structural, and Functional Characterization of Alzheimer's Disease: Evidence for a Relationship between Default Activity, Amyloid, and Memory." The Journal of Neuroscience 25(34): 7709-7717.

EEG and Biofeedback

Introduction to Electroencephalogram

One of the ways neurophysiological changes in the brain can be explored is via the electroencephalogram, or EEG (68). EEG measures the field potential (voltage) generated on the scalp when a group of neurons simultaneously generate electrical activity (68). When neurons are stimulated by an excitatory synapse they generate an excitatory postsynaptic potential (EPSP), and likewise when they are inhibited by an inhibitory synapse they generate a inhibitory post synaptic potential (IPSP) (69). These post synaptic potentials are the basis for the electrical activity seen in the EEG recording. As the recording takes place on the scalp, the voltage signals must pass through meninges, skull and scalp before it is detected by the electrode. Because the electrical potentials generated by individual neurons are small and attenuated by both the distance and conducting

properties of the tissues they pass through, they cannot be detected on the scalp. A large population of neurons acting in synchrony is required in order to generate a recording in an EEG lead (68).

The EEG is used in clinical practice to assist with diagnosing and managing neurological disease (70). The EEG can detect abnormal patterns of electrical activity in the brain, which can be used to help characterise and manage epilepsy. Changes to the material of the brain, such as caused by tumours or trauma, can be detected and localised on EEG, but this is second line to imaging techniques such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scanning. EEG can also be used to detect viral encephalitides (70).

The Magnetoencephalogram (MEG) is a conceptually related technique that measures the magnetic field generated by currents in neurons (71). Both EEG and MEG measure the physiological activity of neurons over milliseconds (72).Depending on the type of leads used, it produces a similar pattern of activity, though it tends to image a smaller group of sources at a higher spatial resolution. The equipment required is much more expensive and bulky compared to EEG, so it is generally only used for research.(71)

The standard EEG has electrodes placed in accordance with the '10 – 20 system' of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology, which is demonstrated below in Figure 1-6 (73). This system uses bony landmarks to determine the position of the electrodes. The distance is measured from the nasion to the inion, and the first electrode is place at 10% of that distance from the nasion. The second is placed at 20% of that distance, until there are five electrodes placed in line, with the last one being 10% of the distance from the inion (73). The same process is used place electrodes in the coronal plane, measuring between the left and right pre auricular points (73). This system creates consistency in lead placements between subjects and within subject having multiple recordings. This system has subsequently been extended to the 10 – 10 system, where additional electrodes are at the mid points between the 10 – 20 electrodes, and further to the 10 -5 system. Nomenclature is as for the 10 -20 system, but electrodes

placed in between the standard 10 -20 electrodes take on the name of the both electrodes they are in between, for example FCz is at the midpoint between Fz and Cz, and POz is at the midpoint between Pz and Oz. AF1 and AF2 are located on the line halfway between Fpz and Fz (74).

The EEG traces can be generated in two major ways, with monopolar montages, or using bipolar montages (75). Both methods have their advantages and disadvantages. Monopolar montages measure changes in activity with respect to a common reference. Often the common reference is chosen to be the earlobe. This method is prone to artefacts arising from activity in muscles and from the heart. But it allows for comparison between the activities of adjacent electrodes (75). Bipolar montages measure the difference in potential between adjacent electrodes, so are less prone to internally generated artefacts, but information can be lost. This is because voltage changes affecting both electrodes equally will not result in a deflection in the EEG recording (75).

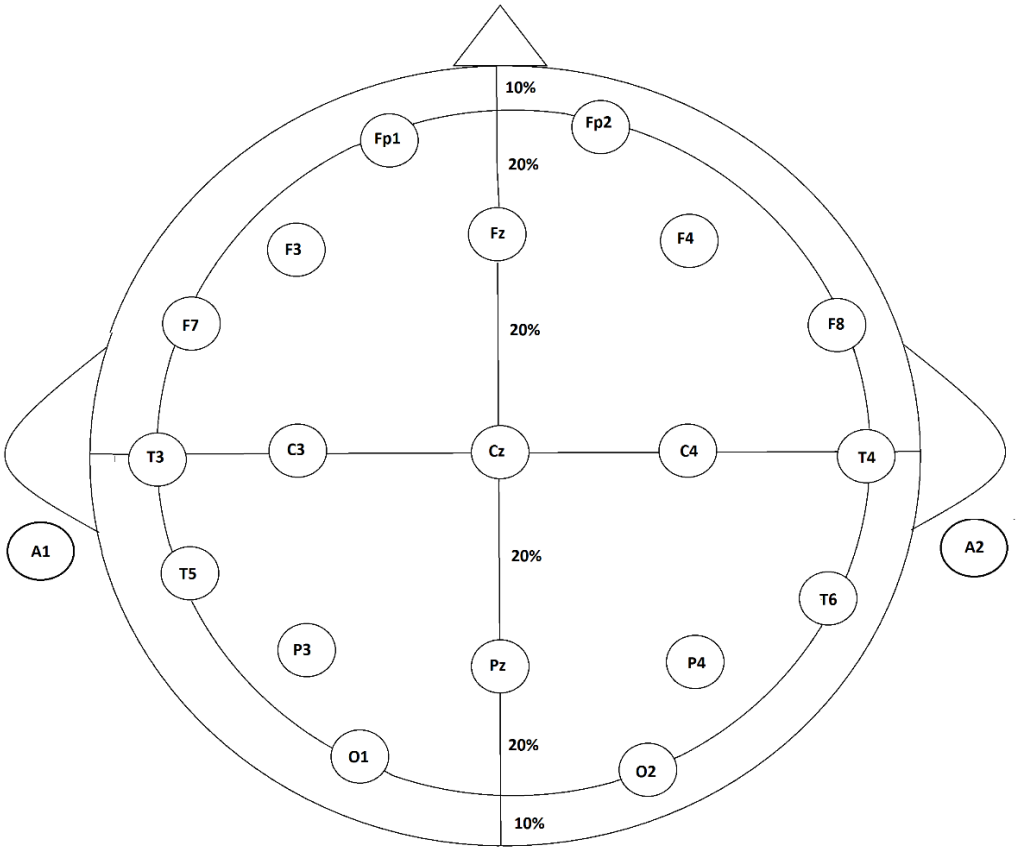


Figure 1-6 Position of the electrodes as determine by the 10 20 system. Note that A1 and A2 are reference electrodes placed on the ears

The EEG generates a montage of activity which generally takes waveform in real time (76). These waveforms represent the oscillations in electrical potential caused by neuronal activity. (68). Often these waveforms are separated historically into four different classes, based upon frequency, for descriptive purposes. Delta waves are classified as 0.1-4 Hz, theta waves 4 Hz to 8 Hz, Alpha waves 8 Hz to 13 Hz, beta waves > 13 Hz. (76). In addition higher frequency classes have also been defined as technology became available to detect them, such as gamma waves, which are in the frequency range of 30 – 100 Hz (77). These waveforms arise from the interaction of populations of neurons (78).

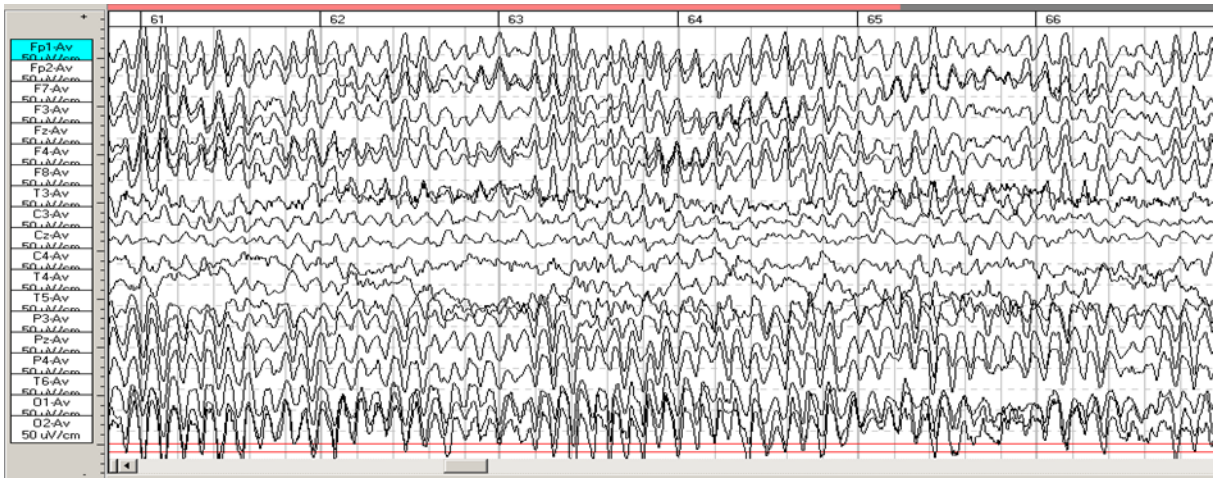


Figure 1-7 Example of an EEG recording. Note the electrodes are named on the left side of the image, and are referenced to an average common reference. The tracings have a waveform that represents the combined activity of thousands of local neurons near the recording electrode.

EEG technology can be used to measure the physiological activity in the brain in real time (76). One of the reasons that this is useful is it allows us to measure the functional connectivity of parts of the brain, which might be affected by Alzheimer's pathology.

Basic Signal Analysis

When recorded digitally, oscillating signals like the EEG can be analysed quantitatively. The most fundament of these analyses is the Fourier transform, which takes a complex oscillating signal and splits it up into its frequency components, see Figure 1-8. The output of the Fourier transform can be used to calculate the power of a particular frequency, or more simply, the amount of that frequency which makes up the waveform. (79) The power of each frequency can be linked to physiological and pathological variables, such as the memory function in traumatic brain injury (80). Using a Fourier transform to generate a frequency power curve for each electrode generates data map called a quantitative EEG (qEEG) (81).

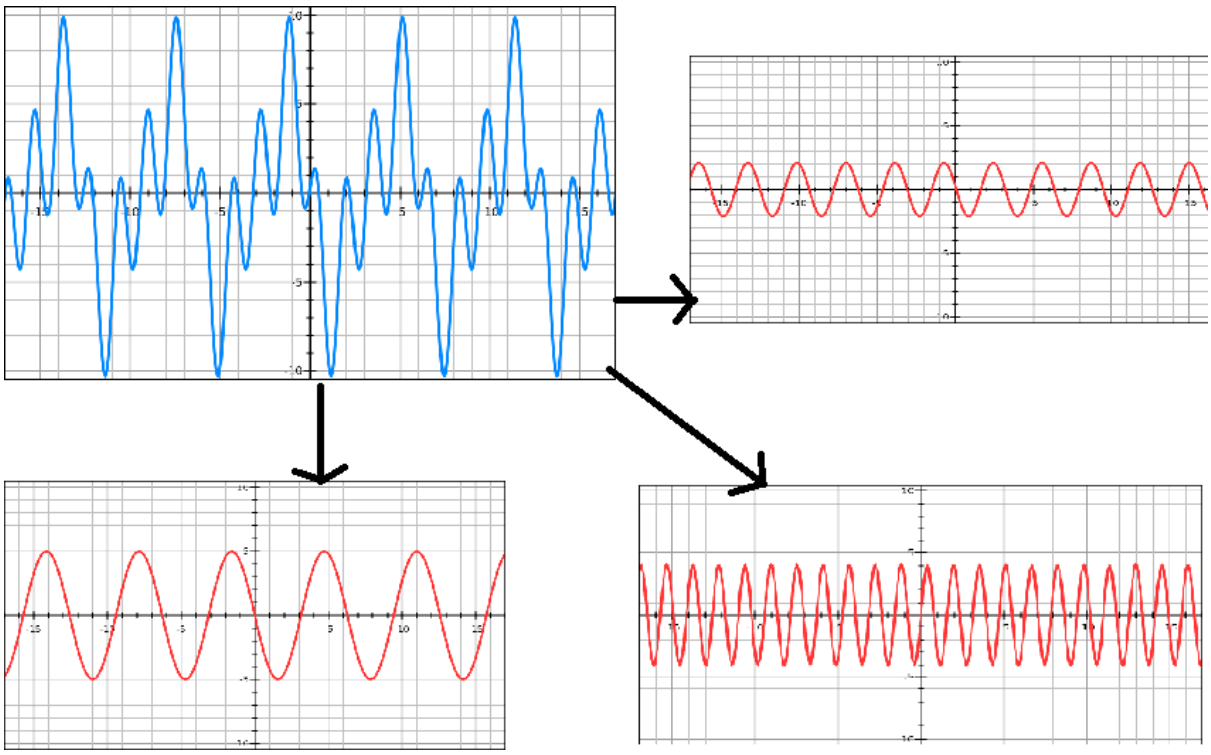


Figure 1-8: The Fourier transform allows a complex waveform to be separated into component simple waveforms

A method of performing the Fourier transform is called the Fast Fourier Transform. It is called the Fast Fourier Transform because the computing power required to run the transform is less than is required for other methods (82), and thus it can be performed in real time with modest computing power.

Source Localisation

Analysis of EEG can be used to measure the activity of the brain cortex deep within the skull (83). This is called source localisation. The methods of doing this all involve taking the measurement of generated voltage at the scalp and estimating where the source of that generated voltage is in three dimensions. This is an inverse problem mathematically, which has multiple solutions (84). While the forward problem has one unique solution, the inverse problem has multiple solutions.

Standardised low resolution electromagnetic tomography (sLORETA) is a method of performing an inverse solution on a set of electrode potentials (85), as is the related method exact low resolution electromagnetic tomography (eLORETA) (86). Both of these methods are derived from Low

Resolution Electromagnetic Tomography (LORETA), which was the first in this family of inverse solution methods designed to calculate the current density state across the whole brain (87). sLORETA method works by applying a set of electrode potentials to a mathematical model of a brain and head. This model contains

- 3 shelled, spherical model, with shells representing the head, with shells representing the skin, the skull and the cortex (85)
- A brain map containing 6430 voxels, which are volumes of cortical grey matter, co-registered to a standard brain map called the Montreal Neurological Institute (MNI) 125 brain (88).

The method then models the interaction of current in each of the voxels with the head model. It applies the recorded electrode potentials to this model in order to generate a map of current density at each voxel that would produce the potentials at the electrode (85).

sLORETA has been shown to accurately localise sources with zero error under ideal conditions. However, their limitation is that they are relatively low spatial resolution techniques, and so these methods localise a generated potential to a relatively large area compared to fMRI tools (85).

The sLORETA tool can be used to assess the functional connectivity of two parts of the brain. This is done by first applying the sLORETA method to generate a stream of activity for two separate neural masses. Then, the phase lagged synchronisation between those two activity streams is calculated. This will give us a measure of functional connectivity between those two pre-specified areas of the brain(86). For a description of phase lagged synchronisation, see the functional connectivity section below. Synchronisation different frequencies or frequency bands such as theta band and alpha band might reflect cross frequency coupling type communication in different brain regions, and thus be a marker of functional connectivity (89). Cross frequency coupling is further discussed in the functional connectivity section below.

EEG biofeedback

It may be possible to change the pattern of activity and connectivity in the EEG to reduce symptoms of neurological disease, change pathological processes or generally improve cognitive function (90). This is the principle of biofeedback treatments. EEG biofeedback is a kind of learning procedure where the subject is trained to alter the pattern of activity in their brain by entraining the desired pattern to a stimulus (91). This involves rewarding the patient when the desired pattern of activity is present so that they can learn to self-regulate the activity (90). This has been shown to have a benefit in a number of clinical conditions such as Attention Deficit Hyperactivity Disorder (92), epilepsy (93), addiction disorders (94) and tinnitus (95).

EEG biofeedback can be used to alter the rhythmic EEG activity of the brain (90). To achieve this, EEG recordings are analysed in real time using the Fast Fourier Transform (82) to give the relative power of discrete bands of EEG frequency. The power is a measure of how much of a given frequency of signal is present. If the power of the specified frequencies is in the desired range, the subject is rewarded by a change in a display on a computer screen, for example, elevation of a bar graph. Over time, the subject learns to maintain the relative EEG frequency-specific powers at levels to achieve the desired output (90). In this way the person undergoing biofeedback learns to self-regulate the ongoing activity of the cortex (93). The process of EEG biofeedback is represented diagrammatically below in Figure 1-9. In addition, sLORETA can be used to source localise EEG activity in real time to train deeper structures, rather than superficial cortex.

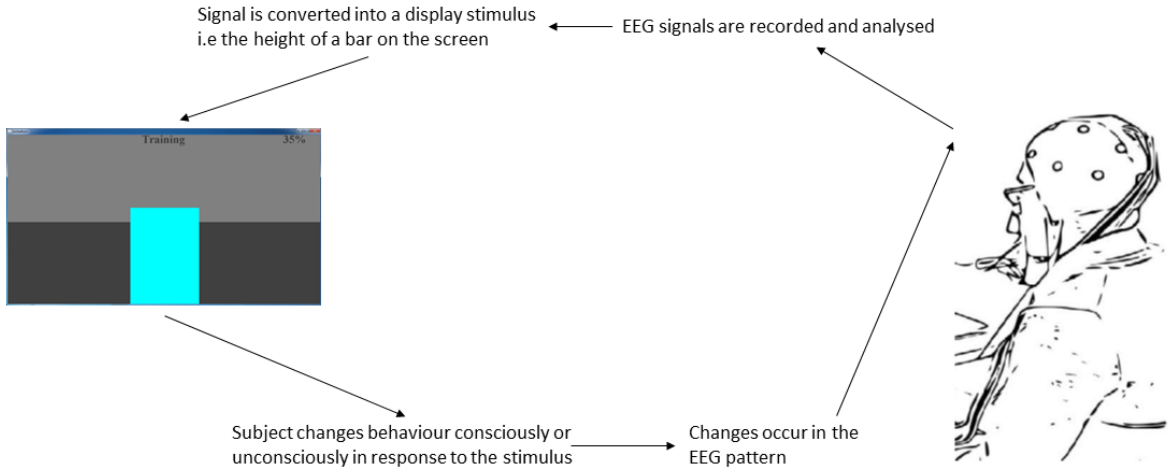


Figure 1-9: Schematic of the biofeedback process

EEG biofeedback down-training of alpha rhythms has been shown to increase functional connectivity in the salience network, a network involved in sensory attention (96). The study used the alpha power at Pz as the feedback variable, indicating that EEG biofeedback of frequency power at a particular location can be used to alter functional connectivity. A detailed description of what function connectivity is and a methodology for calculating it is contained in the section below. Additionally, direct training of functional connectivity has also been demonstrated using MEG technology (97). Using biofeedback to improve functional connectivity may be more effective at changing behavioural outcomes than changing the power of a particular frequency at a particular location (98). Supporting this, there is also evidence that biofeedback training can alter white matter networks as well (99). The potential to change the connectivity of the brain is promising, as disruptions to brain networks may be responsible for the emergence of neurological symptoms in disease. This is described below for Alzheimer's disease, but it is also true for conditions such as schizophrenia (100), ADHD(101) and tinnitus(102).

Functional Connectivity

Functional connectivity is the synchronisation of patterns of activity, such as the oscillations in electrical potentials measured in the EEG, between distant regions of the brain. It is a purely statistical correlation (103). For example, when the PCC has EEG waveform activity that is synchronised with the EEG waveform of the parahippocampal gyrus, it is said to have high functional connectivity. Figure 1-10 demonstrates the basic principle of functional connectivity. Functional connectivity can be measured with a variety of techniques, including functional magnetic resonance imaging (fMRI) studies with blood oxygen level dependent contrast imaging (BOLD) as well as with EEG. Although the various methods are similar and have been shown to correlate in some circumstances (89, 104), the different methods may not show exactly the same phenomenon. BOLD imaging measures slow changes in blood oxygen utilisation in areas of the brain. Areas that show synchronised changes in blood oxygen utilisation are said to be functionally connected (105) which is different to EEG. EEG methods of characterising functional connectivity involve measuring the synchronisation of oscillations in neuronal activity in specified frequency bands (106). EEG measures of connectivity and fMRI BOLD measures of connectivity may not correlate well in the resting state.

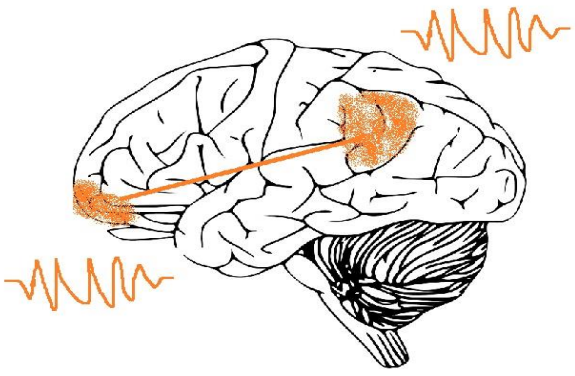


Figure 1-10: Demonstrates the principle of functional connectivity. The two regions in orange are communicating. The oscillations in electrical potential are synchronised between the two regions. These oscillations can be measured by EEG. Adapted from public domain

Phase lagged Synchronisation

EEG methods of calculating functional connectivity take the montages of activity measured by the electrodes of the EEG and produce calculations of how synchronised the activity between two regions is. Functional connectivity between EEG signals is called coherence. One way of calculating this is phase synchronisation (107). Given a wave with a repetitive waveform, the phase is how far along one cycle it is (108). To calculate phase synchronisation, the phase of one wave is compared to another wave at different time points. If the phase is the same at those times, then the phase synchronisation is high (107). On the other hand, if the phase do not align often then the phase synchronisation is low. The total phase synchronisation consists of two components, the instantaneous phase synchronisation plus phase lagged synchronisation, which is synchronised but at a time offset. The principle of phase synchronisation is demonstrated below in Figure 1-11.

One of the issues with measuring functional connectivity using EEG is the problem of volume conduction (109). Volume conduction is the transmission of electric fields from an electric primary current source in the brain through biological tissue such as skin towards distant sensors. This is as a signal produced in the brain can be detected by multiple electrodes, which makes finding the source of that signal difficult as there are multiple places it could be based on scalp measurements. When measuring synchronisation, this can lead to high false levels of coherence, because what is being detected is a single oscillator in multiple electrodes (110). Using the phase lagged component (110) avoids volume conduction giving false positive synchronisations. That is, for two different oscillators to be synchronised they must have a phase lag of greater than 0. This takes into account the fact that neural masses, if they are any significant distance apart, will not communicate instantaneously because time is needed for action potentials to conduct down axons. Phase lagged measures of synchronisation tends to underestimate true levels of synchronisation, as one common source. For example, the thalamus can send signals to different parts of the cortex resulting in instantaneous coherence. But phase lagged synchronization more accurately detects true

connectivity under simulated conditions than other measures (110).

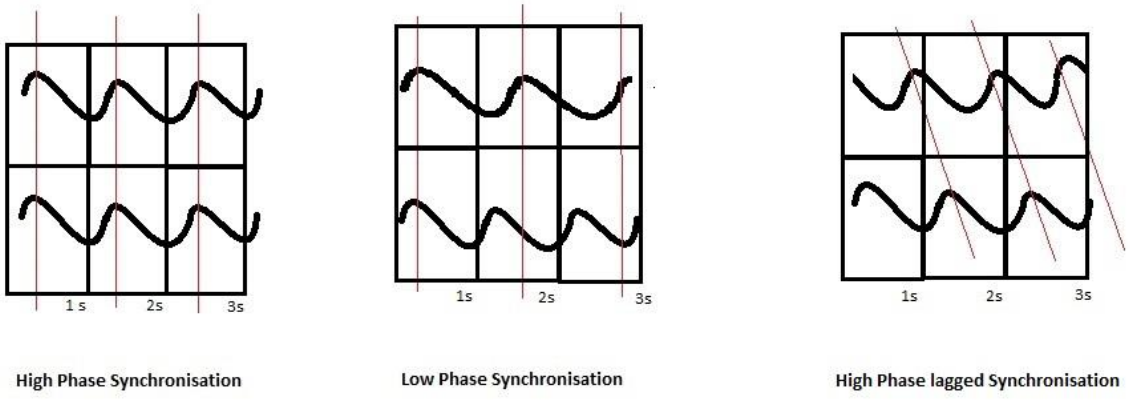


Figure 1-11 Demonstrating Phase Synchronisation. The left most waves have high phase synchronisation, because the waves are often in the same phase, for example the peaks and troughs occur at the same times. The middle set of wave has low phase synchronisation because the wave are not synchronised, for example the peaks and troughs do not align. The final set of waves have high phase lagged synchronisation because the waves are synchronised, but are offset by some amount of time.

Cross frequency coupling

It is hypothesised that low frequency oscillations such as theta, alpha and beta waves act as carrier waves, which distant neural masses use to encode and decode information stored in gamma waves (111), so that the two regions which are communicating will be synchronised in a theta oscillation in order to be 'reading the same message'. It has been found that this kind of cross frequency coupling correlates to fMRI based measures of functional connectivity (89). Cross frequency coupling often occurs through a process called phase amplitude coupling. This is where the amplitude of a high frequency wave is modulated by the phase of a low frequency wave. For example, if a high frequency wave occurs at the peak of the low frequency wave, its amplitude will be maximal. Conversely, if it occurs during a trough of the low frequency wave, its amplitude will be minimal (111). Phase amplitude coupling in the theta band to the low gamma band may be important to human cognition, including memory. The amplitude of waves in the 30-60 Hz range is modulated by the phase of waves in the 4-8 Hz range, and it is thought this particular theta -gamma coupling is important to the retrieval of memories (112).

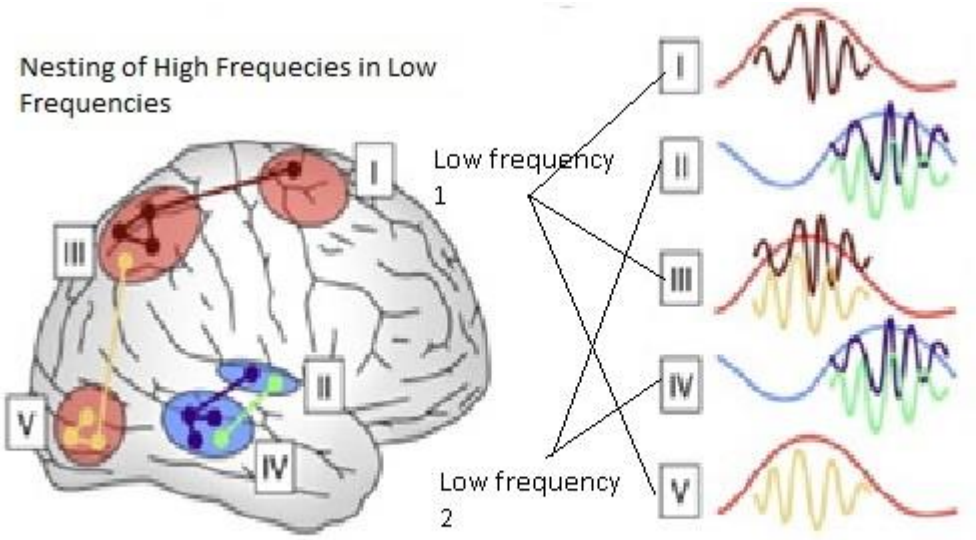


Figure 1-12 Demonstrating the nesting of high frequency waves in low frequency waves. Areas communicating with low frequency one are functionally connected. Areas communicating in low frequency 2 are also functionally connected. High frequency messages are embedded in the low frequency carrier waves. Adapted from Figure 7, Engel, Andreas K., et al. (2013). "Intrinsic Coupling Modes: Multiscale Interactions in Ongoing Brain Activity." Neuron 80(4): 867-886.

Neural Oscillations in Relation to Memory

Alpha and theta frequency oscillations are likely important to memory function. As previously mentioned, memory retrieval relies on theta band oscillations in the hippocampus with information encoded on the theta wave by theta gamma phase amplitude coupling (111). The white matter structural connection between the parahippocampal cortex and the PCC (56) likely facilitates the functional connectivity necessary to transfer information in the coupled wave. Therefore, functional connectivity in the theta domain between the PCC and parahippocampal cortex is likely to be important to the retrieval of memory. Without the connectivity between the PCC and the parahippocampal cortex the information encoded in gamma frequency waves cannot be decoded by the default mode network (111).

The integrity of the DMN functional connections is also important to the retrieval of memory. Functional connectivity in the alpha domain in EEG studies have the strongest correlation to the fMRI measured connectivity (113). These fMRI measures are strongly associated with memory function (114). Therefore, connectivity between the nodes of the DMN in the alpha domain is also

likely to be important for memory retrieval. It is possible that alpha waves may be phase amplitude coupled to gamma waves in a manner similar to theta waves (115). Thus alpha wave connectivity could be transferring memory data from the PCC to the rest of the DMN, as a mechanism for memory retrieval.

AD and Structural Connectivity Changes

The accumulation of beta amyloid plaques and neurofibrillary tangles in Alzheimer's disease results in loss of connectivity, which leads to the hypothesis that AD symptoms are the result of the failure of connectivity (19). The parahippocampal gyrus and medial temporal lobe structures are often affected by neurofibrillary tangle pathology (64). This area has strong links to the PCC in primates, which has been shown in dissection of the brains of macaque monkeys (56), and the reduced connection may be one of the reasons for the observed reduction in metabolism in the PCC (116). The parahippocampal gyrus is the link between the self-referential default mode network and the medial temporal lobe memory system, as demonstrated by functional imaging (117). It is suggested that symptoms of AD may arise not mainly from damage to a particular part of the brain, but from a loss of connectivity between different regions of the brain, particularly the connection of the DMN to the medial temporal lobe. This is caused by anatomical disruption of neurons by neurofibrillary tangles and the death of neurons. The disconnection results in the symptoms seen in Alzheimer's disease (19). This is supported by evidence that medial temporal lobe white matter tracts to the PCC are disrupted in AD, and that this disruption is correlated to cognitive symptoms (118).

A study looking at the graph theoretical analysis of networks in AD found that the white matter networks had a tendency toward randomness, and a loss of small world topology (119). That is, there is a loss of long range connections and increased tendency to form short range connections. In addition, the number of nodes information must pass through to get to any other particular node increases. This is called increased path-length. These features are demonstrated in Figure 1-13. The analysis was modelled on diffusion tensor imaging which highlights anatomical connection in white

matter tracts. This suggests a loss of integration of function in the brain, which is directly related to anatomical disconnection in white matter tracts. This may be the result of damage to hubs, which are preferentially affected by AD (58). A computational study has suggested that this pattern of damage specifically to hubs may be due to Activity Dependent Degeneration (120). This found that highly connected hubs have higher activity, and that if this higher activity was linked to higher rate of damage occurrence. The simulation closely resembled the increasing randomness seen in AD. This study is corroborated by findings which show neural activation correlates with beta amyloid plaque deposition, suggesting that the higher activity of the hubs may be the cause of the pattern of damage seen (121).

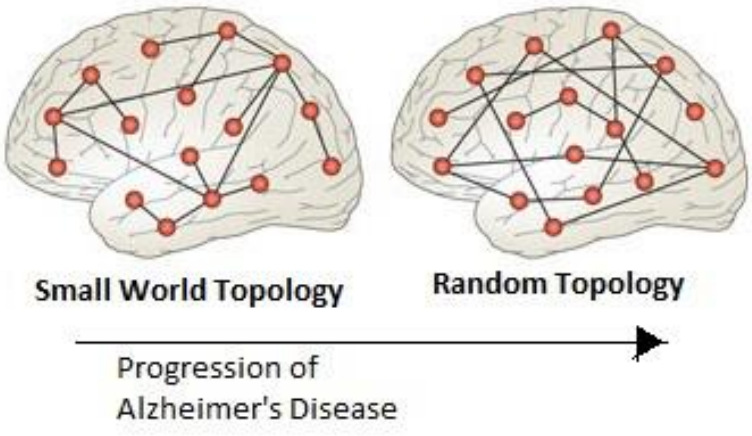


Figure 1-13 As Alzheimer's Disease progresses there is a loss of small world topology. There discrete modules seen on the left are not seen on the right. There is loss of long range connections and an increased tendency to form short range connections. Adapted from Bullmore, E. and O. Sporns (2012). "The economy of brain network organization." Nat Rev Neurosci 13(5): 336-349.

Alzheimer's pathology begins accumulating years before the onset of clinical symptoms (65). This has led for a drive to identify people who are at early stages of the disease and may benefit from intervention to change the pathological process (122). This fact caused the drive to develop the concept of mild cognitive impairment as an intermediate stage between normal aging and dementia, which presumably a person with AD would pass through as their condition progresses (122).

AD and Functional Connectivity

Studies of functional connectivity, as measured by EEG synchronisation, show that there is altered connectivity in AD and MCI (123) (124), These studies in general support the hypothesis that Alzheimer's can be conceptualised as a disconnection syndrome (19), and the evidence presented below points to the default mode network, and specifically the PCC as a potential target for intervening in changes seen in functional connectivity. Furthermore, some of the studies below show there is a correlation between functional connectivity and cognitive performance, suggesting that changing connectivity measures may result in some clinical benefits.

Stam et al. (123) found that there was a reduction in the beta frequency coherence in electrode/sensor space found in people with Alzheimer's They also found that this reduction in beta connectivity was associated mini-mental state examination (MMSE) scores. The Mini Mental State Examination (MMSE) is a short assessment of memory and cognition that is often used to screen for dementia (116). This suggests that the reduction in beta connectivity was associated with the pathological process of Alzheimer's disease. Rossini et al. (125) similarly measured coherence. They targeted people with MCI as a way to predict whether they would convert to AD. This study found that higher parietal-frontal coherence was associated with conversion to AD, and MCI with normal coherence didn't convert. In both, deranged connectivity across the whole brain was shown in people with AD and in those who would convert to AD. However, neither Stam et al nor Rossini et al used phase lagged synchronisation, so are affected by volume conduction effects. Neither study was source localised, which limits the ability to interpret the study in the context of damage to functional networks.

Hsaio et al. (126) looked specifically at default mode network connectivity in mild AD compared to MCI, using source localised EEG and imaginary coherence, which is another method for calculating coherence with the aim to reduce the effect of volume conduction. Participants were tested cognitively with the MMSE. They showed that compared to people with MCI, people with AD had

altered connectivity throughout the default mode network. The PCC had reduced connectivity to inferior parietal cortex, anterior cingulate cortex and the precuneus region. Increased connectivity of the left PCC with the right medial temporal lobe in the theta band was associated with lower MMSE score. This increase in connectivity may indicate a compensation for loss of connectivity to other regions. This study identified the PCC as a hub where altered connectivity is a marker for disease progression.

These changes in connectivity have an impact on the organisation of functional relationships within the default mode network. Canuet et al. (124) used eLORETA to measure cortical sources of activity and relate the pattern of coherence to network topology. Reduced levels of alpha and beta synchronisation were identified compared to normal controls, and increased levels of theta synchronisation. They found that theta frequency synchronisation was negatively correlated with MMSE score. Overall, the network topology showed a tendency toward randomness and as loss of 'small world' topology, as a result of reduced long range connections. However, the measures of connectivity used in the first study were measures of gross connectivity between the different lobes. This does not give us information about the effect on discrete networks like the Default Mode Network, which may be more relevant to the pathological process of AD than general measures of connectivity. These results are similar to those of Vecchio et al. (127) who also found that there was an increased tendency toward randomness of network structures, with increased path-length and increased clustering. This points to a change in network characteristics which may be due to the degeneration of long distance connections from hubs. Therefore an area like the PCC which is a highly active hub is a good target to intervene at if the goal of treatment is to maintain small world type topology in the brain.

The findings of deranged connectivity are replicated in MEG. Buldu et al. (128) found that there was an increased tendency toward functional connectivity between lobes. They suggest that there is a decreased modularity of functional connectivity relationships in MCI, meaning that there is loss of

segregation of function found in MCI. The study's authors hypothesised that this may be a compensatory mechanism for loss of connectivity. This study was also limited by not having source localisation. Also, it focussed on connectivity between the lobes of the brain. A lobe may contain multiple networks, some of which may be up-regulated and down-regulated. So, looking at connectivity between the lobes is an average of all the different affected networks, which cannot tell us anything specific about those networks.

BOLD based studies of connectivity show that the default mode network definitely has altered connectivity (129). In particular there is decreased functional connectivity between the PCC and medial temporal lobe structures (130, 131). Also increased functional connectivity between the PCC and other parts of the brain in MCI has been observed (130, 131), including between the PCC and the frontal lobe, and the PCC and the anterior cingulate cortex. It is hypothesised that the increase of functional connectivity is due to the brain adapting to the reduced connectivity to other regions (130). When the person has developed AD this connectivity is lost and there is a decrease in functional connectivity seen throughout the brain (132). These changes in connectivity correlate with changes in cognition seen in MCI (130, 131), suggesting that the changes in connectivity are directly impacting on cognitive functioning. The spatial distribution of the accumulation of tau proteins appears to correlate with decreased functional connectivity in those areas, as measured by fMRI BOLD (133). However, these studies use fMRI BOLD activity to detect functional connectivity, which may not correlate well with the phase lagged EEG synchronisation in the resting state that is being looked at in this study.

The evidence above points to a change in functional connectivity in the default mode network, in particular the PCC in AD. This is consistent with the pattern of pathology seen in AD (65). The PCC is vulnerable because it is a highly active hub, and it becomes anatomically disconnected as a result of Alzheimer's pathology. It is even suggested that these changes in functional connectivity may be harmful, putting the remaining neurons at risk of counter-productive compensatory activity

dependent damage (120). This suggests that reversing these changes in functional connectivity may prevent further damage to the PCC, and therefore preserve memory function.

Low frequency training of the DMN

Training of the PCC, as the primary hub of the DMN, may change the connectivity of the DMN as a whole. Vanneste et al (134) found this in a study of alpha feedback localised to the PCC by sLORETA in order to treat tinnitus. A key clinical feature of tinnitus is distress. The authors used a protocol that up train alpha current density and down train beta connectivity in the PCC. The original intention with this protocol was to change the ratio of alpha and beta current density within the PCC. However they found that there was no difference in the power of these frequencies after training. However, the authors did find that the connectivity decreased between the PCC and areas associated with distress such as the dorsal anterior cingulate cortex. Tinnitus is characterised by hyper-connectivity between the DMN and these areas (102). It was concluded that the training of the PCC didn't influence the localised activity of the cortex, but rather normalised abnormal functional relationships within the DMN. Furthermore, the functional connectivity between the PCC and parahippocampal cortex increased with the alpha training. In training the PCC in a similar manner, it might be possible to strengthen the connectivity between the DMN and the memory centres in people who have disrupted networks.

Summary

Alzheimer's disease is a chronic and progressive condition characterised by loss of memory function. Biochemical processes beginning with the deposition of amyloid plaques results in the anatomical disconnection of neurons, through disrupted axons and cell death. When there has been sufficient damage to the structural connectivity of important structures, such as the DMN, this results in alterations of the functional connectivity of those structures. Loss of functional connectivity in the default mode network is related to the loss of memory function seen early in AD. Intervention before the onset of full dementia could improve memory function and prevent the onset of AD. At the aMCI stage of AD, it may be possible to change altered connectivity relationships in order to

restore memory function, and potentially prevent further decline. Targeted EEG biofeedback of the PCC, to normalise altered functional connectivity relationships in the DMN, could be such an intervention.

Aims

This thesis aims to demonstrate whether EEG biofeedback of activity in the posterior cingulate cortex can be used to improve memory outcomes in mild memory loss associated with possible Alzheimer's pathology.

The general aim of this thesis are:

1. To find out whether 15 sessions of sLORETA biofeedback training of the PCC improve memory outcomes on objective testing
2. Find out whether sLORETA biofeedback of the PCC changes the neural activity as measured by the EEG, and whether this change is correlated to changes in objective memory scores
3. To find out what covariates influences the effectiveness of sLORETA biofeedback training of the PCC.
4. To find whether EEG variables such as current density and phase lagged synchronisation calculated using sLORETA can be used as a biomarker for memory dysfunction in aMCI

Hypothesis

The central hypothesis is that Alzheimer's pathology results in structural changes in the default mode network, which in turn causes changes to the functional connectivity of the network.

Changes in functional connectivity will result in cognitive changes seen in MCI, and specifically results in memory loss. Biofeedback intervenes in this process by optimising the functional connectivity, restoring functional connectivity relationships toward normal, which normalises memory outcomes restores memory function. This hypothesis is summarised in Figure 1-14 below.

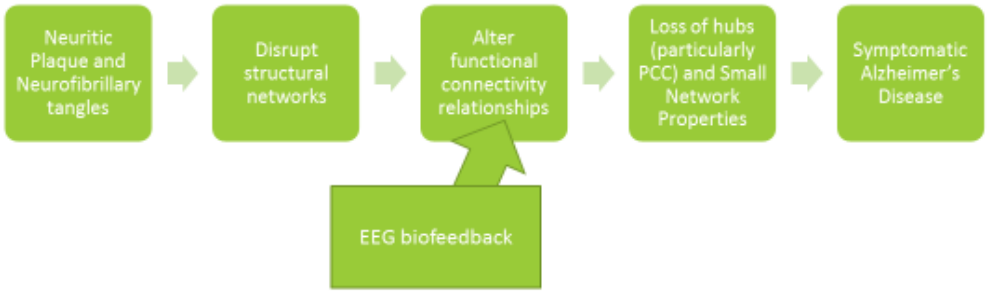


Figure 1-14 Summary of Alzheimer's model and rationale for using biofeedback as an intervention

Specifically, when we use source localised phase lagged synchronisation to measure the functional connectivity of the PCC we will see altered synchronisation patterns in people with MCI compared to aged matched people with normal cognition. If it is similar to the patterns seen in fMRI based studies, then we would expect to see reduced connectivity to the medial temporal lobe structures and increased connectivity to frontal lobe structures. These changes may occur in the frequency bands which act as carrier waves, the theta waves and the alpha waves.

Using EEG biofeedback to increase levels of theta and alpha in the PCC may improve functional connectivity in these bands. We hypothesise that increased levels of theta synchronisation within the default mode network will correlate with increased cross frequency coupling.

Chapter Summary

In chapter 2, a review of experimental studies looking at EEG biofeedback as a treatment to improve memory outcomes is presented. Common experimental procedures are identified and some basic analyses are done to try to identify factors which influence the effectiveness of biofeedback training.

In chapter 3, the methods of data collection and analysis are given. Here, the EEG equipment and setup, and the subsequent processing and analysis of the EEG data is described. The cognitive tools used to characterise the participants in the biofeedback trials are also described.

Chapter 4 describes the trial design and results of the pilot study conducted in 2015. This study was a pre to post internally controlled study, looking at the effect of biofeedback training in 10 people. This study tested the feasibility and trialled the methods for the larger randomised trial subsequently conducted.

Chapter 5 outlines the trial design and clinical results of the randomised trial conducted in 2016. This was a larger scale trial than the pilot trial, conducted in a more general population. This trial was designed to test source localised against a placebo biofeedback program, and also test the effect of changing the biofeedback parameter. The results of cognitive testing are also described in this chapter, focussing on the memory sections of the cognitive test. Basic analysis of the EEG data is also presented in this chapter

Chapter 6 describes further analyses of the randomised controlled trial. This chapter particularly focuses on connectivity markers in the PCC and DMN. The aim of this kind of analysis is to identify EEG biomarkers that might be able to track the progress of individual biofeedback recipients and may be able to provide some explanation for the change in clinical outcomes. In addition, further analysis of the use of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is presented in this chapter

Chapter 7 summarises the findings of the pilot trial and the randomised trial. This chapter discusses the interpretation of the results of the randomised controlled trial and discusses the methodological issues with this study.

Chapter 8 discusses aspects of the results and makes recommendations for future trials and for the development of sLORETA biofeedback as a treatment for memory issues in older age. This chapter also discusses methodological considerations for research of biofeedback as a treatment for neurological conditions, using biofeedback for memory as an example.

Chapter 2 Review of Biofeedback and Memory

Method

Search Strategy

In order to investigate the use of biofeedback to improve memory, we conducted a systematic review of studies using biofeedback to change objective memory outcomes. The databases MEDLINE (Ovid SP), PsycINFO (Ovid SP), Embase (Ovid SP), Web of Science (Thomas Reuters Web of Science) and Scopus (Elsevier B.V Scopus) were searched. The keywords "'biofeedback OR neurofeedback' AND 'memory' " were used to identify articles. Further articles were identified through citations. All articles through to November 2015 were included in the review.

Articles identified by this search strategy had to meet the following criteria to be included in this review:

1. Participants had to be treated with any kind of non-invasive biofeedback of the central nervous system, such as EEG biofeedback, real time fMRI neurofeedback, or hemoencephalographic feedback
2. Participants had to be over the age of 18
3. Other forms of biofeedback were excluded, including heart rate variability training
4. Objective measures of memory had been used, regardless of whether this was a primary or secondary objective.
5. Studies using measures of procedural memory, such as motor memory, were excluded from the review.

Detailed analysis

A more detailed analysis was carried out on a subset of the studies identified. The characteristics of studies included in the meta-analysis are as follows:

1. The report stated that participants were free of pre-existing conditions, particularly neurological conditions.
2. Participants were randomised into either an intervention group or a control group.

3. Biofeedback presented EEG parameters to the participants
4. Results of the study were reported so that the effect size could be calculated.

The aim of this analysis was to identify how the parameters of biofeedback training sessions affected the result of the study. We aimed to look at the length of biofeedback training, how often the biofeedback training occurred and total number of sessions, and how each one impacted the change in the cognitive tool the study was using.

Meta regression

Because the studies included each used different cognitive tools, the effect size was calculated for each study. First, the effect size of for the experimental group was calculated using the following formula.

$$Effect\ Size = \frac{Mean\ Score\ after\ training - Mean\ Score\ before\ training}{Pooled\ Standard\ Deviation\ (s_{Pooled}\ )}$$

Where

$$s_{Pooled} = \sqrt{\frac{(n-1){s_1}^2 + (n-1){s_2}^2}{n+\ n}}$$

And

$$n = number\ of\ people\ in\ the\ group$$

$$s_1 = standard\ deviation\ before\ training$$

$$s_2 = standard\ deviation\ after\ training$$

The same formula was used to calculate the effect size in the control group. This generates a statistic representing the impact of either the intervention or the placebo on the cognitive score. Next, the

difference between the effect size in the experimental group and the control group was found. This gives an estimate of the effect of training over the placebo effect.

The difference in effect size was then plotted in a scatter plot against the length of biofeedback session, the number of biofeedback sessions in total and the number of biofeedback sessions per week. In studies which used biofeedback training that lasted less than a week, the number of biofeedback sessions per week was extrapolated. Studies that reported biofeedback as '3 or 4' times a week were assigned as 3.5 biofeedback sessions per week.

We then used Wilson's meta-regression macros for SPSS (135, 136) to determine the direction of any relationships between the parameters of biofeedback sessions and the difference in effect size. The difference in effect size, study weight calculated using Revman 5.3 software (137), and the covariates length of session, sessions per week, number of sessions, and total study size were used as inputs.

Because of the heterogeneity of the kind of biofeedback used in the different studies and the different cognitive tools used, only very broad conclusions can be drawn from this type of analysis and interpretation of any regression or other analyses needs to acknowledge the caveat around validity due to heterogeneity.

Validation

In a three part review of EEG – biofeedback for optimising performance (138-140), a model for assessing the validity of the outcomes for biofeedback studies was put forward. Broadly this model requires specificity, and comparison against a control group or a relationship between neurofeedback learning and memory assessments.

Specificity here refers to a number of different elements within a neuro-feedback study. The first element is band specificity. This refers to whether only the trained bands are affected by the biofeedback training or whether there is are additional effects in other bands. Cognitive specificity

refers to whether the training only had an impact on a particular cognitive process, such as memory, or whether other cognitive processes were affected as well. Topographical specificity refers to whether the training only had an effect on the specific training site, or whether a change in the EEG pattern can also be found at distant sites.

When an EEG change in an experimental group occurs, this change can be validated against the cognitive outcomes. For example, if an experimental group has been exposed to alpha training at a particular site, and they have successfully increased the alpha power at that site compared to a group exposed to placebo training, then if the training is validity, there should be a cognitive difference between the experimental group and the placebo group. A second way to assess this evidence is whether feedback learning, such as increased alpha power, has a direct relationship to cognitive outcomes. Participants who have been able to increase their alpha power more should increase their cognitive outcomes more, and therefore there will be a correlation between the neurofeedback learning and the cognitive outcome.

An analysis for these elements of validity was performed of all the controlled studies and the pre – post studies. These studies were assessed for whether they showed band specificity, cognitive specificity and topographical specificity. Then, the studies were assessed for whether the cognitive outcome was unique to the experimental group, and absent from other experimental and control groups. Finally, they were assessed for whether there was a correlation between the neurofeedback outcome and the cognitive outcome.

Studies which demonstrated band or cognitive specificity, and at least one element of validity were included in this third section. Topographical specificity is not considered here given the importance of topographically dispersed cognitive networks, such as the DMN, to memory. The common characteristics of these studies are reported here.

Key Definitions

The following section explains key definitions related to the studies. Terminology varies between the studies, so for ease of reading the following terms are used.

Young and old refer to less than 65 and older than 65 respectively. Some studies have different definitions than this, so where this is the case that definition is stated.

The standard definition of frequency bands in the EEG is given below in table 2-1.

Table 2-1: Standard definitions of Frequency Bands

Name of Frequency Band	**Band range (Hz)**
δ (delta)	0 – 4 Hz
θ (theta)	4 – 8 Hz
α (alpha)	8 – 12 Hz
β (beta)	13 – 31 Hz
γ (gamma)	31 – 64 Hz

Another frequency band often used in studies of biofeedback is Sensory Motor Rhythm (SMR). It is typically the predominant frequency found over the primary sensory and motor cortices, and is in the frequency range of 12 -15 Hz (141).

Sometimes alpha frequency is not defined in terms of an absolute band range, but rather in terms of an individualised alpha peak. When a segment of EEG is Fourier transformed, and the power is plotted over the frequency, often a peak occurs in the 10-14 Hz range under the closed eye condition, and frequency of this peak will vary from individual to individual. This is the peak alpha frequency (PAF), see Figure 2-1 below. For a basic explanation of the Fourier transform and power, see chapter 1. Individual upper alpha band is generally defined as the PAF to the PAF plus 2Hz, and individual lower alpha band is defined as the PAF to the PAF minus 2Hz (142-146). Nan et al (147)

define upper alpha as the band between the PAF and the point where the eyes closed Fourier transformed curve intersects the eyes open Fourier transformed curve.

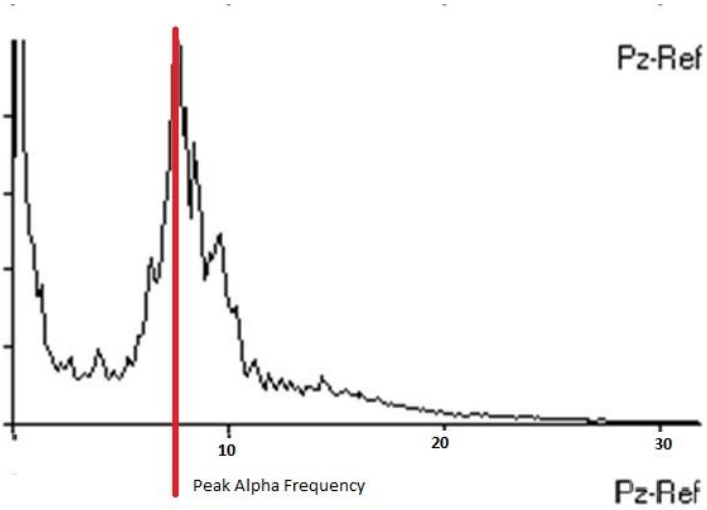


Figure 2-1 Demonstrating Peak Alpha Frequency

When a Fourier transform is done, the output is the power of a signal in a frequency range. Absolute power refers to this power output. Relative power refers to the percentage of the power in the band range over the maximum power output. Relative power is a slightly different measure of EEG power as relative power can remain the same even is the absolute power changes, if other frequencies are affected similarly by biofeedback training for example (147).

Electrode positions are stated according to the standard 10 –5 configuration (74). Hseuh et al (148) use a 64 electrode cap with twin electrodes in the 10 -20 configuration, for example C3a is an electrode anterior to the C3 position, and C3b is posterior to the C3 position.

EEG montages are monopolar montages referenced to a non-cerebral location such as the earlobes unless otherwise stated. Bipolar recordings used for biofeedback are stated with the two electrodes used to make the bipolar montages.

Several of the studies identified looked at memory encoding during sleep (149-151). There are several key definitions related to sleep used. Sleep spindles are a EEG event that occurs during stage two sleep (152). These studies often used computerised techniques to measure the duration of time of sleep spindles.

Low Resolution Electromagnetic Tomography (LORETA) feedback refers to EEG biofeedback that uses the LORETA technique (85) in order localise the current density in the cortex from the electrode space. For an explanation of the LORETA and its related methods, see the functional connectivity section in chapter 1. The feedback signal is the current density in a particular band-range, source localised to a particular location in the cortex.

A few studies use quantitative EEG (qEEG) databases to generate specific biofeedback parameters (153-155). This compares the Fourier transformed EEG data from an individual with a particular neurological process (for example, traumatic brain injury) to a database of healthy controls in order to identify the abnormal EEG patterns in that subject. Generally these abnormal patterns are defined by both the frequency and location (for example there is increased theta power at P3 and decrease beta power at Cz). The biofeedback parameter is then designed to reverse these changes (for example, the stimulus will be positive when the theta power at P3 decreases and the beta power at Cz increases).

Two studies have unique biofeedback strategies. Lee et al (156) used EEG while undertaking a test of attention to identify a frequency and electrode parameter that signified attention on an individual basis, and used that as a biofeedback parameter. Thomas et al (157) used ‘sample entropy’, a measure of signal complexity, as a biofeedback parameter. The theory behind the measure, as stated by the authors was that attention state EEGs have more signal complexity than inattention state EEGs.

fMRI (158-162) was also used in some studies. Real time fMRI uses BOLD signals as the feedback parameter, with high spatial localisation, but with relatively poor temporal resolution. There is generally a delay between a change in the BOLD signal and change of the biofeedback display on the order of 10 seconds, due to the time it takes to process the BOLD signal.

Hemoencephalographic biofeedback (163) uses an infrared signal to measure cerebral blood flow in order to generate a biofeedback signal. In theory, this biofeedback procedure should allow the subject to control cerebral metabolism.

There are several different strategies for recruiting a control group used in these studies. Waitlist controls are controls that are tested contemporaneously with the experimental group, both before and after the biofeedback training, but do not undergo training themselves. Sham controls undergo biofeedback training, but the signal displayed to them is not linked to their neurophysiological recording. They are either presented with a recording from a previous participant or a randomly generated stimulus. Random frequency training is where controls are allocated to a random frequency each time they participate. So if they underwent 10 sessions of biofeedback, they might be exposed to 10 different frequencies, and so would not effectively train any frequency.

Memory Tests

Individual tests cited

Verbal and paragraph recall

Verbal memory list (164) and paragraph recall tasks (154) generally require the participant to listen to a list or words, or a short paragraph, and repeat back immediately what was said verbatim, and then again after a delay or distraction.

N-back

The N back task is a test of working memory. A sequence is presented, such as a sequence of letters or a sequence of positions of an object. The subject is asked to respond when the current item is the same as the nth previous item. For example in the 2 back, the subject is required to respond the items which are the same as the item two times before in the sequence. Errors are measured as

omissions, where a correct stimulus is ignored, or commissions, where an incorrect stimulus is responded to. See chapter 3 for a detailed description of a spatial 2-back test (165)

Span tasks

Span tasks are also used to assess working memory. In digit span tasks, the subject is presented with a series of numbers. In the forward digit span task, the subject is asked to immediately repeat the sequence verbatim. In the backward digit span task the subject is required to repeat the sequence in the reverse order presented. If the subject correctly repeats the sequence, a new, longer sequence is presented until the subject is unable to correctly repeat the sequence. Conceptual span uses semantically linked words in place of digits (166).

Paired Associate Recall

Paired associate recall tasks involve presenting a series of paired words. The subject is then presented with one of the words, and asked to recall the other. Paired associate recognition is where the subject presented with a series of paired words, and after a delay presented with one of the words, and required to select the correct pair from a list (167).

Motor Free Visual Perception

The motor free visual perception test is primarily a measure of visual perception, but contains elements of memory. In the memory portion of the test, the subject is presented with a stimulus item, which is subsequently removed. The subject is then asked to select a matching item from a list (168, 169).

Boston Naming Test

The Boston Naming test is a test of long term semantic knowledge. The subject is presented with a series of images of increasing complexity, and asked to name them (169).

Sternberg task

In the Sternberg task a series of items is presented. The subject is then presented with a second set of items, and required to respond whether each item in the second list was presented in the first set (170).

Corsi Block tapping test

The Corsi block tapping test requires the subject to repeat a sequence of taps on blocks made by an investigator. Much like the digit span, the outcome is the longest sequence that is repeated correctly (171).

Category recall

In category recall, the subject is presented with a series of objects from a few semantic categories. Afterward, the subject is required to select all the words belonging to one of the categories (172).

Recall Order of Faces

The recall order of faces task required participants to remember a sequence of 12 faces that they had previously sorted by preference themselves. The outcome is the number of permutations required to achieve the original sequence (173).

Old/New Remember/Know

The old/new remember/know paradigm is designed to separate recognition responses from recall responses. The subject is presented with a series of pictures, each one is coloured one of two colours. A new series of pictures is then presented in black, contain both old and novel pictures. The subject is required to select the old pictures, and when correctly selected they are required to say what colour that picture was. Recognition responses (remember) are correctly selected old pictures with incorrectly identified colour. Recall responses (know) are correctly selected old pictures with correctly identified colours (174).

Rey Auditory Verbal Learning test

Rey Auditory Verbal Learning Test (RAVLT) consists of a list of 15 unrelated words, which the subject is required to memorise. This list is repeated five times. The subject's ability to learn the words gives an immediate memory score. The subject is then required to repeat the list again after a second list of unrelated words has been read to them, giving an interference score. The subject is then required to repeat the list again after a 30 minute delay, giving a delayed memory score (175).

Neuropsychological Batteries

Weschler Adult Intelligence Scale III

Weschler Adult Intelligence Scale III (WAIS III) is a battery of 13 tests, which make up four sub-indices. These sub-indices are working memory and verbal comprehension, under the index verbal IQ, and the sub-indices perceptual organisation and processing speed under the index performance IQ. Verbal IQ and performance IQ can be combined to produce a full scale IQ. The working memory sub index includes the tests digit span and arithmetic (176).

Weschler Memory Scale

Weschler Memory Scale (WMS) is made up of seven subtests, which correspond to five indices. These indices are auditory memory, visual memory, visual working memory, immediate memory and delayed memory. The subtests are spatial addition, symbol span, design memory, general cognitive screener, logical memory I and II, verbal paired associates I and II, and visual reproduction I and II (177). The WAIS III uses the scores individual tests to create the indices, which represents the competency in that neuropsychological domain.

Repeatable Battery for the Assessment of Neuropsychological Status

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) see chapter 3 for a detailed description of the RBANS. (178)

National Institute of Mental Health and Neuroscience battery

National Institute of Mental Health and Neuroscience battery (NIMHANS) is a neuropsychological battery constructed by the National Institute of Mental Health and Neuroscience in India. Memory tests included in the battery are a logical memory test, complex figure test, design learning test, and an auditory verbal learning test (179).

Signoret memory battery

Signoret Memory battery is a battery that consists of two subtest. The recall sub test consists of delayed recall of six images, and the learning sub test consists of list learning (180).

Note that each these batteries contain a number of tests, which encompass the domains and testing procedures listed above.

Results

The search strategy identified 630 articles sourced from the following sources: MEDLINE 21, Embase 163, PsychINFO 50, Web of Science 198, Scopus 194, additional references 4. After removal of duplicates and rejection of articles based on the inclusion criteria, 51 articles about 45 different studies remained (80, 142-151, 153-163, 181-209). The details of the articles referring to randomised trials are listed in table 2-2 below. Not all these trials have control groups. Articles referring to internally controlled pre-post designed studies are listed in table 2-3. Articles referring case series or case studies are listed in table 2-4.

Table 2-2: Randomised trials

Authors	Year Published	Number of Participants	Description of Participants	Number Male	Number in Intervention Group	Number in Control Group	Description of Intervention	Description of Control	Number of Biofeedback Sessions	Length of Biofeedback Session	Pattern of Biofeedback Sessions	Memory Test	Summary of Result	Summary of EEG outcomes
Angelakis	2007	6	Old Healthy	2	5	1	Increase Peak Alpha Frequency OR increase alpha amplitude at POz Audiovisual feedback	Sham	31-35 sessions	24 minutes	1-2 sessions per week	Verbal memory wordlis, visual memory, N-back	Peak alpha group increase verbal memory, Alpha amplitude group increased visual memory	Increased Peak Alpha frequency at frontal sites in training group
Becerra	2012	14	Old Healthy (>60)	5	7	7	Decrease Theta at lead with maximum deviation from normative database	Sham	30 sessions	30 minutes	3 sessions per week	WAIS III, NEUROPSI	Training group had increased working memory (not significant), Both groups had increased memory	Increased Alpha in the training group
Berner	2006	11	Young Healthy	4	11	11	Increase sigma (11.6-16Hz) at Cz Audiovisual feedback	Sham Cross over design	2 Sessions	40 Minutes	Once before sleep, memory was tested after sleep	Paired Associate word task recall	No difference between groups	No difference in wakeful EEG, No effect on sleep spindle, increased memory was associated with increased spindle time
Cannon	2009	14	Young Healthy	6	2 Anterior Cingulate, 2 Right Prefrontal Cortex, 2 Left Prefrontal Cortex		LORETA current density in beta of the Anterior cingulate OR right prefrontal cortex OR Left prefrontal cortex, audiovisual feedback		20 sessions	6 minutes	3 times a week	WAIS III	All groups increased working memory index score	Increased current density in the Anterior cingulate in all groups
Cho	2015	27	Young and Old Stroke	19	13	14	Increase 12-18Hz, decrease 0.5-4Hz and 22-36Hz at C5 or C6	Waitlist	30 sessions	30 minutes	5 times a week	motor free visual perception test	NFB showed improvement in visual memory	Increase in relative beta
Di Loreto	2011	16	Young Healthy				LORETA feedback of Dorsal Anterior Cingulate OR Bilateral Prefrontal Cortex OR Precuneus		20 to 30 sessions	5 minutes		WAIS Working memory index	Increase	Increased current density at regions of interest
Dias	2012	16	Young and Old Healthy (31-81)		8	8	Hemoencepholgraphic feedback of the prefrontal cortex	Waitlist	3 sessions	40 minutes	3 sessions in a week	Recall order of faces	Higher recall compared to controls	Improved hemoencephalgraphic feedback score of 4.6%
Enrique-Geppert	2014	40	Young Healthy	19	19	21	Individual Theta at Fz, FC1, FC2, FCz, Cz visual feedback	Sham	8 sessions	30 minutes	Consecutive working days	3 back	Increase accuracy in training group	Increased frontal midline theta in NFB group. Increased alpha nd beta in both groups
Escalano	2014	60	Young Major Depression	19	40	20	Increase individual upper alpha at P3, P2, P4, O1, O2, visual feedback	Waitlist	8 sessions	30 minutes	2 sessions per week	RAVLT	NFT group had increased recognition on RAVLT	Upper alpha increased in the training group, during resting state and in-training, increase Alpha current density (calculated by sLORETA) in the Anterior cingulate cortex
Escalano	2014	19	Young Healthy	14	40	20	Increase individual upper alpha at P3, P2, P4, O1, O2, visual feedback	Waitlist	1 session	30 minutes		RAVLT	Increase recognition in the training group	Training group had increased upper alpha, increased task related lower alpha 2, decreased Peak individual alpha
Escalano	2011	16	Young Healthy	9	10	6	Increase individual upper alpha at P3, P2, P4, O1, O2, visual feedback	Waitlist	5 sessions	25 mintues	Consecutive days	Conceptual Span	Increased span in trianing group	Increased upper alpha power across sessions, decreased individual alpha peak within sessions
Guez	2015	30	Young Healthy	10			Increase SMR at C4 OR Increase P2 Upper Alpha Audiovisual Feedback	Sham	10 sessions	30 minutes	2 sessions per week	Paired Word Recognition, Paired Word Associative, Mindstreams computerised cognitive test Immediate and Delayed recall	Paired Word recognition and immediate and delayed recall were higher in the SMR group, Asscociative word task was higher in the Alpha training group	No Impact on qEEG measures
Hoedlmoser	2008	27	Young Healthy	13	16	11	Increase SMR at C3 Audiovisual	Random training	10 sessions	1 hour	Consecutive days	Paired Associate word task recall	SMR group had increased recall	SMR group had increased SMR during training, and increase sleep spindle time

Authors	Year Published	Number of Participants	Description of Participants	Number Male	Number in Intervention Group	Number in Control Group	Description of Intervention	Description of Control	Number of Biofeedback Sessions	Length of Biofeedback Session	Pattern of Biofeedback Sessions	Memory Test	Summary of Result	Summary of EEG outcomes
Hseuh	2012	70	Young Healthy	28	SMR group 23, Mu group 25	22	Increase SMR OR Increase Alpha (8-12Hz) at C3a-C3b and Cza-Czb and C4a-C4b Bipolar, visual feedback	Random Training	12 sessions	36 minutes	3 sessions per week	word pair, backward digit span, operational span	word pair recall and backward digit span increased in mu training group, word pair recall increased in SMR group	Mu group increased alpha power, SMR group increase SMR
Keizer	2009	17	Young Healthy	22	8 Gamma group, 9 Beta group		Increase Gamma Power at O2 OR increase beta power at O2 and Fz		7 or 8 sessions	30 Minutes	1 per day	Binding Response task, Memory Old vs New, Remember vs Know	Gamma group had decreased recognition and increased recollection, Beta group had increased recognition	Beta band coherence was related to familiarity
Kober	2015	20	Young Healthy	20	10	10	Increase SMR at Cz	Sham	10 sessions	20 minutes	3-4 sessions per week	Digit forward span, Corsi block tapping test, backward digit span, Verbal memory long, verbal memory short	Verbal memory long increased in the SMR group	SMR group had increased SMR and decreased coherence between motor and parietal areas
Lecomte	2011	30	Old Healthy	7	10	10 relaxation training, 10 waitlist	Increase Alpha/Theta Ratio at C4-Cz and C3-Cz bipolar Audiovisual feedback	Waitlist Control and Relaxation training Control	4 Sessions	30 mintues	4 sessions per week	Signeret Memory battery, Recall (visual memory), Learning (verbal memory)	No significant improvement over controls	1 participant increaed alpha, 2 partiicpant decreased theta, 2 significantly changed the alpha theta ratio
Lee	2013	31	Old Healthy (>60)	13	15	15	Increased Attention Discriminated by stroop task Audiovisual	Waitlist	24 sessions	30 minutes	3 sessions per week	RBANS	Increased Immediate and delayed memory, not significant between groups	
Nan	2012	32	Young Healthy	16	16	16	Increase Individual Alpa at Cz, visual feedback	Waitlist	20 sessions	3 minutes	3 to 4 sessions per day	Digit Span Forward and Backward	Increased Score in Neurofeedback group	No increase in resting alpha. There was an increase in Alpha in training. Higher relative Alpha correlated with memory
Pavlov	2015	20	Young Healthy	9	10	10	Increase Individual Upper Alpha at O1 and O2	waitlist	6-8 sessions			Working memory (not specified)	no improvement	No change in EEG measures
Reddy	2013	60	Young Traumatic Brain Injury	54	30	30	Increase Alpha/Theta Ratio at O2 and O1	Waitlist	20 sessions	40 minutes	4-6 sessions per week	National institute of Mental Health and Neurosciences Neuropsychological battery	NFB group had increased 2 back, Increased verbal immediate and delayed recall, and increased delayed recall of a complex figure	No change
Reis	2015	14	Old Healthy (>55)	6	8	6	Increase alpha and increase theta at Fz visual feedback	Sham	6 sessions increase theta, 6 sessions increase alpha	30 mintues	1session per day	Backward digit span	Increased digit span in the NFB group	Only NFB group increase Alpha and theta power
Scharnowski	2015	7	Young Healthy	1	3 supplementary motor area-parahippocampal gyrus, 4 parahippocapmal cortex-supplemantary mototr area		Realtime fMRI feedback to increase and decrease the BOLD signal in the Supplementary Motor Area referenced to the Parahippocampal Cortex OR the Parahippocampal Cortex referenced to the Supplemantary Motor Area	Controlled cross over design	12 to 22 sessions	32 mintues	3 sessions per day	Word recognition old vs new, remember vs know		Increase Parahippocampal Cortex Activity Associated with decreased Word recall
Schabus	2014	24	Young Insomnia	7	24	24	Increase SMR at C3 visual feedback	Random training cross over design	10 sessions	1 hour	3-5 sesssion per week	Paired Associate word task recall	No change in performance	Higher SMR post training, memory was associate with fast sleep spindles
Sherwood	2016	25	Young Healthy	14	18	17	Realtime fMRI feeback of the BOLD signal at the Dorsolateral prefrontal cortex	Memory (n-back) training	5 sessions	6 minutes	3 sessions per week	2 back	no change over controls	Increase of self regulation across training sessions

Authors	Year Published	Number of Participants	Description of Participants	Number Male	Number in Intervention Group	Number in Control Group	Description of Intervention	Description of Control	Number of Biofeedback Sessions	Length of Biofeedback Session	Pattern of Biofeedback Sessions	Memory Test	Summary of Result	Summary of EEG outcomes
Staufenbiel	2013	20	Old Healthy	14	10 beta group, 10 gamma group		Increased Beta at Fz OR increased Gamma at Fz, Auditory feedback		8 sessions	30 minutes	5 sessions per week	Memory task, Old vs New, Remember vs Know	Increased familiarity in the gamma group	Able to increase trained variable in both groups, though didn't correlate with clinical outcome
Vernon	2003	30	Young Healthy	18			Increase Theta, Decrease Delta, Decrease Alpha at Cz OR Increase SMR, Decrease Theta, Decrease Beta at Cz Audiovisual		8 sessions	15 minutes	2 sessions per week	Conceptual Span task, Accuracy of Category recall	SMR group had increased hits and lower omissions on Span task, and increase recall	SMR had increase SMR/Theta Ratio
Wang	2013	32	16 Old Healthy, 16 Young Healthy	11 Young, 11 Old	8 Old, 8 Young	8 Old, 8 Young	Increase Theta at Fz Audio visual feedback	Random training	12 sessions	15 minutes	3 sessions per week	Modified Sternberg Task, Old vs New	Old Neurofeedback group had increased recall after training	Young Neurofeedback and Old Neurofeedback group both increase frontal-midline theta
Wei	2015	20	Young Healthy	20			Increase Alpha at C3	Random training	12 Sessions	25 minutes	4 sessions per week	word pair, backward digit span	Increase in NFB group	Increase in Alpha duration and alpha power
Xiong	2014	48	Young Healthy	25	12	12 Sham, 12 behaviour training, 12 waitlist	Increase theta and decrease alpha at Fz, FCz, Cz, C1, C2	Sham OR Behaviour training Or Waitlist	5 sessions	2 minutes	1 sessions per day	2 back	NFT group increased accuracy and speed, Behaviour group had increase accuracy, waitlist had increased speed	
Zhang	2013	30	Young Healthy	16	15	15	Real-time fMRI feedback to increase the BOLD signal in the Dorsolateral Prefrontal Cortex, Visual Feedback	Sham	2 Sessions	6.5 minutes	1 session per week	Forward Digit Span, Backward digit span, Letter Memory, Spatial 3 Back	Increase in Forward and backward digit span in experimental group	

Table 2-3: Internally controlled pre -post trials

Authors	Year Published	Number of Participants	Description of Participants	Number Male	Description of Intervention	Number of Biofeedback Sessions	Length of Biofeedback Session	Pattern of Biofeedback Sessions	Memory Test	Summary of Result	Summary of EEG outcomes
Bauer	1976	16	Young Healthy	13	Increase Alpha at P3-O1 Bipolar	10 sessions	1 hour	4 sessions per day	Word List Memory, digit span	No difference between increased Alpha state and normal state	In training Alpha Increased
Cannon	2006	8	Young Healthy	4	Increase LORETA current density in the Anterior Cingulate in beta	30 sessions	40 minutes	3 sessions per week	WAIS III	Increase working memory index	
Escalano	2013	46	Young Major Depression		Increase individual Upper Alpha at P3, Pz, P4, O1, O2, visual feedback	8 sessions	20 minutes	2 sessions per week	RAVLT	Increased Recognition and Recall	
Kovaleva	2012	10	Young Primary Headache	0	Increase Alpha at 8 leads	5 sessions			Short term memory (unspecified)	Decreased error, decreased test time	Increased alpha power and coherence
Nan	2012	15	Young Healthy	11	Increase individual upper alpha at Cz	20 sessions			Digit span forward and backward	Score improved more in Chinese language group	
Thomas	2013	5	Young Healthy		Sample Entropy (signal complexity) at AF3, AF4, F7, F3, P7, O1, O2, P8, F4, F8	1 session	variable		Fill in matrices	Scores improved over time	
Thornton	2013	44	12 Young Healthy, 15 traumatic brain injury, 17 Specific learning disability	6 Normal, 9 Traumatic Brain injury, 11 Specific learning disability	qEEG database identified deficits audiovisual	Approximately 45 sessions			Auditroy memory, reading memory	Auditory memory increased most in TBI group, reading memory increased in TBI group and SLD group more than controls	Increase in spectral correlation coefficient of alpha correlates with memory

Table 2-4: Case Series and Case Studies

Authors	Year Published	Number of Participants	Description of Participants	Description of Intervention	Number of Biofeedback Sessions	Length of Biofeedback Session	Pattern of Biofeedback Sessions	Memory Test	Summary of Result	Summary of EEG outcomes
Thornton	2002	5	Young Traumatic Brain Injury	qEEG database identified deficits audiovisual	varied	40 minutes	3 sessions per week	Paragraph immediate and delayed recall	All participants had increased memory after training	Improved coherence was Demonstrated after training
Bearden	2003	1 male	Young Left posterior/ thalamic stroke	Decrease Theta at P3 or T3 -C3 bipolar	18 sessions at P3, 11 sessions at T3-C3 bipolar, 11 sessions at P3	25 minutes	3 sessions per week	WMS	Increased digit span, decreased immediate recall	Decreased theta alpha and delta, particularly decreased theta over trained area
Rozelle	1995	1 male	Young Left internal carotid artery stroke	21 sessions of Electroencephalographic entrainment feedback + decrease theta and increase beta at Cz, F7, T5, C3-T3 bipolar, F7-T5 bipolar, C4-T4 bipolar, P3-T5 bipolar, audiovisual feedback	12 sessions Cz, 11 sessions F7, 3 sessions T5, 8 sessions C3-T3 bipolar, 6 sessions F7-T5 bipolar, 4 sessions C4-T4 bipolar, 4 sessions P3-T5 bipolar		4-5 sessions per week	Boston Naming test	Increased memory after training	Decreased theta power at F7, F3, C3, P3. Increased beta in midline frontal areas
Toppi	2014	1 young male, 1 old female	Stroke	Increase SMR at Cz	10 sessions	25 minutes		Rey Auditory Learning task, Sternberg task, Corsi block tapping test	Older female increased score on Rey Auditory Learning and Corsi block tapping test, male remained unchanged	Older female increased SMR
Reddy	2009	1 male	Young Traumatic Brain Injury	Increase Alpha and Decrease Theta at O1, O2	20 sessions	45 minutes	2 sessions per week	NIMHANS Battery, Auditory verbal learning test, Complex figure recall	Increase on both memory measures	Increased Alpha and decreased theta
Decker	2014	2 Female	Young ADHD	LORETA Z score training at region of maximum deficit	10 sessions			Numbers reversed, Auditory working memory, Digit Forwards	1 Case increased scores after training	Treatment affected theta and beta waves
Pachalska	2012	1 Female	Young Traumatic Brain Injury	Increase beta and decrease theta at Fz to Cz bipolar	40 sessions	20 minutes		WMS III	Increased memory scores after training, increased recognition	Decreased alpha power in posterior cortex

Narrative review by Methodology

Alpha Training

These studies used protocols that are designed to increase the power in the standard alpha band or individualised alpha band. There are 10 randomised trials (142, 143, 145-147, 181, 195, 197, 199, 208), four internally controlled trials (144, 147, 182, 194), and one case study (198) that used this kind of protocol. Three of these studies, Lecomte et al (195) and Reddy et al (198) and Reddy et al (199), used the ratio of alpha power to theta power as the feedback parameter. Alpha training protocols generally used the posterior O or P electrodes as the training electrodes. Lecomte et al (195) Nan et al (147, 196) and Wei et al (208) trained the central electrodes, Cz, C3 or C4. On the various tests used, most studies found that scores improved after the training. Lecomte et al (195) and Pavlov et al (197) found no effect of alpha training on memory scores. Lecomte et al used the

alpha/theta ratio as the biofeedback parameter, and was the only method in this group that used bipolar electrodes in this group. Either of these two factors could have led to the null result.

Some of these studies found that the training had no impact on alpha power (146, 147, 195, 197, 199), and a few found changes in memory scores despite no change in alpha power (146, 147, 199). The study by Bauer et al (182) trained individuals to enter a higher alpha state by biofeedback. The memory test was then performed while in this higher alpha state. This was compared to individuals who had undergone training but were in a relaxed state and individuals who hadn't undergone training, in a randomised crossover design. It was found that whether individuals were in the enhanced alpha state had no impact on memory. Other studies did find that training had an impact on alpha power (142-145, 181, 194, 198, 208). This suggests that alpha training in posterior electrodes has an impact on memory, regardless of whether self-regulation of that parameter is achieved. Training alpha power centrally had equivocal results.

SMR Training

The SMR protocol is designed to increase SMR, generally over the primary somatosensory and motor cortices. There are seven randomised trials using protocols to increase SMR (146, 148, 150, 151, 193, 197, 206), and one case study (205). These studies generally used central electrodes, C3, Cz, or C4 as training electrodes, in order to target the somatosensory and motor cortices. These studies also tended to find that participants had increased memory scores after training. Pavlov et al (197) was the only study to use occipital electrodes to train, and did not find increased scores after training.

There were two studies that used SMR training to influence memory consolidation during sleep. Schabus et al (151) used SMR training to increase memory in insomniacs and Hoedlmoser et al (150) used a similar procedure to increase SMR in healthy people. Schabus et al found no change in memory, but Hoedlmoser et al did with more intensive biofeedback sessions. Also, the particular training might be more effective in normal participants.

Participants who undergo central SMR training generally show increased scores after the training is complete, and this score is often correlated to the change in SMR power. It is not known whether this effect is sustained, because long term follow up was not carried out.

Theta training

A few studies have looked at the impact of increasing theta power on memory. There are four randomised trials (190, 206, 207, 209) that use this biofeedback technique. Enrique et al (190), Wang et al (207) and Xiong et al (209) use anteriorly located electrodes as training electrodes. Vernon et al (206) used Cz as the training electrode. Vernon et al found no change in memory scores. Training Theta anteriorly appears to have a positive impact on working memory, and may improve verbal memory in older people.

High Frequency training

There are three randomised trials assessing the effect of training to increase beta (187, 192, 204), and two of these randomised trials also assessed the effect of increasing gamma (192, 204). There is additionally one case study by Pachalska et al that aimed to increase beta power at Fz (80). Keizer et al (192) suggested that training to increase gamma power improved recollection, but in general these studies have found that training of these higher frequencies results in increased recognition of items, but does not increase unaided recall.

LORETA Training

Two randomised trials (184, 189), one internally controlled study (186) and one case study (188) used LORETA to increase memory. Cannon et al (184, 186) and DiLoreto et al (189) used LORETA to target parts of the cortex involved in the 'working memory network' which includes the dorsolateral prefrontal cortex (DLPFC). These studies report an increase in working memory when the working memory network is targeted. Decker et al (188) used LORETA to identify areas that were different in normal controls to tertiary students with ADHD, and found that one of two cases targeting that area resulted in improved memory scores.

Real Time fMRI training

Three randomised trials looked at the effect of real time training of BOLD activity in using fMRI (158, 159, 161, 188). Two studies targeted the DLPFC. Zhang et al (161) found that after two sessions the experimental group had higher digit span scores, but Sherwood et al (159) found no change over the control group after five sessions. Scharnowski et al (158) randomised people to one of two groups, one where the signal was derived from the Supplementary Motor Area (SMA) subtracting the signal from the parahippocampal gyrus (PHC), and the other where the signal was derived from the PHC subtracting the SMA. Participants were required to train the signal both up and down. It was found that under the increased activity in the PHC condition, participants recall decreased. Studies assessing real time fMRI training appears to produce mixed results

Other training strategies

A variety of different training strategies have been trialled by researchers. One strategy that appears to be successful in improving memory outcomes for some individuals is comparing their EEG to a qEEG database to identify the electrode and band most deviant from normal, and using that electrode and band as the training parameter. Decreasing the power of theta was an unsuccessful biofeedback strategy trialled by Becerra et al (153).

Comment on Participant selection

Most studies recruited participants from a young community, without underlying conditions. Often these people were undergraduate university students. Seven studies recruited from an older, healthy population, but the definition of what constituted 'old' varied from study to study. One study by Wang et al (207) suggested that older people may have greater clinical outcomes from their biofeedback training than a younger cohort.

Traumatic Brain Injury (TBI) was the most common clinical condition studies (80, 154, 155, 198, 199). Thorton and Carmody (155) and Thornton (154) used qEEG database methods for biofeedback, whereas Reddy et al (198, 199) used occipital training of theta in two different studies. Both

strategies tend to show improvement of memory, even after a significant period of time has passed since the TBI occurred.

Escalano et al (143, 144) has used biofeedback to improve memory performance in individuals with major depression. The protocol used is designed to increase upper alpha in posterior regions. This strategy appears to improve working memory in both people with major depression and healthy individuals (142, 145).

Another condition which has been targeted for biofeedback training to improve memory is stroke (183, 187, 201, 205). The strategy for targeting memory in stroke varied, Cho et al (187) and Toppi et al (205) targeted central areas to increase power in the 12 – 18 Hz range, approximating SMR, whereas Bearden et al (183) and Rozelle et al (201) used qEEG database methods. Most methods seemed to have an effect on memory outcomes, though Toppi et al found that one of two people did not respond to biofeedback training.

Further individuals with Attention Deficit Hyperactivity Disorder (ADHD) (188), headache (194), specific learning disorder (155) and insomnia (151) have undergone biofeedback to improve memory outcomes. Only the study on insomnia (151) was a randomised trial, and there was no improvement in memory shown in that trial. Biofeedback training in the other conditions generally showed an increase in memory, though none of these trials were controlled.

Discordant memory and EEG scores

Four studies overall report a significant change in memory scores, but on EEG measures no significant difference is found (146, 192, 199, 204). Staufenbiel et al (204) trained the beta band and gamma band, and although participants were able to increase the trained parameter, this did not correlate with improved memory outcomes. Keizer et al (192) also trained beta or gamma, but found only changes in the beta band correlated with memory outcomes. Guez et al (146) and Reddy et al (199) trained the alpha band, but found no changes on qEEG measures. Guez et al also used SMR training which was affected by training.

Additionally four studies report a significant change in EEG scores, without a corresponding improvement in memory scores (151, 153, 182, 195). Lecomte et al (195), Becerra et al (153) and Bauer (182) report increased levels of alpha in the experimental group, but no significant improvement in memory over controls. Schabus et al reports increased levels of SMR in the experimental group, but no change in memory performance (151).

Detailed Analysis of Randomised Controlled Trials

There were seven studies included in this analysis. Due the heterogeneity of the studies, only the broadest trends can be identified from the data. Table 2-5 shows key characteristics of the studies included in the meta-analysis.

There were four studies that used biofeedback to increase upper alpha (142, 145, 147, 195), including Lecomte et al (195) that trained the alpha/theta ratio. Two studies that used biofeedback to increase theta (190, 209), and two studies used biofeedback to increase SMR (150, 193). Lee et al (156) trained individual 'attention' patterns derived from a pre training EEG taken under an attention task.

Table 2-5: Studies included in Meta-Analysis

	Biofeedback Strategy	Cognitive tool	Experimental group size	Effect size Experimental group	Control group size	Effect size Control Group	Difference in Effect size	Number of sessions	Sessions per Week	Length of Session (minutes)
Nan 2012	Increase Upper Alpha	Digit Span	16	0.81	16	0.69	0.12	20	3.5	3
Xiong 2014	Increase Theta	2 back	12	1.45	12	0.32	1.13	5	35	2
Hoedlmoser 2008	Increase SMR	Paired word task	16	0.81	11	0.40	0.41	10	7	60
Escalano 2014	Increase Upper Alpha	RAVLT	10	2.57	9	1.65	0.92	1	1	30
Escalano 2011	Increase Upper Alpha	Conseptual Span	10	1.41	6	0.17	1.24	5	7	25
Enrique 2014	Increase Theta	3 Back	19	1.06	21	0.35	0.71	8	7	30
Kober 2015	Increase SMR	VVM Construction	10	1.11	10	0.37	0.74	10	3.5	20
Lecomte 2011	Increase Alpha/Theta Ratio	Signeret Battery Recall	10	0.94	10	0.82	0.12	4	4	30
Lee 2003	Increase 'Attention'	RBANS immediate Memory	15	0.45	16	-0.10	0.56	24	3	30

Figure 2-2 shows a scatter graph of the difference in effect size between the control group and the intervention groups against the number of sessions. In general there a tendency toward a downward trend (slope = -0.0209, 95% CI -0.34, 0.28), that is with more sessions the difference in effect size between the intervention group and controls is less.

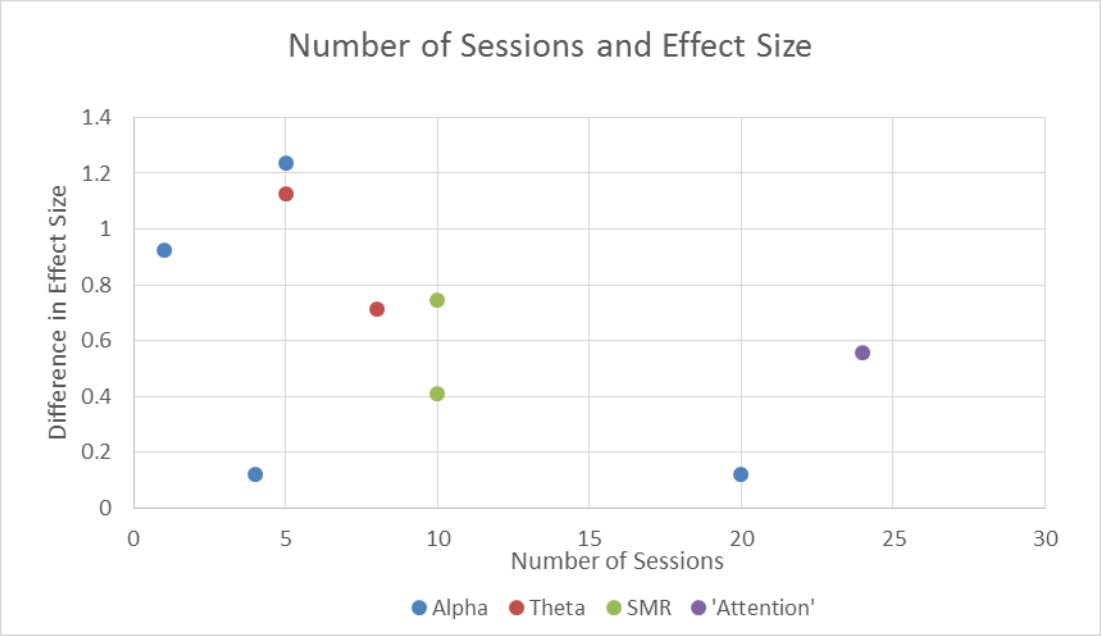


Figure 2-2: Number of Sessions vs Difference in Effect Size

Figure 2-3 shows the difference in effect size against the number of biofeedback sessions per week. There does not appear to be an obvious pattern to the pattern of biofeedback and the difference in effect size (slope = 0.0025, 95%CI -0.52, 0.53). The outlier on the far right of the graph is Wang et al (207), where the pattern of feedback was five sessions in one day.

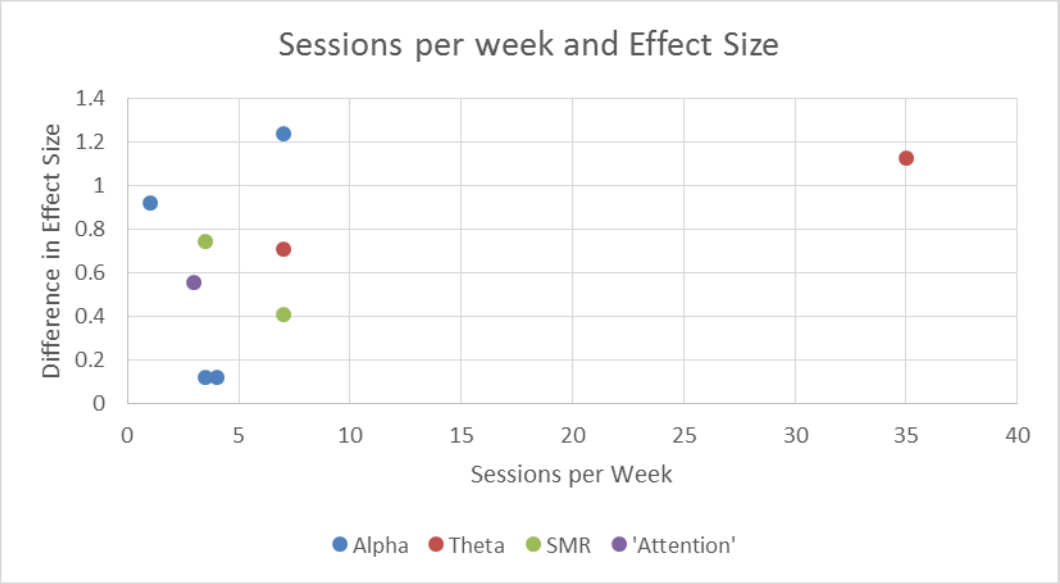


Figure 2-3: Number of Sessions per Week vs Difference in Effect Size

Figure 2-4 shows the difference in effect size against the length of individual biofeedback sessions. In general, studies with longer biofeedback sessions does not appear to have an effect on the effectiveness of the feedback (slope = 0.0131, 95%CI -0.1718, 0.1980).

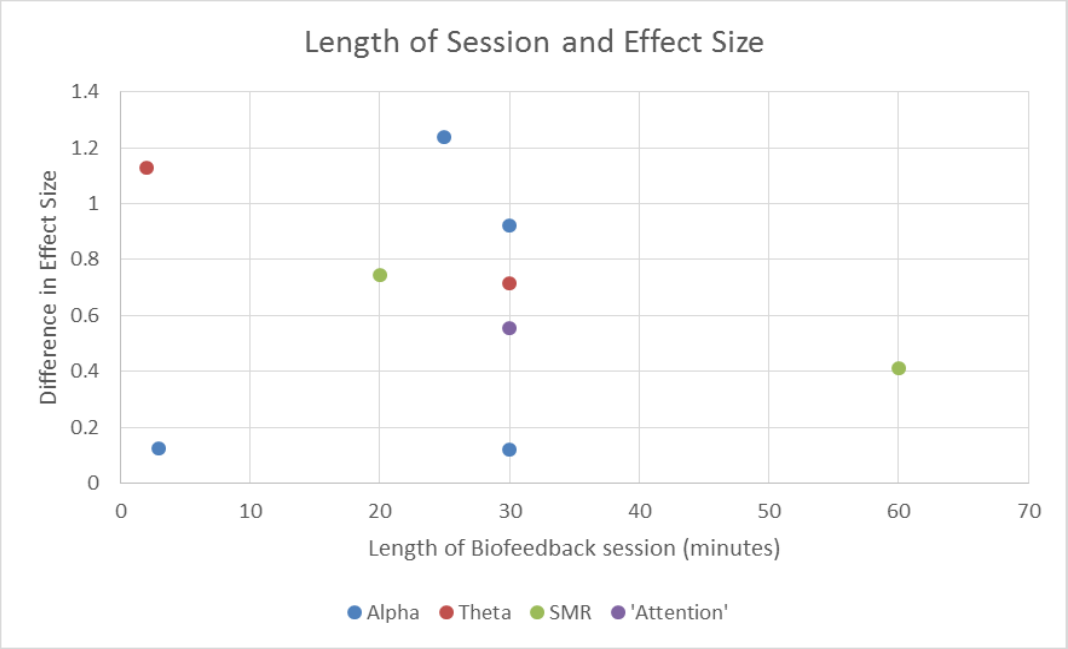


Figure 2-4: Length of Biofeedback Sessions vs the Difference in Effect Size

Figure 2-5 shows the difference in the effect size plotted against the number of participants in the study. Studies with larger number of participants should be more reliable. There does not appear to be a relationship between the number of participants and the effect size found (slope = -0.0017, 95%CI -0.2173, 0.2139). However, it should be noted that all these studies are positive, with a tendency of large studies to find a lower effect size.

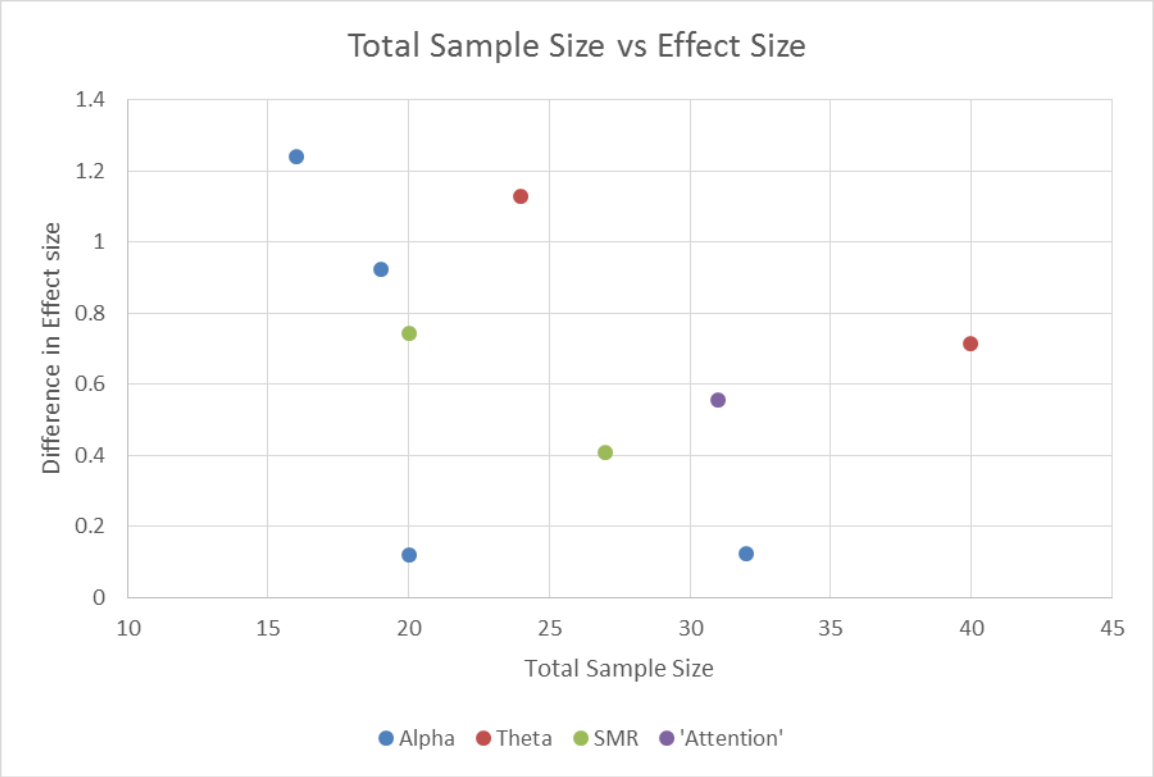


Figure 2-5: Total Sample Size vs the Difference in Effect size

Validity

Ten studies (143, 146, 148, 158, 161, 190, 192, 206, 207) demonstrated one of either band or cognitive specificity, and one of either unique cognitive change compared to a control group or a correlation between the cognitive change and the neurofeedback change. Most of the other studies examined for this review (35 of 45 studies) did not fulfil the criteria because they did not include any information on frequency bands other than the trained bands, or did not include any information on aspects of cognition other than memory.

Of the ten studies demonstrating aspects of validity, three studies used SMR rhythm training. Four other randomised trials did not demonstrate these elements of validity for SMR training. Guez et al (146)failed to demonstrate group neurological response to the SMR training or alpha training, demonstrated cognitive specificity of SMR training to improved paired word recognition, in comparison to the alpha training group which had improved associative word task performance. On the other hand, Hseuh et al (148) and Vernon et al (206) demonstrated neurological response to

SMR training, and both studies demonstrated band specificity. Vernon et al showed that the SMR group had increased performance on the span task, and increased recall, but there is no description of a correlation between SMR response and either memory test. No study was able to correlate the SMR response to a response in the cognitive variables.

Hseuh et al and Guez et al, along with Escalano et al (143), also demonstrate elements of validity for alpha band training. Seven other randomised trials did not show the elements of validity. Escalano et al and Hseuh et al show band specificity, but neither shows cognitive specificity. Additionally both studies show a correlation between the response to alpha training and improved memory score. Guez et al shows cognitive specificity, in that the associative word task score was higher in the alpha training group alone.

Two studies demonstrated validity of the theta feedback. Two other randomised trials did not demonstrated validity for theta training. Enrique-Geppert et al (190) showed band specificity, because only the experimental group increased their theta power beyond non-specific effects. This study also showed that working memory was uniquely increased by this type of training. However, Wang et al (207) showed, using a similar protocol, that the modified Sternberg task (a recognition task) was uniquely improved compared to a control group.

Two studies demonstrated the validity of fMRI feedback training. One trial did not demonstrate validity for fMRI training. Band specificity is not a relevant concept to fMRI feedback, but the training has much greater localising power, and therefore locality specificity has a higher importance. Therefore locality specificity was substituted for band specificity in analysing the fMRI studies. Only one of the studies demonstrated locality specificity, which was Scharnowski et al (158). This demonstrated locality specificity in both the parahippocampal cortex and the supplementary motor cortex. This training demonstrated cognitive specificity with word recall, but unexpectedly it was decreased PHC activity that resulted in increased recall. Zhang et al (161), in contrast, examined working memory, and found that it was uniquely improved by feedback at the dorsolateral pre-

frontal cortex. Neither of these studies demonstrated a correlation between change in fMRI variables and the memory outcomes.

Keizer et al (192) demonstrated validity for both gamma and beta training. Two other randomised trials did not demonstrate validity in high frequency bands. Both training gamma and training beta showed band specificity. Gamma training uniquely improved recollection, whereas beta training uniquely improved recognition in an Old vs New task.

Discussion

Studies looking at biofeedback are extremely heterogeneous, in terms of the biofeedback parameter selected, the site of biofeedback, and the assessments used to measure the cognitive effect of biofeedback. This means that drawing conclusions from between studies is difficult, and limited to ecological observations. Analyses that produced summary measures from all or a large part of the studies will have limited value in interpretation. They have been used here to broadly assess the parameters which may influence the effectiveness of biofeedback training.

Several authors produced serial studies of the same procedure, such as Escalano (142-145), who tested biofeedback training of posterior alpha in normal healthy participants and in major depressions. This group started testing on a healthy sample, then progressed onto an internally controlled study with major depression, then a randomised controlled trail with major depression. Cannon (184-186) tested LORETA training of the working memory network, starting with a small internally controlled trial, then a randomised uncontrolled trial. The precedent in both series is to start with a small internally controlled trial.

There were no studies identified which were designed specifically to assess the use of biofeedback to improve memory in people with demonstrated greater than normal for age memory loss. We identified some studies looking at biofeedback in older adults, but these tended to recruit either from a healthy population, or from a population with a significant neurological condition such as stroke. There is a gap in the literature about the use of biofeedback to treat Mild Cognitive

Impairment and memory disorders of aging. It is possible that this group would react to biofeedback training differently than healthy older adults.

Common strategies adopted by researchers include posterior alpha training and SMR training. Both of these method of biofeedback appear to be able to improve memory scores to some extent. Other strategies are less consistently used. Both alpha and SMR training could have an impact on default mode network integrity. Alpha band connectivity appears to be important for the functioning of the default mode network (113), and alpha band activity from the default mode network could project to posterior electrodes. SMR is commonly associated with an 'idling' state in the primary motor and primary sensory cortices (141), which could represent a resting state in these cortices where the default mode network is active. Default mode network integrity is important for memory retrieval, both in working memory (210) and episodic memory (62). Both SMR training and alpha training could affect memory scores on neuropsychological testing through affecting default mode network integrity.

There were no strong trends identified from the biofeedback pattern. It might be expected that longer feedback sessions, done more frequently for longer might have a strong impact on cognitive outcomes. However, no such strong effect could be identified. This suggests that other study factors, such as the exact mode and positioning of biofeedback, or the kind of cognitive test that was used, have a far greater impact on study outcome. Interestingly, it appears that studies that included more biofeedback sessions tended to have lower effect size differences. It could be that the gain in memory scores found from biofeedback are achieved in five to 10 biofeedback sessions, and further training results in fatigue that interferes with those gains. However, there isn't any supporting evidence for this hypothesis, and the trend that appears in this data could be the result of other study factors.

Interestingly, some studies reported an improvement in memory scores without a corresponding improvement in EEG characteristics that were studied (146, 192, 199, 204), or conversely found an

improvement in EEG characteristics that did not correspond to an improvement in memory score (151, 153, 182, 195). Three studies found an improvement in the alpha band with no improvement in the memory score (153, 182, 195), and one study training alpha found no improvement in alpha with an improvement in memory scores (199). This would suggest that while alpha training does appear to result in improved memory scores in general, the mechanism by which this occurs is not necessarily by increasing alpha band power detected by scalp electrodes. There is therefore a need to identify other parameters that are more reliable indicators of improved memory, which may result in more effective training with consistent improvements in memory shown.

Internally controlled studies and some of the randomised studies lacked active control groups. Two common strategies for active control groups are sham controls or randomised frequency controls. Waitlist controls are used as passive controls. The use of active control groups is important to biofeedback studies looking at cognition, particularly in older people. Studies involving a high number and high frequency of biofeedback sessions creates a social environment for the participant, which in itself may have an impact on cognition (211). It is therefore important to subject the control group to the same environment as the intervention group. A number of the studies identified in this review found increases in memory scores over time, but no significant increases over control group (149, 153, 156, 159, 195, 209). This suggests that teams developing biofeedback techniques to improve memory should use an active control group early in their program.

Few studies demonstrated validity as set out by Gruzelier in his three part review of EEG-biofeedback to optimise performance (138-140). This was most often due to a lack of data regarding frequency bands other than the ones that were trained, and failure to assess other cognitive domains to demonstrate whether the cognitive change after training has a unique neuropsychological profile or not. There is some evidence that SMR training demonstrates specificity for recognition performance, alpha training has some specificity to recall performance, frontal theta

has some specificity to working memory and fMRI training specificity depends on the voxels selected for training. These strategies are likely to be able to be replicated in other settings.

Chapter 3 Methods of Data Acquisition and Analysis

This chapter contains the methods used for gathering EEG data, general setup of the biofeedback apparatus and cognitive data from the Repeatable Battery for the Assessment of Neuropsychological Status and 2-back testing. These methods were used in both pilot study conducted in 2015 and the randomised trial conducted in 2016. Specific biofeedback parameters and details of the trial design can be found in chapter 4 for the pilot study and chapter 5 for the randomised controlled trial. Methods for additional analyses done on the data of the randomised controlled trial can be found in chapter 6. The equipment used in the pilot study and the randomised controlled trial was the same.

Cognitive testing

RBANS

All participants in both trials underwent cognitive assessment before undergoing the biofeedback training and after the biofeedback training, and the participants in the randomised controlled trial completed the assessment a third time. Participants were evaluated using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (212). The RBANS is a series of tests designed to be a quick assessment of cognitive abilities in five neuropsychological domains. There are also four equivalent versions of the test, which allows for retesting in a short time while minimising retesting bias. This is an advantage for this study because the participants were retested immediately after the intervention ended, which was between one month and two months after they had been first tested. Additionally, we chose to use the RBANS because it does not have to be administered by a clinical psychologist, it can be administered by other health professionals such as occupational therapists, or doctors (178).

The RBANS assessment consists of 12 subtests. The scores for these tests can be converted into index scores for five cognitive domains. The list of the 12 tests and the different cognitive indices they contribute to can be found in table 3-1. A total scaled score can also be calculated from the sum of the five cognitive indices.

Table 3-1: Tests and Cognitive Indices of the RBANS

Test Name	**Cognitive Index**
Word List Immediate Recall	Immediate Memory Index
Story Immediate Recall	
Figure Copy	Visuospatial Index
Line Orientation	
Picture Naming	Language Index
Semantic Fluency	
Digit Span	Attention Index
Coding	
Word List Delayed Recall	Delayed Memory Index
Word List Recognition	
Story Delayed Recall	
Figure Copy Delayed Recall	

Description of the RBANS subtests

Below is a brief description of each of the RBANS sub tests

Word list immediate recall; the subject is asked to immediately repeat a list of 10 words. There are 4 trials, and each time the list is read out.

Story memory immediate recall; the subject is asked to immediately recall a 2 sentence story. There are 12 details the subject is marked on. There are 2 trials, and the story is read out each time.

Figure copy; the subject is asked to copy a figure, and is scored on the accuracy and placement of 10 details.

Line orientation; the subject is shown a key with 10 numbered radial lines, and presented with a test pair of lines. They are then asked to identify which lines on the key the test pair correspond to.

Picture naming; the subject is asked to name ten pictures printed on the test booklet.

Semantic fluency; the subject is asked to list all the words they can think of within a stated category within a minute. For example 'name as many fruit and vegetables as you can think of in one minute'.

Digit span; the subject is asked to immediately repeat a sequence of numbers. After each successful trial, a new sequence one digit longer is tested. The largest sequence is eight digits long.

Coding; the subject is given a key with a 9 symbols corresponding to the digits 1 to 9. On the same page they are presented with an 81 item random sequence of the symbols in the key. They are instructed to decode as many of the symbols, one after the other, as they can in 90 seconds.

Word list delayed recall; the subject is asked to recall the list that was read out in the immediate recall, without prompting.

List recognition; A list of 20 words is read out, 10 of which are contained in the immediate recall list. The subject is asked to identify which of the 20 words was on the original list.

Story memory delayed recall; the subject is asked to recall the story from the immediate trial with one prompting detail.

Figure recall; the subject is asked to recall the figure copied in the figure copy trial, without prompting.

Test re-test reliability and the RBANS

The test-retest reliability is the likelihood that a test gives the same result in the case that no true change in the underlying variable has occurred. In psychological testing, this is affected by practice effects, where participants remember elements of the test when they are first exposed to it, and score higher when they are subsequently exposed to the same test. This particularly occurs in tests where an optimal strategy can be identified, for example semantic fluency can be influenced by the strategy used to generate the words (213). Alternate forms can prevent participants from

remembering the content of the test, which can increase the test re-test reliability. However, some inflation of the test score still occurs due to participants optimising strategy for particular tasks and reduced anxiety due to familiarity with the test procedure (178, 213).

Alternate form equating studies have shown that Form A and Form B have high test retest reliability (178). That means that when tested in a population where change is not expected, the scores in each cognitive domain are very similar between Form A and Form B. This means that on repeat testing any significant change that may be seen between pre- and post- training scores is less likely to be due to repeat testing effects or differences between the forms.

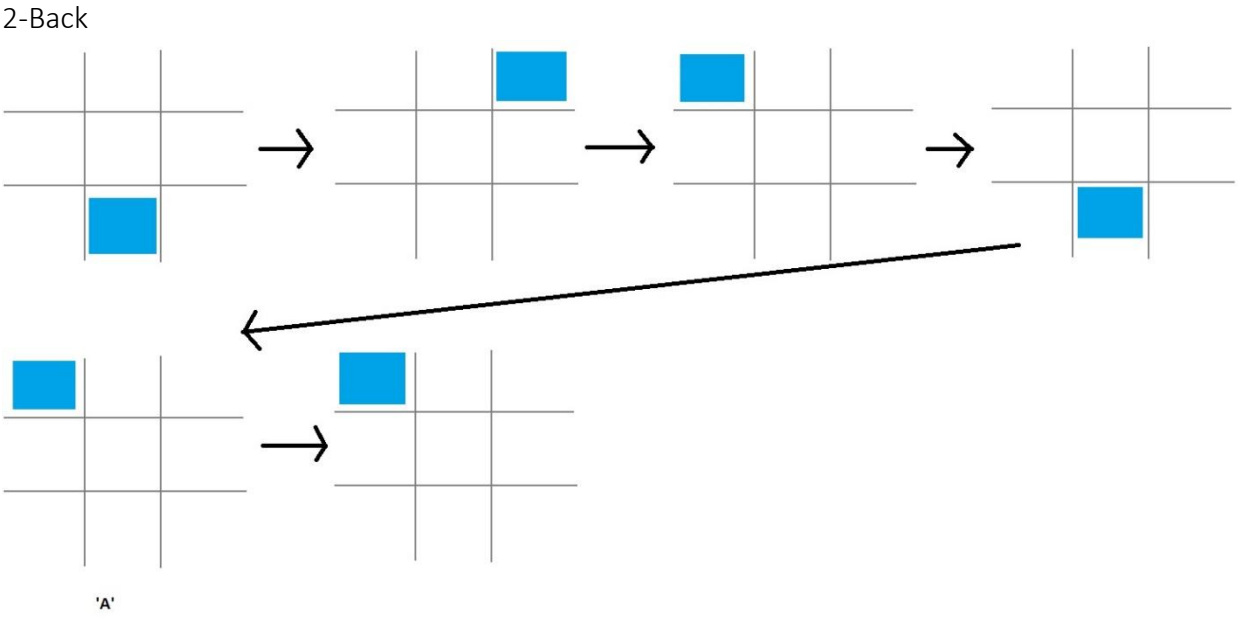


Figure 3-1: Demonstrates the 2 back test. The square appears in a random sequence in a 3 by 3 grid. The 5th position requires a response because the blue square is in the same position as it was two steps previously in the sequence

In the randomised trial, we additionally used a 2-back test to characterise the participants before and after biofeedback training. The 2-back test is a short test involving simultaneous attention and memory processes, often thought to involve working memory processes (214). A free, open source 'n-back' training program was used for testing the participants (215). The task specifically used in this program was position 2-back task. The laptop screen displayed a three by three grid. When the program is started, a blue square appears in a sequence of 24 different positions on the grid. The

sequence of positions is randomly generated each time the program runs. The objective of the test is to respond, by pushing the letter 'A' on the keyboard, whenever the current position of the square matches the position of the square seen two positions previously. The number of correct matches in each sequence is randomly generated between three and 10. Incorrect responses were recorded when the participant failed to respond to the correct match, or when they responded to an incorrect match. When program was complete, a score is produced. This score is shown in the equation below. This score was used to track working memory.

$$Score = \frac{Number\ of\ correct\ responses}{Number\ of\ correct\ responses + Number\ on\ incorrect\ responses}$$

Baseline EEG acquisition in the resting state

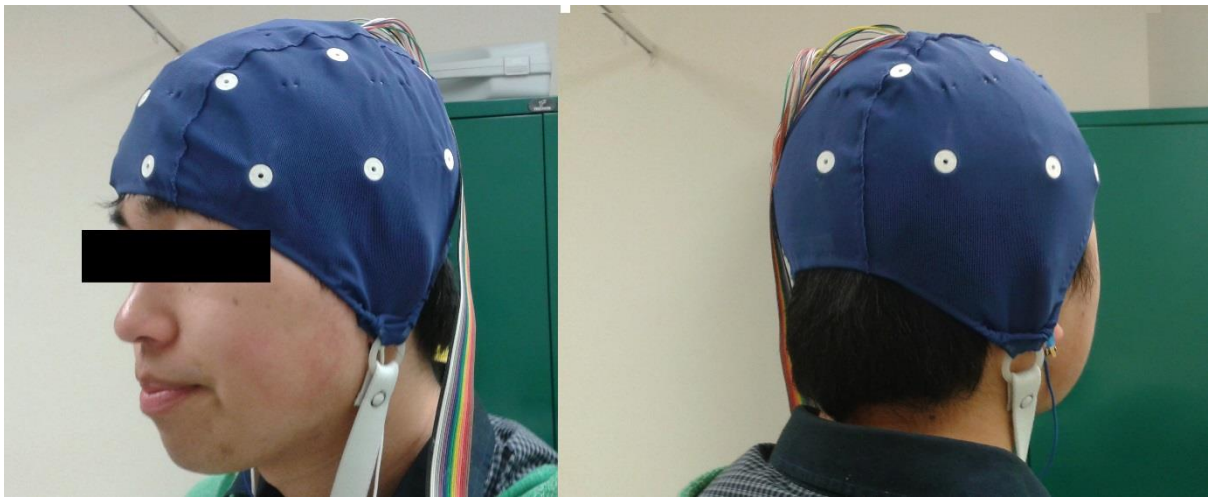


Figure 3-2 Electro-caps in position

Baseline activity and functional connectivity of the PCC and the DMN is acquired before we started on the biofeedback training. We used a 21 lead Mitsar 202 amplifier (Mitsar Co. Ltd, St Petersburg, Russia) with electro-caps from Electro-Caps International (ECI International Inc., Ohio, USA (216)) as electrodes. These 'electro-caps' are caps with 19 embedded electrodes fitted in the 10-20 system (73). The position of the electrodes is demonstrated on Figure 1-6 in chapter 1. Electrode impedance was kept below 5 kΩ by using conductive gel on the scalp surface where the electrode contacted the skin surface. This gel consists mainly of water and salt, in order to increase the conductance of electrical signals to the electrode. Also, an applicator stick was used to lightly scratch the scalp to

further improve the conductance of the electrical signals. The conductive gels was also used on the reference electrodes. An additional electrode, located at position Fpz in the 10 – 10 system (74), acted as the ground electrode which was used as the reference for the calculation of electrode impedance by the Win EEG program (217) .

Measurements of resting state EEG were taken before the first biofeedback training session, after the eighth training session, after the twelfth training session and after the fifteenth training session. In the randomised trial it was additionally recorded at a 6 week follow up session. Using this data we could compare the resting state EEG data overtime to see if the training was having a significant effect on the resting state EEG. The EEG was recorded digitally using WinEEG software, version 2.89.52 (217). A five minute segment was recorded with eyes closed. The participant was instructed to sit quietly with their eyes closed, and not think about anything in particular. In this way we hoped to capture the EEG activity in the resting state. The EEG was recorded at a sampling frequency of 250Hz.

Processing of the raw data

The raw data from the EEG recording was exported with a low pass filter of 1.6 Hz, which eliminated rhythms of frequencies below 1.6 Hz. A notch filter was also applied to eliminate frequencies between 45-55Hz, which is often due to electrical interference artefact. A high pass filter at 50Hz was also applied, which effectively meant the highest frequency recorded was 45 Hz. The raw data from the EEG recordings were then processed to remove artefacts like eye movements and muscle tension in the muscles of the head. This was done by deleting segments contaminated with eye blinks and movement artefacts using EureKa! software (218). After the artefacts were removed, the EEG data was only considered valid if at least two minutes of artefact free data remained. This was then loaded into the program Independent Component Neurofeedback (ICoN) (219), and blind source separation was performed on the data. Examples of the types of artefacts removed by the whole process included

- High frequency sources indicated by the LORETA key viewer to be located unilaterally in the temporal area are most likely to be muscle tension
- High frequency sources at high amplitudes located solely in the medial frontal area were likely to be artefacts produced by eye movements
- Spikes restricted to one particular electrode, which are most likely due to movement interfering with that electrode
- Spikes affecting all electrodes simultaneously which are most likely movement artefacts

Processing of Resting State Data

The data acquired by the baseline acquisition procedure was loaded into sLORETA and eLORETA software (220) to perform source localisation. This software was used to generate a number of different analyses of the EEG data. Firstly it was used to generate comparisons of band defined activity across the cortex. Secondly it was used to calculate phase lagged synchronisation across the whole brain and DMN. Thirdly, it was used to generate time series data of both the band defined current density activity in the PCC. Finally it was used to generate the band defined phase lagged synchronisation between the left PCC and left Medial Temporal lobe over time.

Source Localized Activity Maps

The sLORETA software applies the sLORETA method (see chapter 1 for overview of the sLORETA method) in order to perform source localisation. Here, sLORETA software refers to the computer program that analyses the EEG data, and sLORETA method refers to the calculations performed on EEG data to perform source localisation.

To generate the comparison of band defined activity in the cortex, EEG data from the first and last baseline EEG recording was loaded into the sLORETA software. First, the time series data from each of the electrodes was decomposed using the Fast Fourier Transformation, which is a specific method of generating a Fourier transform from an oscillating signal (82), using the following frequency bands shown in table 3-2. This generates the power, which quantifies the amount of a frequency present in

the signal, n each of the frequency bands in each electrode. This data is then processed using the sLORETA method to localise current density from the voltage recorded by the electrode sensors. This generates a topographical representation of the current density of each frequency band in each part of the cortex for that EEG recording. The sLORETA software has an in built statistical package that performs permutation testing in each voxel in each frequency band to generate maps of statistically significant changes in relative power of current density (221). A voxel defined here is a 5mm x 5mm x5mm volumes of grey matter registered to the MNI 125 brain model. The data was processed using this statistical package as follows. The activity from the first resting state EEG recording is subtracted from the final resting state recording, in order to generate a topographical map of the difference in power in each frequency band between the last and the first resting state EEG recording. A full discussion of permutation testing is contained in the statistical procedures section below.

Table 3-2: sLORETA defined frequency bands

Name of Frequency Band	**Band range (Hz)**
δ	0 – 4 Hz
θ	4 – 8 Hz
α 1	8 – 10 Hz
α 2	10 – 12 Hz
β 1	12 – 19 Hz
β 2	19 – 25 Hz
β 3	25- 31 Hz
Ω (full power band)	1 - 31 Hz

Whole brain connectivity maps

For generating the whole brain connectivity map, the preloaded ROIs for 88 Brodmann's areas (44 left sided and 44 right sided areas), which are available as part of the sLORETA software, were used. ROIs were registered to the Montreal Neurological Institute (MNI) coordinates, which are derived

from an average of 152 MRI scans in healthy adults. This model can be used to generically define brain regions without the need for high resolution brain imaging (222). Using this model, any point in the brain can be defined consistently in three dimensional Cartesian space. The MNI coordinates of these regions of interest can be found in Table A-2 in Appendix A2. The software took the artefact free EEG data and performed source localisation using the sLORETA method for the coordinates that were predefined. This generates a source localised activity stream for each of the coordinates, which is then decomposed into the frequency bands as defined above in table 3-2. This results in a source localised activity stream in each frequency domain for each specified coordinate. The software then compared each frequency domain at each coordinate for phase lagged synchronisation. The final output is a series of matrices which plot the functional connectivity between each of the predefined coordinates, one matrix for each frequency domain.

Default Mode Network Connectivity Maps

For the analysis of DMN connectivity, the 11 MNI coordinates given in (223) were used, which are shown in table A-1 in appendix A1. The DMN coordinates were selected from a meta-analysis of fMRI based studies, which did not include medial temporal lobe structures. As mentioned in the introduction, it is thought that the parahippocampal cortex links the medial temporal lobe memory centres to the default mode network (224). Because of the importance of functional connectivity in memory networks to aMCI pathology, parahippocampal coordinates were added to the DMN analysis. The coordinates for these were obtained from an fMRI based study of resting state connectivity of the DMN (224). The MNI coordinates for these regions of interest can be found in Table A-1 Appendix A1. To calculate the DMN connectivity of an EEG, the current density for each voxel at each of the 11 DMN coordinates was generated at all time points. The phase lagged synchronisation of each of the coordinates to each of the 10 other points was then calculated.

Using the in-built statistical package in the sLORETA software, the connectivity of the last resting state EEG was compared to the first resting state EEG. The program did this by subtracting the connectivity of the first resting state EEG from the connectivity of the last in order to generate a

series of differences. The significance of the connectivity changes was tested by permutation testing. The details of the permutation testing are given in the statistical procedures section below. These were then used to generate images showing the change in connectivity between those two time points. The processing pipeline for the resting state EEG is shown in Figure 3-3 below

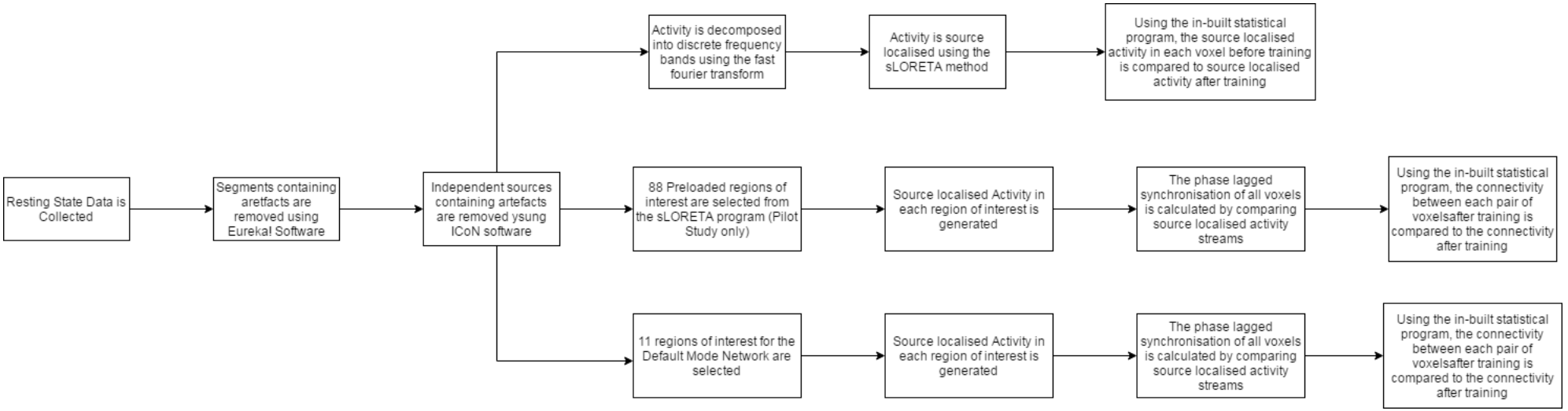


Figure 3-3: Processing pipeline for the resting state EEG data

Biofeedback procedure

Participants were invited to participate in up to 15 biofeedback training sessions. We used a Mitsar ® 202 amplifier with electro-caps to acquire EEG data which was processed on a Toshiba® Techra ™ laptop computer. The computer had a 15.6 inch screen, and was positioned approximately 40 to 50cm from the participant. The screen has a resolution of 1366 by 768 pixels, and refreshes at 60Hz. The processor had an Intel ® Core ™ with a processing speed of 2.50 $x10^6$ Hz.

The EEG was sampled at a frequency of 500 Hz. Braintuner © biofeedback software (225) generated the biofeedback visual display generated in real time from the EEG.

Biofeedback Training Setup

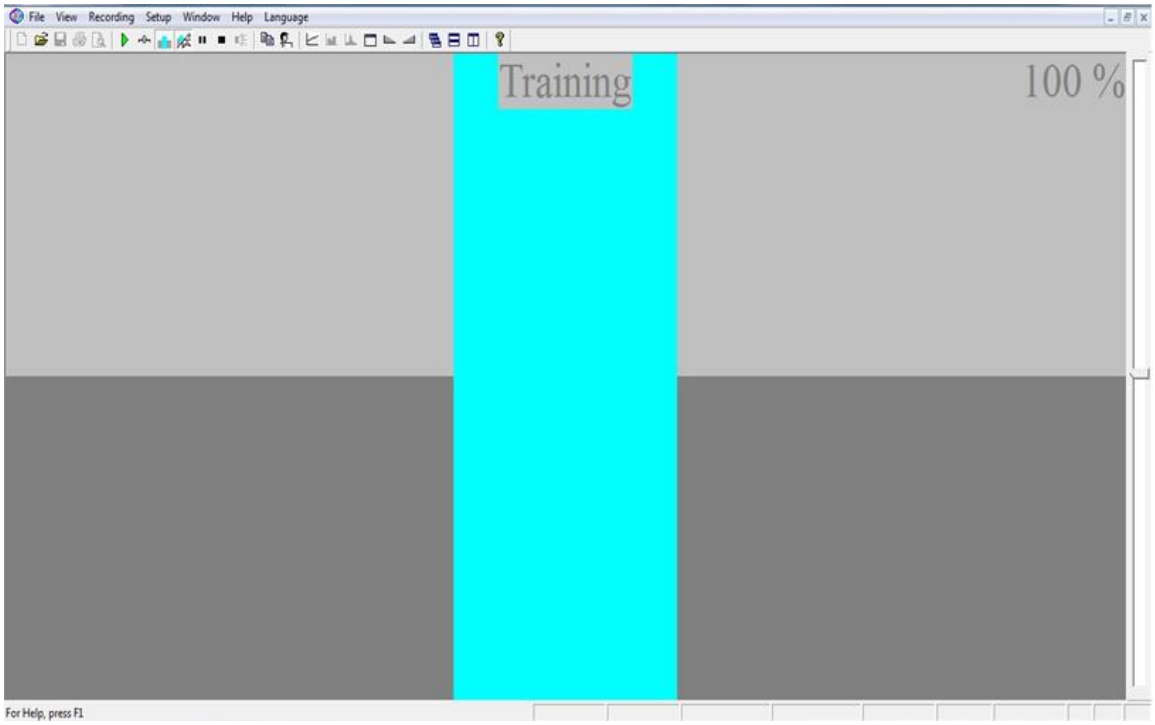


Figure 3-4 Display of the biofeedback training program. The blue bar represents the parameter we are training. The participants are instructed to try and keep the blue bar on the top half of the screen. The percentage in the top right hand corner is the cumulative percentage of the time that the bar has spent in the top half of the screen in the current phase of the program.

The EEG data was source localised in real time using the sLORETA method, so that we could target the feedback to the PCC. The biofeedback parameter was source localised to activity in five voxels located in the left ventral PCC, as this is the part of the PCC most strongly connected with memory (226). The MNI coordinates x=-5, y=-50 and z=10 were used being the centre of the cluster of voxels.

Additional voxels were selected at (x, y, z) = (-4,-50, 10), (-6,-50, 10), (-5,-49, 10) and (-5,-51, 10) to represent just the ventral PCC, and so better target the memory network.

$$Height\ of\ the\ bar = \frac{Power\ of\ frequencies\ 4 - 14Hz}{Power\ of\ frequencies\ 20 - 40\ Hz}$$

The parameter used for the 2015 pilot study was to maximise the ratio between the power of frequencies between the ranges 4Hz to 14Hz and 20Hz to 40Hz. That is, the parameter would be maximised if the power of the frequencies in the 4Hz to 14Hz was high, and the power of the frequencies in the 20Hz to 40Hz range was low. The equation above shows the formula for calculating this ratio. This was calculated in real time and displayed as the height of the vertical bar on the laptop screen, which is seen in Figure 3-4. The display is separated vertically into two halves. A threshold was set at the beginning of the training session as the goal to improve the biofeedback parameter, see threshold setting below. The threshold is represented as the junction between the two halves of the screen, the lower half of the screen is values below the threshold, and the upper half of the screen is above the threshold. Participants were instructed to try to maintain the height of vertical bar in the upper half of the screen.

The bar was refreshed every 0.125 sec, and calculated as the average value of the parameter over the previous four seconds. Deviations of the EEG recording of greater than 120µV in any of the electrodes resulted in the suspension of calculation of the biofeedback parameter, and freezing of the visual display, as it was assumed that any activity over 120 mV was artefact. Active updating occurred when the electrode potential returned to between -120µV to 120µV.

Training session design

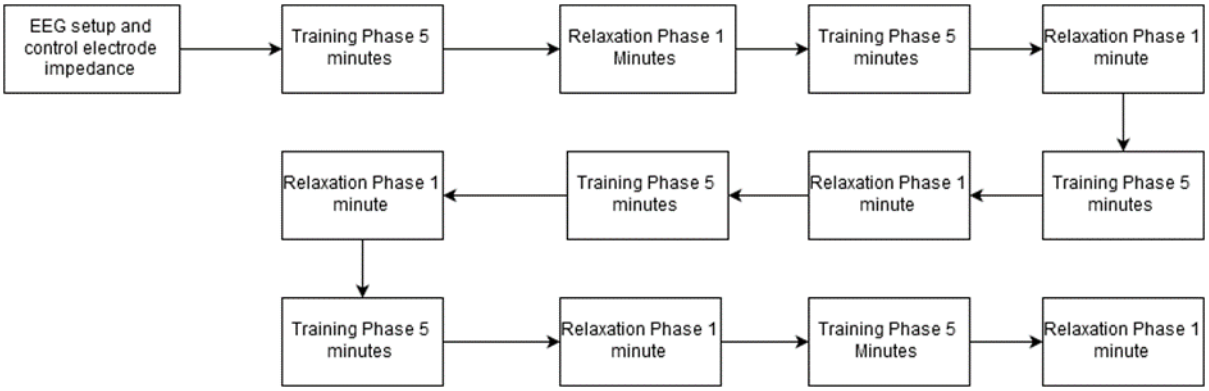


Figure 3-5: The process of one biofeedback training session

Figure 3-5 demonstrates one biofeedback training session, with a total training time of 36 minutes. Each training session consisted of six cycles of training with each cycle having two parts, a training phase and a resting phase. Each training phase lasted five minutes. During the training phase the vertical bar was active and the participant was encouraged to raise the vertical bar during this time. Interspersed were resting phases lasting one minute. During the resting phase the bar was not active, and participants were encouraged to take a break from concentrating on the bar. The software continued to record the EEG and plot the training parameter for later analysis.

Setting the threshold for the biofeedback parameter

In the first biofeedback training session, the threshold was set. As the program begins, it displays the recording of the raw EEG data, and below plots a line graph of the biofeedback parameter. For the parameter used in the pilot study, see chapter 4, or for the parameters used in the randomised controlled trial, see chapter 5. This graph can be used to adjust the threshold by dragging the threshold marker up and down. The threshold was set to such a level so that the parameter would be over the threshold value approximately 30% of the time. That is, the bar would be in the top half of the screen for 30% of the training phase. This was done so that the participant's internal reward systems would be activated when the bar reached the top half of the screen and facilitate the learning process of the feedback. The cumulative percentage of the time the parameter spent above the threshold value was displayed on the top right hand side of the screen. If the participant reached

the target threshold less than 15% of the time during one training phase, the threshold would be manually reduced by one unit in the following resting phase. The amount of change represented by that unit was determined by the Braintuner © software, increments in an approximately exponential stepwise fashion. For example moving one unit down if the threshold was set at two reduced the threshold to 1, but moving one unit down if the threshold was set at 15 moved the threshold to 12. If the participant reached threshold more than 45% of the time during a training phase, then the threshold was raised by one unit during the following resting phase.

The threshold at the beginning of each training session would be set at two units below the threshold of the last cycle of the previous biofeedback session. This was so that the participant could quickly retrain to the level of the parameter reached before, while also reorienting themselves to the biofeedback task.

In-Training Data

While undergoing the biofeedback training, the Braintuner © software also generated an EEG recording of the raw EEG data being collected by the electro-cap before processing for biofeedback, which could be separately analysed later. This was not resting state, but rather task positive data, because the person is engaged in the sensory task of watching the biofeedback screen.

The in training recording was taken from the first five minute training phase. The placebo group in the randomised trial did not have an EEG recording that was marked with the different phases of the biofeedback training, so the first five minutes was defined as the recording between 33 seconds and 333 seconds. This first five minutes of EEG was used for analysis, except where the recording had too many artefacts to generate two minutes of artefact free data. Artefacts which may have caused a whole five minute segment to be rejected included malfunctioning electrodes and movement artefacts particularly those generated by the ear electrodes. In this case, the second five minute training phase was used. If the second five minutes was also unusable, the third five minute training

phase was used. Where none of the data in the first half of the training were usable, EEG biomarkers for that timeframe were not calculated.

Recordings were also analysed for the last five minute training phase. For the placebo group, this was defined as 1433 seconds to 1733 seconds on the recording. Where the last five minute training phase could not be used due to artefacts, the 5th training phase was used. Where the 5th training phase and the last training phase could not be used, the 4th training phase was used. So the EEG biomarkers generated from the in training recordings represent the brain states in the first half and last half of the training session. These biomarkers can be used to track within sessions and between session effects on the EEG.

Analysis of the In-training data

We analysed the in-training EEG data using the sLORETA software. First the software decomposed the data into the separate frequency domains as described above in Table 3-2. The current density was then calculated for each frequency at each voxel, similarly to the analysis of the resting state data described above. The source localised data for one voxel was taken, the central voxel in the cluster we were training, located at MNI coordinates (x, y, z) = (-5, -50, 10). The power was then calculated in that voxel in the each of the separate frequency domains. The activity in the different domains could then be plotted over time with respect to the number of sessions completed, as we had processed EEG data for the first five minute training phase and the last five minute training phase for each participant in each biofeedback session. The theta, alpha 1, alpha 2 and beta 1 frequency bands were selected for plotting over time because those were the bands the biofeedback was targeting

An index measure of connectivity was taken to track changes in connectivity over time, as follows. The connection between the PCC and the left parahippocampal gyrus appears to be important to memory (118), and so we used the phase lagged synchronisation between these two parts of the brain as an index for changes in connectivity. We took the MNI coordinates for the PCC as (x, y, z) =

(-5, -50, 10), the centre of the cluster of voxels we trained, and the MNI coordinates of the left parahippocampal gyrus as (x, y, z) = (-22, -26, -21) (224). We input the EEG data into the sLORETA software, performed source localisation using the sLORETA method for the coordinates that were pre-defined as above. This decomposed the activity into the frequency bands δ, θ, α1, α2, β1, β2, β3 and Ω, and then compared each frequency domain at each coordinate for phase lagged synchronisation, similarly to the resting state data. This generated a measure for the phase lagged synchronisation between the PCC and the parahippocampal gyrus in each frequency domain at each time point. We plotted the phase lagged synchronisation for these two coordinates in the theta, alpha 1, alpha 2 and beta 1 domains over time.

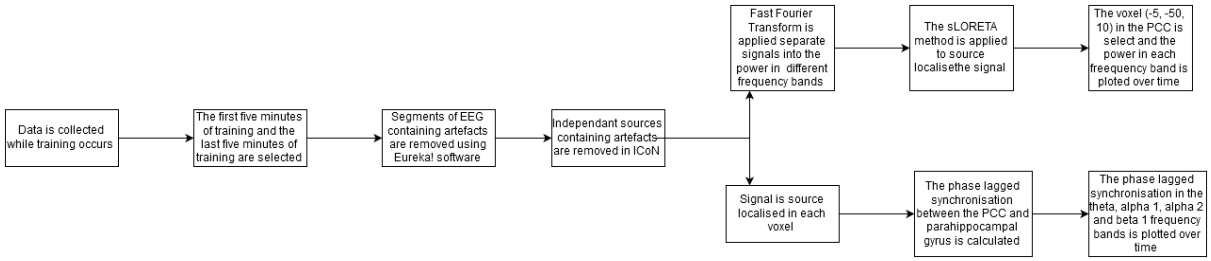


Figure 3-6 Shows the processing pipeline for the in-training EEG data

Measurements of Cross Frequency Coupling

Power to power correlation

Measurement of cross frequency coupling was done using the resting state data from prior to the first training session and after the last training session. Using the sLORETA software, the EEG data for each participant was Fourier transformed to find the power of discrete frequency bands one Hz wide. The first frequency band was 0.5Hz to 1.5Hz, the second 1.5Hz to 2.5Hz continuing on until the last band which was 43.5Hz to 44.5Hz. This was then source localised using the sLORETA method. Then, the power of those frequencies specifically for the PCC was obtained by selecting the power in the voxel with MNI coordinates (x, y, z) = (-5, -50, 10). This produced a list of the power in each of the discrete frequency bands for each of the 44 bands for that EEG recording.

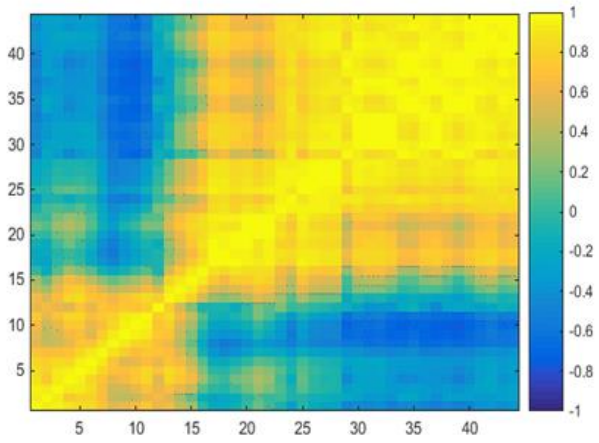


Figure 3-7: Graphical display of the matrix of correlation coefficients

The power output was then assembled into a matrix in MATLAB ® (227). The each row in the matrix was the list of power of frequencies for one participant, and the columns represent a single discrete frequency band across participants. We used the correlation coefficient function in MATLAB® for all the frequencies in the matrix. This generated a new matrix of correlation coefficients. This was then displayed graphically, for example see Figure 3-7 above. Two matrices are generated, one from the pre training EEG recording, and the other from the post training EEG recording. Each matrix was processed individually. The pre and post matrices were displayed side by side to identify regions in which the correlation coefficient between different frequencies had changed over the course of the training. The correlation coefficient can be interpreted as the degree to which those two frequencies occur together, yellow areas represent high correlation and blue areas represent low correlation. High correlation can occur between discrete frequencies whether or not they are physiologically coupled, unlike phase amplitude coupling.

Phase Amplitude Coupling

Once the data were produced and regions of changed correlation coefficients were identified, a more sophisticated analysis of phase amplitude coupling was carried out on those regions. This was done to assess the cross frequency coupling without a priori assumptions about what frequencies would be involved in the coupling. To do this we took the resting state data for both the pre training

and post training EEG, and applied the sLORETA method to source localise activity at every time point in the recording. Then we used the same MNI coordinate as above, (x, y, z) = (-5,-50, 10), to retrieve the source localised activity in the ventral PCC over time.

This stream of activity was loaded into the EEGLAB toolbox in MATLAB®. This data was then processed through the 'phase amplitude coupling add-on tool' in the MATLAB® EEGLAB toolbox. This takes the Hilbert transform (228) of frequencies in a defined low frequency range to generate instantaneous phase, and the Hilbert transform of frequencies in a defined high frequency range to generate the instantaneous amplitude of the high frequency waves. These were used to generate the modulation index (229), and the mean vector length (230). Both of these statistics measure the degree with which the phase of the low frequency wave affects the amplitude of the high frequency waves. These can be interpreted as the degree of phase amplitude coupling.

We also repeated this procedure for the phase amplitude coupling of theta (4-8 Hz) to low gamma (32-45 Hz). We used the tool to assess the modulation of amplitude in the 4-8Hz band on the amplitude of in the 32-45 Hz band. This kind of theta gamma coupling may be important to memory function (112), so this was assessed using the toolbox as well as cross frequency coupling in between frequencies without a priori assumptions.

Statistical Procedures

Statistical tests for cognitive testing data and phase amplitude coupling data were performed in SPSS® version 22 (IBM Corp). For the specific data analysis procedure for the pilot study see chapter 4, for the randomised trial see chapter 5.

Statistical tests for the sLORETA activity and connectivity were performed by the statistical package in the sLORETA software package. Statistical tests in the software are used to determine the statistical significance of changes in the power of defined frequency bands in all voxels between time periods for measures of activity, and the statistical significance of changes in connectivity between time periods for measures of connectivity. These were performed using permutation testing.

Permutation testing is a non-parametric method for assessing significance of activity in neuroimaging studies. It involves swapping the labels attached to data around to test whether there is any impact on outcomes. Significant results are changed by swapping labels, insignificant results are not (221). For changes in current density activity, the log of the F statistic for each voxel is calculated. This happened for each voxel in each of the defined frequency bands. The label on these voxels, whether they were the pre training or post training recording for example, was randomised 5000 times. This generated a threshold for the post training recording over which the log of the F statistic had a 5% probability of occurring by chance. It can be inferred that the direction of change in significant statistics is the same as the direction of change in current density, and the magnitude of the change was proportional.

For connectivity changes, a t –statistic generated for the connection between each pair of ROI in each defined band range was similarly randomised 5000 times to generate a statistical threshold against which the probability of that statistic occurring could be compared.

For the in-training time series data that was produced, the correlation coefficient was calculated for each participant in each frequency band. These were combined to find an average correlation coefficient to find the average strength and direction for change in that band. This data was tested using the two sided t-test where the assumption of normality was met, to compare the average correlation coefficient to 0. Where the assumption of normality was not met, the Wilcoxon signed rank test was used to compare the median to 0. The null hypothesis both cases was that the average correlation coefficient was 0. Where this was rejected, this indicated that there was a significant trend in that frequency band for that condition. Where a significant trend was identified, the regression coefficient and coefficient of determination ass reported. This process was applied to the in-training activity time series and the connectivity time series in the theta, alpha 1, alpha 2 and beta 1 bands. This process was also applied to the resting state time series generated from plotting the

indices from the pre-treatment recording, and resting state recordings from after the eighth, 12th and 15th training sessions.

Chapter 4 Pilot Study

Method

Aim of the Pilot study

This pilot study has three main aims. The primary aim of the trial is determine whether source localised feedback of the PCC can change source localised EEG characteristics of people diagnosed with aMCI.

The secondary aim of the trial is to determine whether source localised feedback of the PCC can change scores on objective memory testing after a training program is completed.

The tertiary aim of the trial is to determine whether source localised EEG biomarkers can predict any change in objective memory scores.

Participants

We aimed to recruit 10 to 12 participants diagnosed as having aMCI into our trial. Biofeedback as an intervention for aMCI has not been tested before, so there is no empiric data of possible effect size for a formal power calculation. However, a recent trial of the same kind of source localised biofeedback has been done in tinnitus (134) and this suggests that 10 participants was sufficient. To recruit participants into the study, we asked for referrals for those had undergone psychometric testing with a neuropsychologist and been diagnosed with aMCI. These were patients who had undergone assessment at Dunedin hospital clinics in the neurology and older person's health service. Exclusion criteria were other neurological conditions such as strokes, multiple sclerosis or Parkinson's disease. Mild psychiatric symptoms did not lead to exclusion. Major psychiatric disorders requiring treatment, such as major depression requiring anti-depressants, or with psychotropic agents were excluded. People who qualified for a diagnosis of established dementia under the NINCDS-ADRDA criteria were also excluded (231).

Participants had to be physically and mentally able to participate in one hour biofeedback sessions. Participants had to be able to see an object eight cm wide and one cm tall at a distance of 50 cm, so

people who had vision problems that prevented this were also excluded. After being referred, hard copy study information was posted out followed up by a phone call within seven days to enquire as to whether they would be interested in enrolling.

Participants' age, sex and years of formal education were recorded at the initiation of the study. Information about their past medical history and current medications was also collected after participants were recruited into the study.

Participants had to be able to come to the Dunedin Public Hospital for up to 15 sessions, once every two days. This meant that feasibly, participants were drawn from the greater Dunedin area, who had reliable access to transport. Several potential participants were located in the lakes district area, in Wanaka and Alexandra. However, they were not invited into the study due to the distance they would need to travel. One participant was recruited in South Otago, from the area around Balclutha. These participants were visited in their home at their preference instead of driving to Dunedin for every session.

Participants were given $20 grocery vouchers at each biofeedback session as a token of appreciation for their time.

Design of the Pilot study

During the first session, the participants were first introduced to the equipment and the procedure for the study, followed by written informed consent. Participants then underwent cognitive testing using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) version A. An initial resting state recording was taken for five minutes. After the resting state recording was taken the biofeedback training was started.

The biofeedback parameter for this study was designed to train up the power of theta and alpha in the posterior cingulate cortex (PCC), and train down the power of beta. The height of the bar in the brain tuner program was calculated using the equation below.

$$Height\ of\ the\ bar = \frac{Power\ of\ 4-14\ Hz\ in\ PCC}{Power\ of\ 20-40\ Hz\ in\ PCC}$$

Participants were encouraged to try and increase the level of the bar, without indicating any strategies. All participants underwent training of the same MNI coordinates (x, y, z) = (-5, -50, 10), (-4,-50, 10), (-6,-50, 10), (-5,-49, 10) and (-5,-51, 10), and the same frequency. No control group was recruited for this pilot study.

The participant came in for 15 biofeedback training sessions. Participants were invited to come in for biofeedback training three to four times a week. Where participants were unable to attend a scheduled session, that session was skipped and added to the end of the sequence, rather than rescheduling another biofeedback session in the same week. Only participants who completed all 15 sessions were included in the analysis.

Resting state EEG recordings were taken after the biofeedback training was completed on the 8th, 12th and 15th session. After the 15th training session was completed, and the last resting state recording was taken, the participant underwent cognitive testing again, using the RBANS version B.

Data analysis was carried out according to the procedures laid out in chapter 3.

Exit Interview

As each participant completed their last training session, a short exit interview was taken. Three main questions were asked:

1. What strategies did you find helped to increase the level of the bar displayed on the screen?
2. Did you notice any changes to your memory after doing the biofeedback training?
3. Did you experience any adverse effects as a result of doing the biofeedback training?

Participants' responses were compared to identify any similarities that characterised the experience of biofeedback.

Data summary

The following data was collected from the participants.

- Age
- Sex
- Approximate total years in formal education
- Presence or absence of neurological disease or psycho-active drugs as indicated by the participant themselves or through medical records
- Pre training RBANS
    - Individual subtest data
    - Combined Indices data (see chapter 3 for details)
- Baseline eyes closed five min EEG
- Resting state eyes closed recordings at session 8, 12, and 15
- In training EEG at every session
- Post training RBANS
- Exit interview responses

Ethics and locality approval

This study was approved by the University of Otago Human Ethics Committee. Approval to conduct the study in the Southern District Health Board locality was obtained through Health Research South.

Statistical Analysis

The cognitive indices from before training were compared to those cognitive indices after training using the paired t test, where the assumption that the differences are approximately normal was met. Where the differences were not approximately normal the Wilcoxon sign ranked was applied.

Statistical significance was set at p=0.05 for all tests. Similarly, before and after effects were assessed for the phase amplitude coupling data using paired t tests or Wilcoxon sign ranked where appropriate.

Statistical significance for the sLORETA current density maps, whole brain connectivity and DMN connectivity were assessed using the in-built statistical program in sLORETA, as described in chapter 3. Methods for the processing of the in training data and generating the cross frequency correlation plots are also described in chapter 3.

Some additional exploratory analyses were done in order to generate hypotheses to explain some of the changes seen in the immediate memory score. Subjects were split into 'responders', who had a change in the immediate memory score of greater than 10, and 'non responders' who had a change in the immediate memory score of less than 10. Responders were then compared to non-responders in the baseline RBANS test scores and indices, change in RBANS test scores and indices, correlation coefficient of in-training current density, and correlation coefficient of in training phase lagged synchronisation, and change in phase amplitude coupling. Statistical significance was assessed with Wilcoxon signed rank test.

Results

Participant Characteristics

A total of 17 subjects were identified as meeting our inclusion criteria. Four subjects were identified using existing clinical records, two were referred by geriatricians from the Older People's Health service of Dunedin Public Hospital, one subject was identified through the Neurology service of Dunedin Public Hospital and 10 subjects were identified through the Neuropsychology service of Dunedin Public hospital. Thirteen subjects agreed to participate in the trial and had at least one session of biofeedback training. Three subjects chose to discontinue the biofeedback training before they completed 15 biofeedback sessions. In one of these subjects, other health issues prevented the participant continuing the study, one participant discontinued the trial because the trial was too

tiring, and one participant objected to the electro-gel. Ten subjects completed all biofeedback sessions and completed both cognitive assessments. The data following refers only to those participants who completed all 15 biofeedback sessions and both cognitive assessments

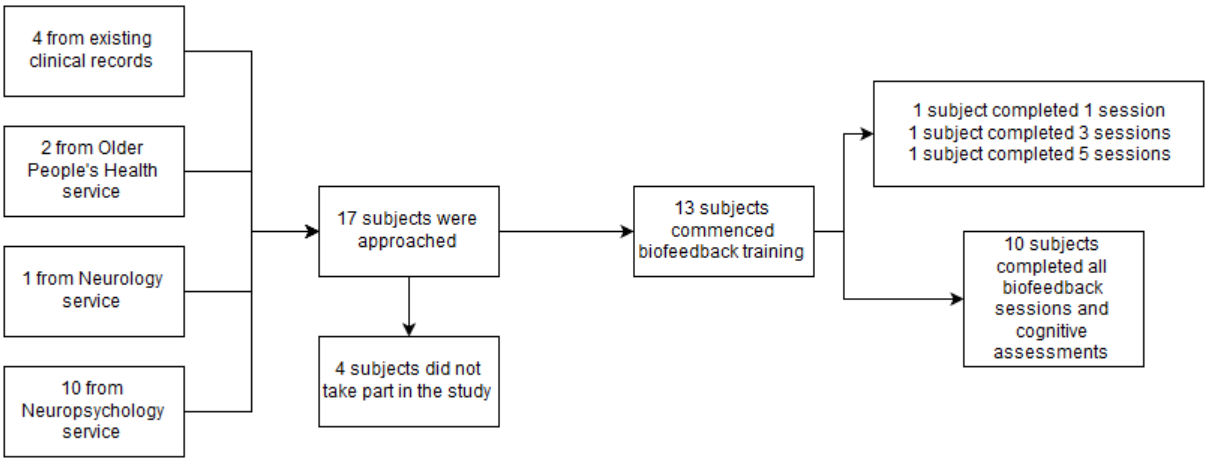


Figure 4-1: Source of participants and loss to follow up

Nine participants resided in the Dunedin City area, one participant resided in the Clutha District area. Basic characteristics of the participants are listed in table 4-1 below.

Table 4-1 : Baseline characteristics of participants

Characteristic	Mean (SD)	Range
Sex	5 Female: 5 Male	
Age	72.7 (9.6)	60-88
Years of Education	13.6 (3.5)	10-18

All participants demonstrated low levels of white matter damage on neuroimaging from their medical records, which is compatible with probable Alzheimer's pathology. One participant demonstrated white matter damage on neuroimaging that was marginal evidence of a vascular type pathology. Another participant was started on rivastigmine patches while on the trial. Sensitivity analysis was carried out using this person's data.

Cognitive Testing

Group level changes

Results of the participant's cognitive testing with the RBANS are listed in table 4-2. The table includes scores for both the individual tests and the cognitive indices calculated from the individual test scores. The RBANS A score is the score from pre training cognitive assessment, and the RBANS B score is the score from post training cognitive assessment. The difference column is the RBANS B score minus the RBANS A score.

Focussing on the cognitive indices, the participants scored lowest in the immediate memory index and delayed memory index, consistent with an amnestic Mild Cognitive Impairment.. These two indices also showed the biggest changes of any of the indices after the training, but still remained lower than the other indices.

Differences between scores were sufficiently normally distributed in most instances to use a paired t test to calculate statistical significance of the differences in the scores below. However, coding score, list recall score, attention index and delayed memory index difference scores were not sufficiently normally distributed. Hence, a Wilcoxon signed rank test was used instead to calculate statistical significance. These results are reported in table 4-3.

The list learning, story memory, immediate memory index, delayed memory index and total scale index showed statistically significant differences between the pre training cognitive test and the post training cognitive test. There were increases after biofeedback training for all of these scores. No other statistically significant differences were seen.

Table 4-2 : Cognitive testing scores from before training (RBANS A) and after training (RBANS B). Statistically significant differences are highlighted in bold. Significance was assessed using a paired t test.

RBANS assessment	RBANS A Score Mean (SD)	RBANS B Score Mean (SD)	Difference (95% CI)	Significance
List Learning	**18.2 (3.4)**	**21.8 (3.3)**	**3.6 (0.2, 7.0)**	**p=0.041**
Story Memory	**10.2 (4.5)**	**13.7 (3.0)**	**3.5 (0.4, 6.5)**	**p=0.031**
Figure Copy	18.5 (1.1)	18.5 (1.6)	0 (-1.0, 1.0)	p=1.000
Line Orientation	17.0 (2.7)	17.0 (2.8)	0 (-1.8, 1.8)	p=1.000
Picture Naming	9.50 (0.67)	9.50 (0.92)	0 (-0.6, 0.6)	p=1.000
Semantic Fluency	15.7 (4.2)	14.2 (2.6)	-1.5 (-4.7, 1.7)	p=0.312
Digit Span	9.70 (2.2)	10.3 (2.4)	0.6 (-0.5, 1.7)	p=0.239
Coding	36.4 (10)	34.0 (9.4)	-2.4	
List Recall	1.40 (1.5)	1.60 (1.6)	0.2	
List Recognition	15.2 (3.3)	16.2 (3.0)	1 (-0.8, 2.8)	p=0.299
Story Recall	3.80 (3.5)	4.60 (3.6)	0.8 (-0.6, 2.2)	p=0.233
Figure Recall	5.70 (5.4)	6.50 (5.1)	0.8 (-0.4, 2.0)	p=0.153
Immediate Memory Index	**73.1 (12)**	**85.5 (8.1)**	**12.4 (3.6, 21.1)**	**p=0.011**
Visuospatial Index	107 (15)	108 (20)	1.1 (-6.5, 8.8)	p=0.754
Language Index	92.4 (12)	88.1 (7.4)	-4.3 (-9.5, 0.9)	p=0.092
Attention Index	95.7 (15)	93.3 (12)	-2.4 (-12.4, 7.6)	
Delayed Memory Index	61.8 (19)	69.1 (21)	7.3	
Total Scale Index	**81.2 (12)**	**85 (11)**	**3.8 (1.1, 6.5)**	**p=0.011**

Table 4-3: Median Scores for the RBANS A and RBANS B for variables which are insufficiently parametric for a paired t test. Statistically significant differences are in bold. Significance was assessed using a Wilcoxon signed rank test

RBANS Assessment	RBANS A Score Median	RBANS B Score Median	Difference	Significance
Coding Score	35.5	32.5	3.0	p=0.777
List Recall Score	1.00	1.00	0.0	p=0.750
Attention Score	94.0	95.5	1.5	p=0.875
Delayed Memory	**61.5**	**68.5**	**7.0**	**p=0.016**

Individual level changes

The most consistently increased variable between the participants is the immediate memory index, followed by the delayed memory index. A few individuals have large changes on the attention index. Individuals with moderate or large increases in the immediate memory index (greater than or equal to 10 points) tended to have small increases or no change on the delayed memory index. Individuals with small changes in the immediate memory index (less than 10 points) tended to have moderate to large changes on the delayed memory index. See table 4-4 for details.

Figure 4-2 has the individual's change in score between pre and post testing, for each of the cognitive indices. There is large variability in change scores between individuals on an inter-individual basis, and there is also large variability between index changes on an intra individual basis.

Table 4-4: Participants' change in immediate memory index and change in the delayed memory index

Participant	Change in Immediate Memory Index	Change in Delayed Memory Index
Participant 1	5	4
Participant 2	-7	24
Participant 3	14	4
Participant 4	20	0
Participant 5	32	0
Participant 6	25	0
Participant 7	13	2
Participant 8	20	12
Participant 9	0	10
Participant 10	2	17

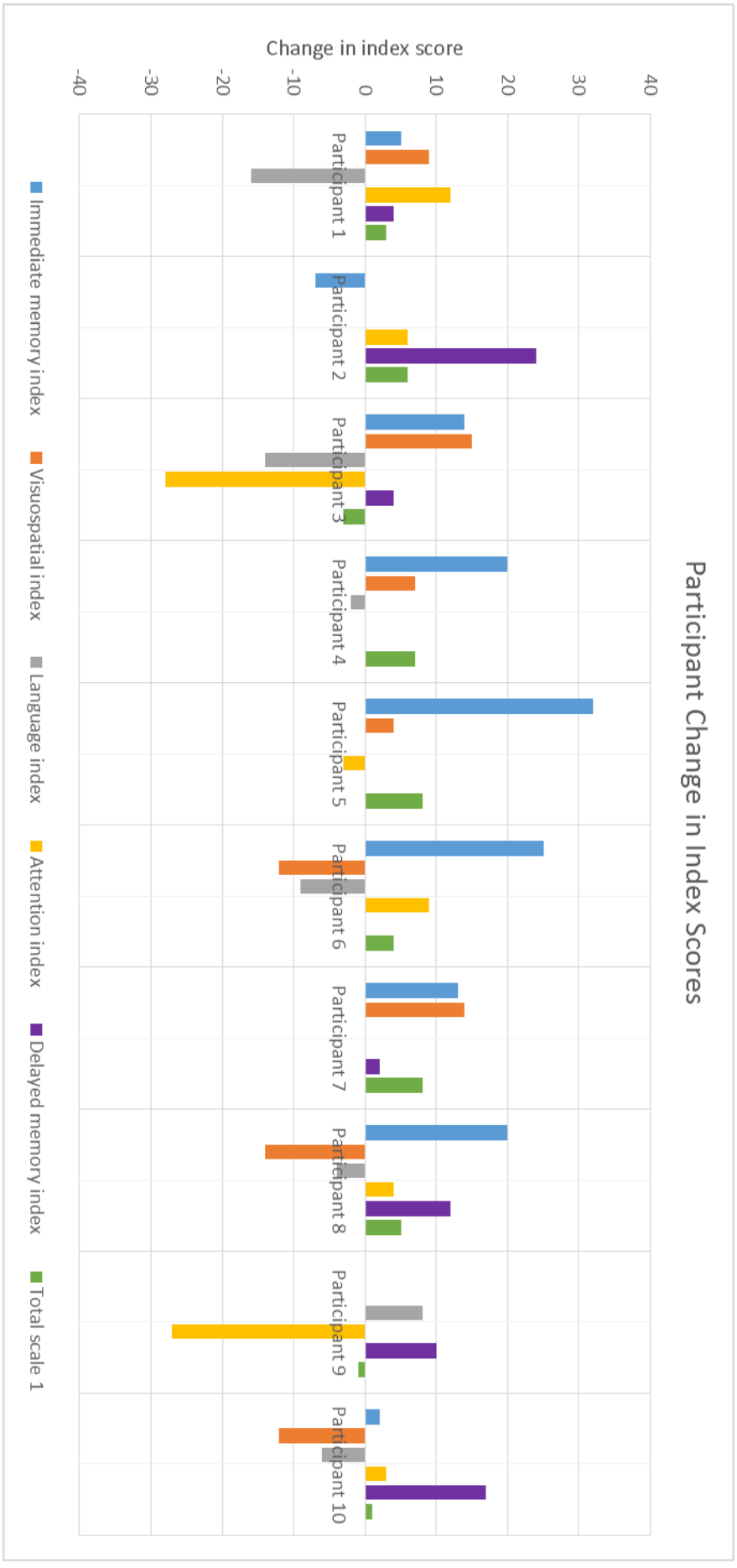


Figure 4-2: Individual changes in index score

sLORETA Activity Changes

There were no statistically significant changes found in the sLORETA activity comparing the post training resting state EEG to the pre training resting state EEG. Diagrams showing the voxels with the largest magnitude of change in each frequency band can be found in Figure B-1 in Appendix B1.

sLORETA Connectivity Changes

Whole Brain Connectivity using 88 Regions of interest

There were statistically significant decreases in connectivity found in all bands. No statistically significant increases in connectivity found in any band Diagrams of the statistically significant decreases can be found in figure B-2 in Appendix B2. The greatest number of decreased connections was found in the delta band. Changes in connectivity at the regions around the PCC are seen in the delta, theta, alpha 1, beta 2, beta 3 and omega frequency bands. The alpha 2 and beta 1 frequency bands show the least decrease in functional connectivity, and this decrease is localised around the frontal region of the brain.

Default Mode Network Connectivity using 11 Regions of Interest

The ROIs chosen are listed in Table A-1 in appendix A2 and are the result of a meta-analysis on the components of the default mode network (223) and including the parahippocampal gyri (224).There were few statistically significant differences found in the phase lagged synchronisation between the regions of interest in the default mode network. A significant increase was found in the theta band right inferior parietal lobule and the left middle temporal gyrus. In the alpha 1 band, there was a statistically significant decrease in the phase lagged synchronisation of the left middle frontal gyrus and the left inferior parietal lobule. In the beta 1 band, there was a statistically significant increase in functional connectivity between the right middle temporal gyrus and the right inferior parietal cortex. No other statistically significant increases or decreases in phase lagged synchronisation were found. The diagrams showing these changes can be found in Figure B-3 in appendix B3

sLORETA indices for tracking change over time

Activity measures

The activity measure was average current density in each of the theta, alpha 1, alpha 2 and beta 1 band in the PCC at each session. The activity in the PCC in the theta, alpha1 alpha 2 and beta 1 frequency bands was measured over time for the first five minutes and last five minutes of each biofeedback session. Graphs displaying the activity in each participant in each session are displayed in Figures B-4 to B-7 in Appendix B4. A significant trend emerged in the Alpha 1 band. The average activity increased with session number (β=0.0039, r^2=0.033, p=0.028 Wilcoxon signed rank test). See Figure 4-3 for details.

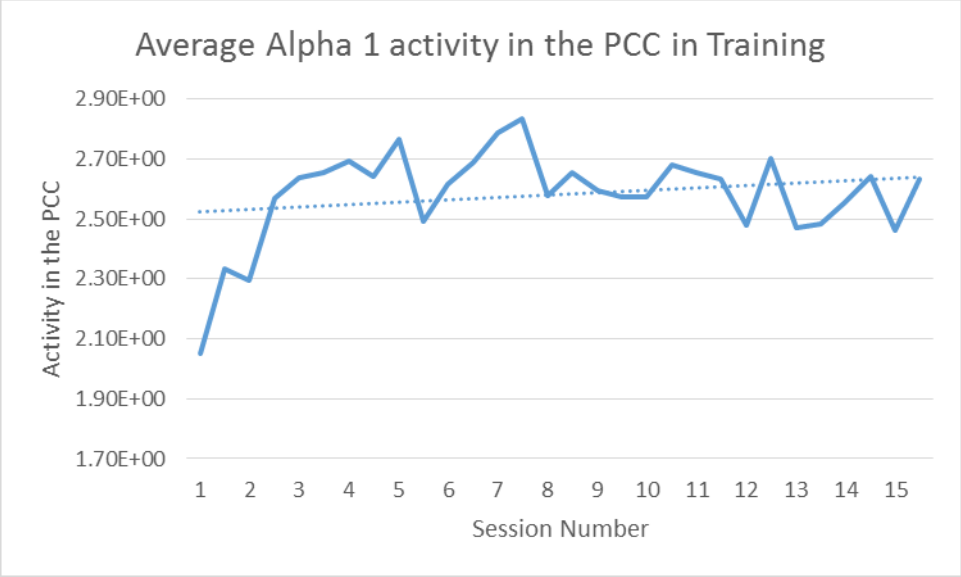


Figure 4-3: Average Alpha 1 activity over time in the PCC in training

Activity in the PCC in the theta, alpha 1, alpha 2 and beta 1 frequency bands was also measured for each of the resting state EEGs that were taken. These were taken at session 1, session 8, session 12 and session 15. The graphs for each participant's activity at each time point can be found in Figures B-8 to B-11 in Appendix B5. No significant trends were found in the resting state data.

Connectivity measures

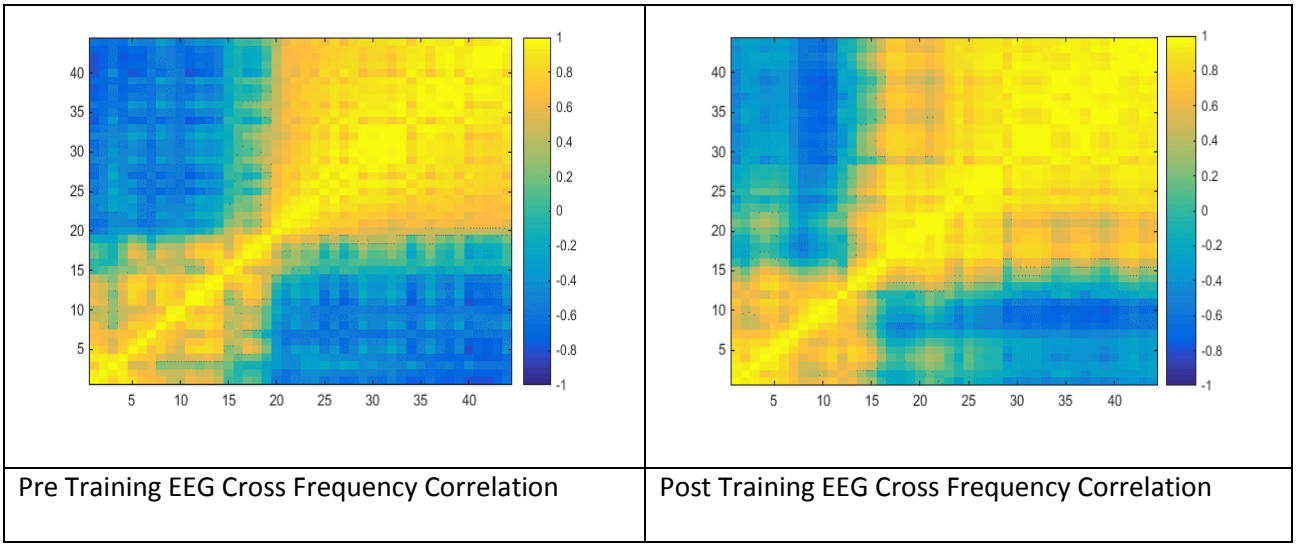
The phase lagged synchronisation between the PCC and the left parahippocampal gyrus was calculated. In each session the phase lagged synchronisation was calculated for the first five minutes and the last five minutes of each session. No significant trends were found in connectivity for each participant over time, see Figures B-12 to B-15 in Appendix B6.

The phase lagged synchronisation between the PCC and the left parahippocampal gyrus was calculated for each of the resting state EEGs (sessions 1, 8, 12 and 15). The graphs showing the connectivity for each participant over time can be found in Figures B-16 to B-19 in Appendix B7.

A table of the statistical tests done on the correlation coefficient for each condition in each frequency band can be found in Table B-2 in Appendix B8.

Frequency Cross Correlation

The cross frequency correlation is displayed graphically below in Figure 4-4 below. Yellow represents frequencies that are positively correlated. This means that they occur together more frequently than average. Blue represents frequencies that are negatively correlated. This means that frequencies occur less frequently together on average. The image on the left of Figure 4-4 displays the cross frequency correlation of the resting state EEG taken on session 1. The image on the right of Figure 4-4 represents the cross frequency correlation of the resting state EEG taken on session 15.



Pre Training EEG Cross Frequency Correlation	Post Training EEG Cross Frequency Correlation

Figure 4-4: Cross Frequency Correlation with the pre training resting state EEG and the post training resting state EEG

In the pre training EEG, high frequencies (above 20Hz) tend to have a positive correlation with other high frequencies. Low frequencies (below 20Hz) tend to have a positive correlation with other low frequencies. High frequencies tend to have a negative correlation with low frequencies.

A similar pattern can be seen in the post training EEG. However, the higher frequencies that correlate to each other tend to be above 15 Hz, rather than 20 Hz as in the pre training EEG. The pattern of cross frequency correlation has changed between the post training EEG and the pre training EEG.

To look at the change in cross frequency correlation we took the pre training cross frequency correlation matrix and subtracted from the post training cross frequency correlation matrix. Figure 4-5 represent the cross frequency correlation of the session one EEG subtracted from the session 15 EEG. Yellow represents an increase in cross frequency correlation after training and blue represents a decrease in cross frequency correlation after training. In green areas no appreciable change has occurred.

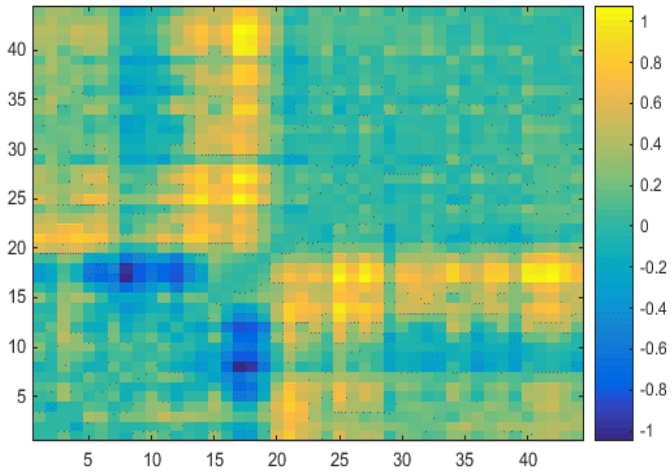


Figure 4-5: The change in cross frequency correlation

An increase in cross frequency correlation occurred in the coupling of the ranges 15 to 20 Hz with 20 to 44 Hz. A decrease in coupling has occurred of the ranges 5 to 15 Hz with 15 to 20 Hz. Elsewhere there is no appreciable change.

Phase Amplitude Coupling

Three analyses were done using mean vector length to calculate the phase amplitude coupling. The cross frequency coupling of 4 to 8 Hz with 32 to 60 Hz, in line with our a priori assumptions. We also calculated the phase amplitude coupling of 5 to 15 Hz with 16 to 20 Hz, and the phase amplitude coupling of 15 to 20 Hz with 25 to 40 Hz. These final two couplings were suggested to be significant by the cross frequency correlation map. Results of the calculation using mean vector length are listed in table 4-5 below.

Table 4-5 : The phase amplitude coupling before and after training. Significance was calculated using paired t tests

Coupling	Pre training Mean Vector Length Mean (SD)	Post training Mean Vector Length Mean (SD)	Difference	Significance
4-8 Hz with 32 to 60 Hz	0.432 (0.11)	0.451 (0.098)	-0.0308	p=0.482
5-15 Hz with 16 to 20 Hz	0.0565 (0.030)	0.0627 (0.031)	0.00624	p=0.532
15-20 Hz with 25 to 40 Hz	0.167 (0.080)	0.147 (0.090)	-0.0206	p=0.432

There was no significant change in phase amplitude coupling measured by mean vector length in any of the pairings assessed.

Participants' Experience of Biofeedback

Participants did not identify a single strategy to influence the biofeedback parameter. Most participants identified not concentrating on the bar, but concentrating on other objects or tasks as a strategy that they employed to change the height of the bar. Two participants identified counting as a strategy they employed. Three participants specifically mentioned not focussing on the bar, and

focussing on or thinking about different things. One participant mentioned squinting as a part of their strategy, another participant mentioned raising their eyes as part of their strategy. Only two participants said they concentrated on the bar in order to raise it above the threshold on the display.

Three participants said that the training might have had a noticeable effect on their memory. One of these participants was sure that his memory had improved as a result of the training, the other two were uncertain but thought that the training could have had an impact. One participant said that they had not noticed any change to their memory, but mentioned that their spouse thought that their memory had improved. All other participants did not notice any changes to their memory.

The only adverse effect noted from the training was tiredness. Four of the 10 participants mentioned tiredness on days that they had done a training session. Two of these claimed that they experience moderate levels of tiredness on days they completed a training session, the other two only claimed a mild tiredness after completing a training session. No other adverse events were noted.

Post Hoc Analysis of Responders and Non Responders

On the immediate memory index, which is the variable that has the greatest change after the biofeedback training, seemed to have a bimodal distribution. There appears to be a group of non-responders, where the change in the index is less than ten points, and a group of responders, where the change in the immediate memory index is greater than ten points. See Figure 4-6.

The group of responders, defined as those who had an improvement in immediate memory of more than 10 points, were compared to the group of non-responders to identify factors which might influence the response to training. Factors which differed significantly between the responder group and the non-responder group are presented in table 4-6. Differences were calculated by subtracting the median from the non-responders from the responders. Therefore, negative differences variables which are higher in the non-responder group.

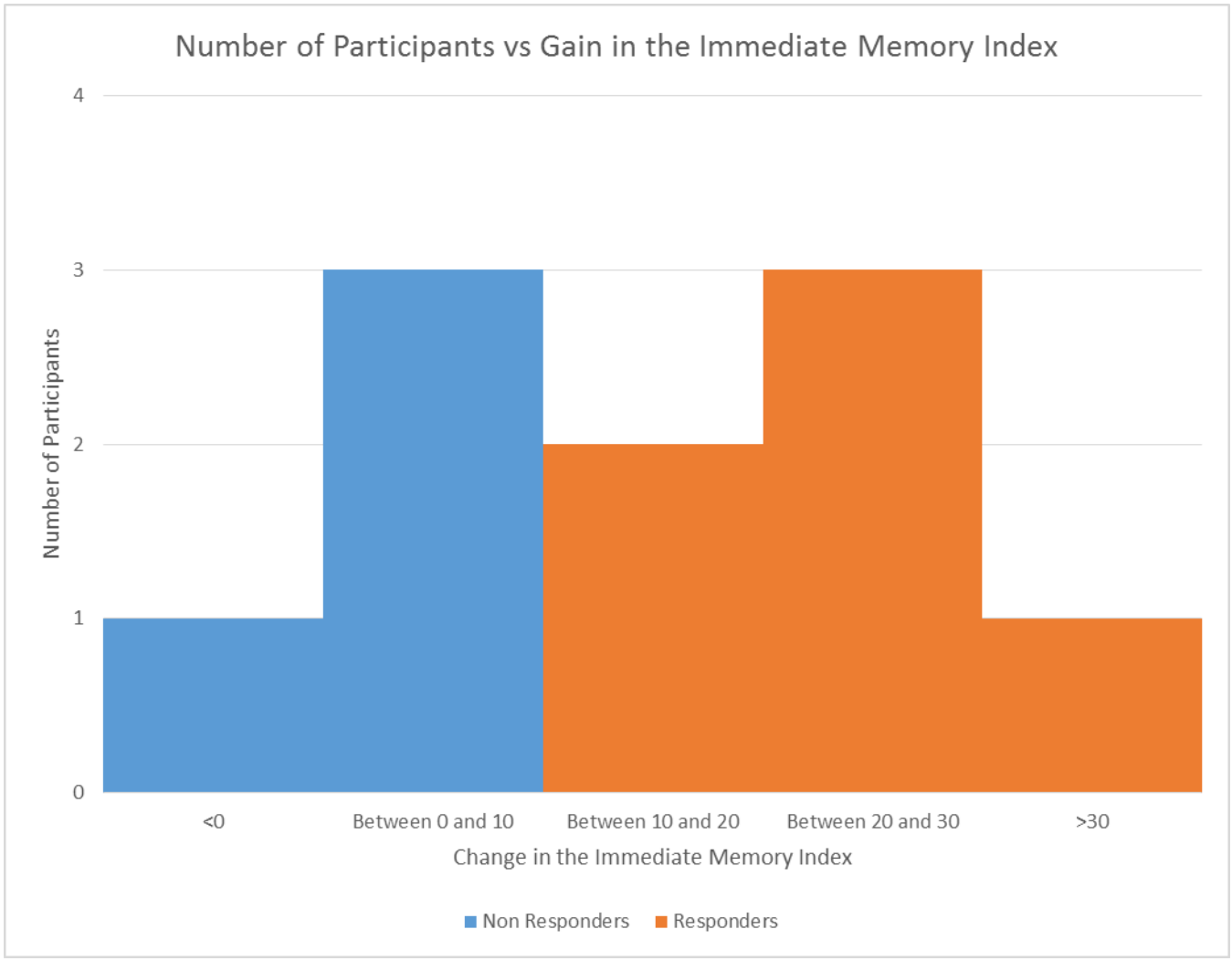


Figure 4-6: Frequency plot of the number of participants increasing their score in the immediate memory index

Table 4-6: Differences between Responders and Non-Responders. Significance was calculated with Wilcoxon Signed Rank

Variable	Median in Responders	Median in Non-Responders	Difference	Significance
Baseline Immediate Memory Index	70.5	84.0	-13.5	p=0.043
Difference in Before and After Delayed Memory Index	1.0	13.5	-12.5	p=0.038
Regression Coefficient of Activity in Alpha 2 band and Session Number	-0.0255	0.0119	-0.0374	p=0.038
Regression Coefficient of Connectivity in Alpha 2 band and Session Number	-0.000950	0.000000	-0.000950	p=0.038

The non-responders had a higher baseline immediate memory index. As mentioned before, the non-responder group experience more improvement in the delayed memory index than the responder group.

The regression coefficient of activity in the PCC in the alpha 2 band over time tended to be more positive in the non-responder group than the responder group. This means that participants who had a trend toward higher activity after the biofeedback training tended to be in the non-responder group. Similarly the regression coefficient of connectivity between the PCC and the left parahippocampal gyrus in the alpha 2 band over time also tended to be more positive in the non-responder group than the responder group. This means that participants with a trend toward increased connectivity in the alpha 2 band were more likely to be in the non-responder group.

Discussion

Key Results

- There was a significant increase of 12.4 points in the immediate memory index from baseline (p=0.011)
- There was also a significant increase of seven points in the delayed memory index (p=0.016)
- The average Alpha 1 activity in the PCC during training increased over time (β=0.0039, p=0.028)
- Three participants indicated that the training might have had an impact on their memory. The most common adverse effect was tiredness, experienced by four participants.

Primary and Secondary Aims

Primary Aim

Our primary aim was to assess whether the phase lagged synchronisation of the PCC to the rest of the default mode network and particularly the parahippocampal gyrus could be improved with biofeedback training. Certainly the connectivity of the default mode network was altered by the biofeedback training. There were statistically significant decreases and increases in the default mode network. However, there were no statistically significant increases in the phase lagged synchronisation in the theta and alpha bands between the PCC and the other default mode network nodes, nor the parahippocampal gyrus in particular as was hypothesised.

There were changes in connectivity seen around the whole brain when 84 regions of interest were selected for analysis. It is possible that the training does have an impact on network changes in the default mode network that are sub-threshold. Notably, when analysis is expanded to the 84 regions of interest, the PCC is involved with changes in connectivity in most frequency bands. With a larger sample, it may be possible to extract more data about what is occurring in the default mode network and the PCC.

Secondary Aim

Our secondary aim was to assess changes to measures of memory. This was to see if the biofeedback had a clinical effect on memory. The participants scored poorly on the immediate memory index and the delayed memory index of the RBANS, in both the pre training and the post training assessment, in line with what other studies have found characterises this group (232). Participants appeared to have difficulty with recall, rather than with encoding of memory. This is indicated by the relatively high list recognition scores compared with the list recall scores on both the RBANS A score and RBANS B score.

There was a significant increase in both the immediate memory and the delayed memory indices after the participants had completed their training. No other statistically significant changes were noted in the other indices measured by the RBANS. Furthermore, the increase in immediate memory for the group was 12.4 points. The RBANS indices are designed using a standardising population have a mean of 100 and a standard deviation of 15 (212). This means an effect size of 12.4 would be considered a 'large' effect size, and represents a clinically significant improvement in memory. There was a smaller increase in the delayed memory index of 7.3 points, which was statistically significant. This index is the most affected index in the RBANS by aMCI (233), and was lowest index score achieved by our cohort.

The biofeedback training seemed to have a specific effect on memory. Other indices which assessed other cognitive domains did not show significant or high magnitude changes. Because aMCI is diagnosed on the basis of isolated memory impairment (122), this suggests that this biofeedback training program has some specificity to improving memory outcomes in aMCI.

Tertiary aim

Our third aim was to identify sLORETA markers which could be used to track changes in future clinical trials. Of all the markers assessed in this study, only one was found to be statistically significant. This was the activity in the PCC in the alpha 1 band from the in-training EEG over time. It was found to increase with the number of sessions. There was no significant change in any other

activity or connectivity measures assessed. Measures of cross frequency coupling that were assessed in this study also did not change significantly.

A linear regression was performed on the alpha 1 activity in the PCC from the in-training EEG data. However, a logarithmic regression could potentially be fitted to data. A linear regression was chosen due to the underlying complexity of the individual participant's data. The method used to assess the statistical significance of the average trend could only assess a linear regression, because linear regressions were fitted to the individual participant's curves. Using the method to calculate the statistical significance described, it would be inappropriate to fit a logarithmic curve the to the individual participant's curves.

Responders vs Non Responders

The data was separated out by whether people had a large increase in the immediate memory index (greater than 10 points) or did not have a large increase (less than 10 points). Six people were placed in the responders group and four people were placed in the non-responders group. This study was not powered to generate conclusions from this type of post hoc exercise, this was purely hypothesis generating.

The two groups were compared on baseline characteristics to find predictors of whether a participant would respond or not. The pre training immediate memory index was found to be a predictor of whether a participant was in the responders group or not. The responders tended to have a lower baseline immediate memory index. This result could be due to regression to the mean; however it could also be that the responsiveness of the immediate memory index to the biofeedback training is modulated by the severity of the of the memory deficit.

Responders and non-responders were also compared on outcome variables, to see if the outcomes of training were different. It was found that non responders has a greater increase in the delayed memory index. In fact, most of the increase seen in the delayed memory index in the group analysis

is attributable to individuals who did not have large increases in the immediate memory index. It would appear that the change in the memory indices is dependent on each other.

The two groups also differed on some of the sLORETA indices. In particular, the groups differed on the regression coefficient of activity in the alpha 2 band in the PCC over time, and the regression coefficient of connectivity between the PCC and left parahippocampal gyrus over time. In both cases, participants in the non-responders group were more likely to have a positive trajectory in these variables. If this result is repeated in larger studies, these could be used as biomarkers to assess whether biofeedback protocols are successful.

Memory and Biofeedback training

The PCC has been implicated in both episodic memory and semantic memory retrieval (59, 234). The default mode network is also strongly involved in memory retrieval (234). A recent study suggested that interactions between the PCC and medial temporal lobes system consolidate memory for greater recall accuracy (235). Training of the PCC through source localised biofeedback appears to be able to increase immediate and delayed recall, and so may be able to modulate this system. However, we were unable to demonstrate a bio marker on our EEG data that would account for the changes seen. This may be due to the low signal to noise ratio of EEG data and the limited number of participants who took part in this study. A larger study with more participants may be able to demonstrate EEG changes with changes in memory score.

Changes in the RBANS indices could also be explained by changes in the interactions with the working memory system. The working memory system stores a small number of items for recall after a short time, independent of the medial temporal lobe storage system (38). A 2012 fMRI study found that resting state connectivity within the DMN predicted subsequent performance on a working memory task, and also that stronger anti-correlation of the DMN and the working memory network predicted improved performance on the working memory task (210). Therefore changes in

memory performance could also be explained through modulation of the DMN in working memory tasks.

The immediate memory score is likely to measure a composite of working memory capacity and medial temporal lobe memory systems. The tasks that contribute to the immediate memory index are immediate in nature, drawing on the working memory capacity. However the length of task and the retention interval of both the list learning task and story memory task exceed theoretical working memory capacity, and the immediate memory index derived from these two scores is therefore supplemented by the medial temporal lobe encoding of memory (39). The immediate memory index therefore reflects in part the working memory capacity and in part the longer term retrieval system in the medial temporal lobe. Both the immediate memory index and delayed memory index appear to be affected by memory impairment, as both are low in this participant group compared to their other cognitive indices.

It is interesting to note that participants with changes in the immediate index seemed to have no change in the delayed memory index, and participants with changes in the delayed memory index experiencing little change in the immediate memory index. It is possible the effect of the biofeedback is modulated by the working memory capacity of the participant. Participants with low working memory have increased capacity as a result of the biofeedback training, but the medial temporal lobe memory retrieval network is unaffected, and hence do not experience improvement in delayed memory. Likewise, participants with high capacity working memory do not increase their working memory capacity, but experience a change in the connectivity between the PCC and medial temporal lobe, resulting in improvement of delayed memory, but do not improve immediate memory significantly because there is no change in working memory.

Potential Sources of Bias

As discussed earlier, there were potential sources of bias in this study. In particular, one participant was started on rivastigmine patches during the trial. Rivastigmine is a cholinesterase inhibitor

generally used to treat Alzheimer's disease. Its use in aMCI is discouraged, because it has not been proven effective to prevent the onset of dementia, nor improve cognitive scores (236). A sensitivity analysis was carried out, using multiple imputation to generate 20 different values for change in immediate memory score. 19 out of the 20 simulations demonstrated preservation of the significant improvement in the immediate memory index. Twelve out of 20 simulations demonstrated preservation of the improvement in delayed memory index. This would suggest that the improvement in the immediate memory index demonstrated in this trial is robust to the presence of this cholinesterase inhibitor.

Limitations in the use of the RBANS Tests

A limitation in this study is that every participant was assessed on the RBANS A form for their pre training assessment and assessed on the RBANS B form for their post training assessment. This has the potential to introduce test specific bias into the study. However, this is not expected to play a significant role in the results of this study because the tests have high reliability between the forms (178). The subsequent controlled trial detailed in chapter 5 and 6 randomised which form is used to assess pre training cognition, to eliminate this potential source of bias.

Design of the Biofeedback protocol

The design of the biofeedback protocol came out of a study of biofeedback in tinnitus patients (134). They found that source localised training of the PCC did not alter the subsequent activity of the PCC, but rather altered the connectivity. Thus this technique could be applied to MCI in order to reverse the changes in connectivity cause by AD pathology. We used a very similar protocol to the one used in the tinnitus study, which is not necessarily optimised for the MCI cohort or for training source localised activity in the PCC in general. Several observations made during the training procedure suggest that other protocol designs should be investigated.

The current protocol is designed to up-train the power of the frequencies between 4 and 14 Hz. This includes both the theta and the alpha band. There is evidence to suggest that default mode network

connectivity occurs in the alpha frequency band (113). Furthermore, significant changes in the EEG were found in the alpha band, and not in the theta band as predicted. A biofeedback protocol that took the source localised alpha activity only of the PCC as a feedback parameter may be more effective at training the connectivity and hence achieve a better outcome in terms of memory. It is possible that using a narrower band for biofeedback will make it easier for participants to gain voluntary control over the parameter, and so improve the participants' response to training.

Generalisability

As recognised from the beginning, this study was a pilot study to assess the feasibility of this intervention as a treatment for MCI. Our sample size was small due to the limitations of the population we were working with. The sample consisted of men and women over the age of 60, all ethnic European New Zealanders. Therefore, the results of this study suggest that the training would have efficacy amongst New Zealanders with MCI over the age of 60. Additional data would be needed to assess whether the training would be effective in people with MCI who were younger, between 40 and 60 years old, for example. The study was not powered to assess sex or ethnicity effects on any of the measures used to assess the training.

Conclusion

In this sample of 10 people undertaking 15 sessions of source localised biofeedback training, there was no significant increase in connectivity between the PCC and the rest of the default mode network, nor the parahippocampal gyrus in particular. However, participants showed improved memory outcomes after completing the training, suggesting that this kind of biofeedback method could be effective in treating the symptoms of MCI.

On the basis of this conclusion, a randomised trial was designed and carried out. This trial was designed to address four main issues arising from this pilot study. These are

1. Address whether training a narrower band of frequencies would have any effect on the effectiveness of the training.

2. Address whether the result may be generalizable to a more heterogeneous cohort.
3. Differentiate the effect of working memory from the effect of the medial temporal lobe system
4. Randomise the RBANS form to correct for any form specific bias

The methods and results of the randomised controlled trial are described in chapter 5 and 6.

Chapter 5 Randomised Controlled Trial of EEG biofeedback in Memory Impairment

Aims

The randomised controlled trial was designed to address four main aims:

1. To test source localised EEG biofeedback in a population with mild memory problems against a placebo biofeedback training.

2. To compare two forms of the biofeedback, broadband versus narrowband, to see if the biofeedback training effectiveness can be optimised.

3. To test the effectiveness of biofeedback training in a general cohort of older people with mild memory deficits, which is a more common scenario than the strict definition of amnestic MCI.

4. To discover/identify EEG based biomarkers that can track memory improvement and decline in response to the biofeedback training

Trial design

This trial had a randomised controlled design, where participants were randomised equally into one of three groups. These three groups were

1. Broadband feedback group, using identical parameters to the pilot study
2. Narrowband feedback group, using a narrower range of source localised frequencies as the feedback parameter
3. A placebo feedback

Statistical power

We aimed to gather data on 45 people completing 15 sessions of biofeedback training, resulting in 15 participants in each group. Using the data from the pilot trial, a sample of this size would have an 80% chance of detecting a difference of 12 on the RBANS immediate memory index between the groups. This difference would be a clinically significant change in memory. Changes of less than 10 on the index are unlikely to be of any practical significance in a clinical setting.

Ethics and locality approval

This study was approved by the University of Otago Human Ethics Committee. Approval to conduct the study in the Southern District Health Board locality was obtained through Health Research South. The trial was registered with the Australian and New Zealand Clinical Trials Register, registration number ACTRN12616001731482.

Participant recruitment

Participants were recruited from the Dunedin general public through advertising. The study was advertised on posters in Dunedin Hospital and other public places around Dunedin. Advertisements were placed in the free local newspaper the Star©. Participants were also invited to participate from the Brain Health Research Centre's healthy brain list, which is a list of people who have disclosed no neurological disorders, who have indicated a desire to be involved in brain related research at the University of Otago. Participants were also asked to invite anyone who they may have thought would be interested in this study to volunteer for this study. The recruitment criteria were

1) Participants be over the age of 40
2) Have no history of dementia
3) Have no history of significant neurological and psychiatric disease

Participants were asked to verify whether they had any neurological disease. They were included in the study if they had a history of depression or anxiety but were not currently on medication. Participants were excluded if they disclosed current use of psychiatric drugs, had Parkinson's disease, multiple sclerosis, a history of epilepsy, bipolar disorder, schizophrenia, a history of stroke, motor neuron disease.

Volunteers were invited to come in for a screening session which lasted about an hour. During this time the volunteers were administered and RBANS test, were administered a 2-back test three times, and where time allowed, a resting state EEG recording was also taken. If a participant who

had an EEG done was subsequently invited to take part in the biofeedback training, this recording would be their baseline resting state recording. If the participant entered the biofeedback training and didn't have a resting state recording taken, this would be recorded at the initial biofeedback training session before the first biofeedback session was initiated. If the participant had a resting state recording, and wasn't subsequently invited to take part in the biofeedback training, this recording would go into a normative EEG database, called the 'normal brain' controls, which could be used to characterise participants who completed the biofeedback training.

Participants were invited to take part in the biofeedback training if they scored at 90 or below on the immediate memory index of the RBANS test. This cut off was designed to separate people with mild memory issues that may be picked up in a general practice setting from older adults with normal memory for their age. The NINCDS-ARDA criteria for aMCI often require a memory deficit of 1 to 1.5 standard deviations below age matched normal values (30). The immediate memory index in the RBANS is designed to have an average of 100 and a standard deviation of 15 according to the standardising population (178). This means that participants scoring 90 on the RBANS are 0.67 standard deviations below the aged matched normal value. Participants in this trial are therefore less impaired than people diagnosed with aMCI. This criteria does not match research or clinical criteria for Mild Cognitive Impairment; however it does indicate a cohort of older adults with objectively reduced memory capacity, which may be amenable to treatment.

RBANS

Participants were initially randomised onto either form A or form B, in a counter balanced designed so that equal numbers of volunteers would be randomised to be screened on either form A or form B. For follow up testing, a 1-2-1 design was followed. For example, a participant who was initially randomised to form A would be tested on form B at immediate follow up, and at the 6 week follow up session they would be tested on form A again.

Randomisation

Participants who scored 90 or less on the immediate memory of the RBANS were immediately randomised into one of the trial arms. The online tool at randomizer.org (237) was used to generate three lists of random numbers. The first two lists, labelled list A and list B have 12 blocks of three numbers. Each block in list A and list B will have a 1, a 2 and a 3 in it, in a random order. List A was assigned to the sex of the first participant to commence biofeedback training, and list B was assigned to the other sex. 1 assigns the participant to 'broadband' biofeedback, 2 assigns the participant to 'narrowband' biofeedback, and 3 assigns the participant to placebo biofeedback. The first number in each block was assigned to the first participant of each sex. When each block was completed that block was discarded and the next block was used.

The third list, list C consists of three blocks of three numbers each. As above, each block contains a 1, a 2 and a 3, with assignations as above. This list was used to randomise participants who use cholinesterase inhibitors regardless of sex.

This randomisation procedure in theory results in three equal groups, with equal proportions of men and women. This randomisation procedure can reliably produce equal sex matched groups under the condition that participants who are lost to follow up present approximately equally in each group and are made up of equal proportions of each sex, and the number of cholinesterase inhibitor users is low.

Trial groups

Participants were randomised into one of three groups

1) Broadband feedback group
2) Narrowband feedback group
3) Placebo feedback group

The broadband feedback supplied to the broadband feedback group was the same biofeedback training as was in the pilot study. The parameter used for biofeedback is given in the equation

below. The height of the vertical bar on the screen was derived from the power of theta and alpha in the PCC, as calculated by sLORETA. This was included in the randomised trial to replicate the findings of the pilot study in the new cohort, and also to make the findings of the pilot study comparable to the control group of this study.

$$Height\ of\ the\ Bar = \frac{Power\ of\ 4\ Hz - 14\ Hz}{Power\ of\ 20\ Hz - 40\ Hz}$$

The narrowband feedback group used the same Braintuner © program (Mitsar Co Ltd, St Petersburg, Russia) as the broadband feedback group, but the output of program trains a narrower range of frequencies with the parameter used shown below in the equation below. The parameter was derived from only the power of alpha in the PCC. This parameter was selected for two reasons. Firstly, it was hypothesised that a narrower range of frequencies would be easier to train for the participants, and therefore might produce further gains in memory compared to the broadband training. Secondly it is suggested that the alpha frequency connectivity is the most important frequency for default mode network integrity (113).

$$Height\ of\ the\ bar = \frac{Power\ of\ 8\ Hz - 14\ Hz}{Power\ of\ 20\ Hz\ to\ 40\ Hz}$$

Finally a placebo feedback group was also included. The placebo feedback program displays to the participant a vertical blue bar of similar dimensions and colour of the bar displayed to the two biofeedback groups. However, the height of the bar was determined by a random number generator. This random number generator generated numbers in a normal distribution pattern, at a rate of five times a second. The distribution was set such that the bar would spend approximately 35% of the time in the top half of the screen. While this was occurring, a simultaneous EEG recording was taken in order to maintain the blinding of the participant.

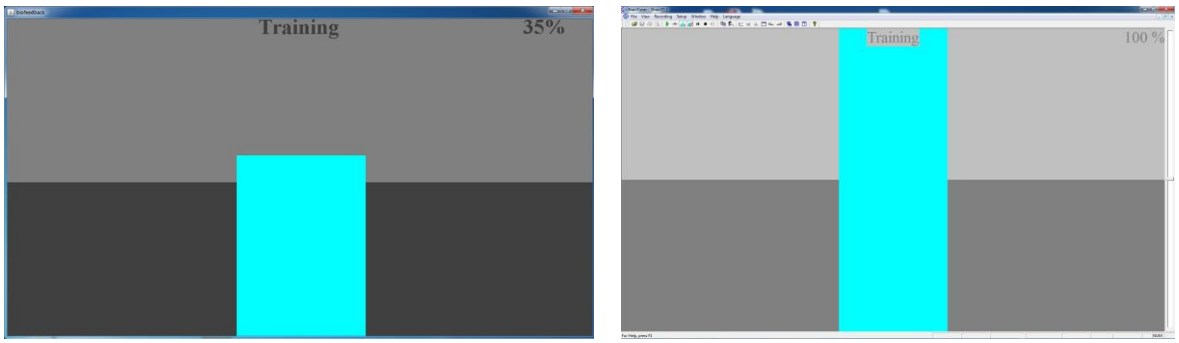


Figure 5-1: Comparison of the user interface of the placebo biofeedback on the left and the genuine biofeedback on the right

Figure 5-1 demonstrates the display differences between the placebo program and the Braintuner © biofeedback program. The placebo program was designed to match the appearance of the Braintuner © biofeedback display on the laptop the feedback was administered on. Due to an artefact of the laptop's display, the placebo feedback and genuine feedback appeared identical on the laptop screen, but appears darker in Figure 5-1 above. The placebo feedback program and the Braintuner © program differed substantially in their capabilities, such that a participant exposed to both programs would easily notice the difference and become un-blinded. Blinding was maintained by preventing participants viewing the interface of the program they were not assigned to. The desktop icon of the placebo program was masked with the image of the desktop icon of the Brain Tuner program, in order to make this blinding believable.

Exit tests and follow up

At the 15th session of biofeedback training, the participants completed their final biofeedback training, and had a resting state recording taken. Next, the RBANS was administered again, using the different test version to the one the participant was initially randomised to. This was to minimise repeat testing effects as described in chapter 3. The 2-back test was then administered three times. Finally the participants completed a short exit interview where they were asked:

1. What strategy they used to try and increase the level of the bar

2. Whether they had noticed any improvement in their memory in day to day life
3. Whether they had noticed any adverse effects, particularly fatigue after completing a training session

The participants were then invited to come back for a final follow up session. This session happened approximately six weeks after the final biofeedback training session took place. During this session

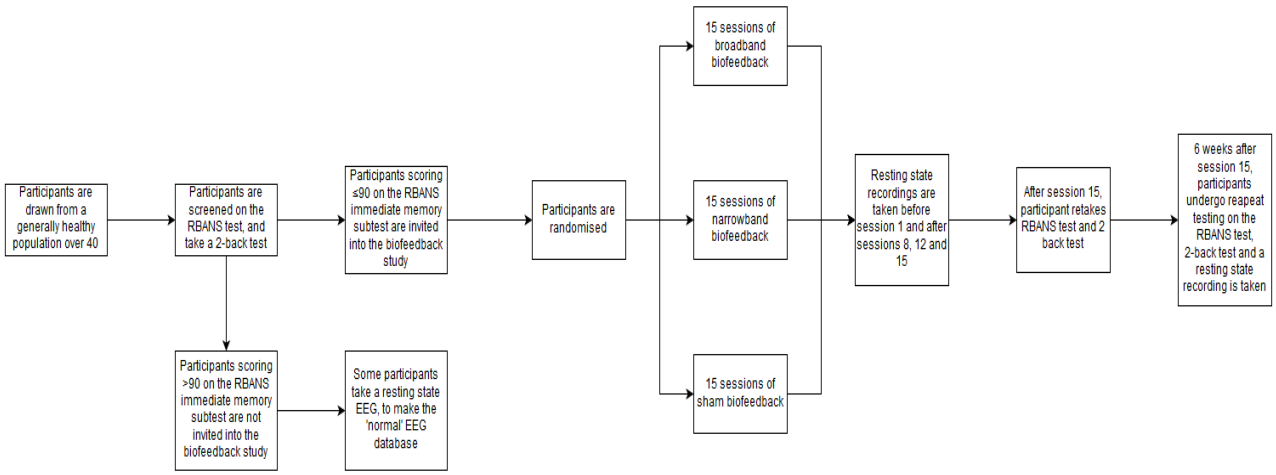


Figure 5-2: Design of the Randomised Trial

the participants underwent cognitive testing with the RBANS, using the form they were initially randomised to, and the 2-back test three times. A final resting state recording was taken as well. A flow diagram showing the trial design is given in Figure 5-2.

Statistical Analysis

Data

The following data was collected from the participants:

- Baseline RBANS
    - Test scores and combined indices
- 3 trials of the 2-back test
- Baseline 5 minutes eyes closed EEG

For participants selected for randomisation, the following data was also collected

- In-training EEG at each biofeedback session

- Resting state eyes closed EEG recordings at sessions 8, 12 and 15
- Session 15 RBANS
    - Test scores and combined indices
- Session 15 2 – Back
- 6 week follow up RBANS
    - Test scores and combined indices
- 6 week follow up 2 – back
- 6 week follow up resting state eyes closed EEG recording

Analysis

The following analysis procedures were planned.

Stage 1: Baseline age and years of education of the participants were compared using a 1-way ANOVA test, to check the effectiveness of randomisation.

Step 2: The significance of changes in RBANS test scores and cognitive indices between the baseline, post training, and 6 week follow up was assessed using a mixed effect model, using time and randomisation as factors.

Stage 3: Baseline EEG data from the randomised participants was compared to the EEG data from the normative (normal brain) database. For details on EEG analysis techniques, see chapter 3. EEGs in the normative database were listed in order of date taken. Randomised participants were matched to the first participant in the normative database on the list which matched the following criteria

a) Same sex as the participant
b) Age was the same as the participant ±2 years, provided that EEG was taken from someone within the same 10 year age bracket (40-49, 50-59, 60-69, 70-79, 80-89, 90+)

c) A second round of matching match the remaining participants to other participants within the same age bracket
d) Participants in the biofeedback training groups who did not have a match after the second round of matching were ejected from the analysis below

The participants who matched these criteria formed the 'normal brain' comparison group.

The following comparisons were planned between the randomised participants EEG data and the matched EEG data

- Current density maps
- DMN connectivity

The current density maps and default mode connectivity maps, the threshold for significance was set at p=0.05, which is significant at the group x frequency band level.

Step 4: Perform repeated t-tests within each group separately to compare the pre training RBANS scores to the post training RBANS scores. Also, repeated t-tests were used to compare the pre training RBANS scores to the 6-week follow up scores.

Step 5: With in each group separately, use sLORETA to find the significant changes in the post training resting EEG compared to the pre training resting EEG in the current density maps and default mode network connectivity.

Similarly, within each group separately compare the 6 week follow up EEG to the pre training EEG.

Step 6: Assess for significant trends within each group in the in training data, specifically assessing the correlation coefficient and regression coefficient of change in current density and change in phase lagged synchronisation of the PCC and parahippocampal gyrus, as defined in chapter 3.

Because eight comparisons were being performed for each group in each condition (resting and in-training), a Bonferroni correction on the significance was performed. The significance was therefore set at 0.00625 for the t-test assessing whether the correlation coefficient was significantly different from 0.

The resting state data used to generate the trend in current density in the PCC and the phase lagged synchronisation of the PCC to the MTL does not include data from the 6 week follow up resting state data, but as outlined in chapter 3, contains data from resting state data taken at baseline, the 8th session, the 12th session and the immediate follow up on the 15th session. If a statistically significant trend was identified, then the same process was repeated again with the 6 week follow up session included at a time point labelled 16. The correlation before and after was compared. If no statistically significant trend was found in the resting state data, an average was taken of the first four data points (pretraining, session 8, session 12 and session 15), and a repeated t test was used to see whether the point 16 differed from the average of the first four points. In this way, we were able to see whether the resting state EEG changed during the training, or changed after the training. This was Bonferroni corrected for four bands so the final significance is corrected to 0.0125.

Within-session change was calculated by averaging the change in the parameter over every session of training. For example, for a particular individual to calculate the within session change in the theta band, in each session the theta band current density in the PCC in the first five minutes was subtracted from the last five minutes. Then the average of that value across all sessions was calculated. This variable was compared to 0 using a one sample T-test to assess whether any group demonstrated the ability to self-regulate the activity in the PCC during feedback. A Bonferroni corrected significance level of 0.00625 was used.

Results

Recruitment

223 volunteers took part in the initial screening session, 142 women and 81 men. Of these participants, 68 scored below 90 in the immediate memory index score, with 31 women and 37 men. Of these 53 completed all 15 biofeedback training sessions and completed the RBANS and 2-back assessment at session 15. 52 people took part in the 6 week follow up RBANS assessment and 2-back. The analysis of the groups in the trial is restricted to the 53 participants who completed all the training sessions. A summary of the recruitment is presented in Figure 5-3 below.

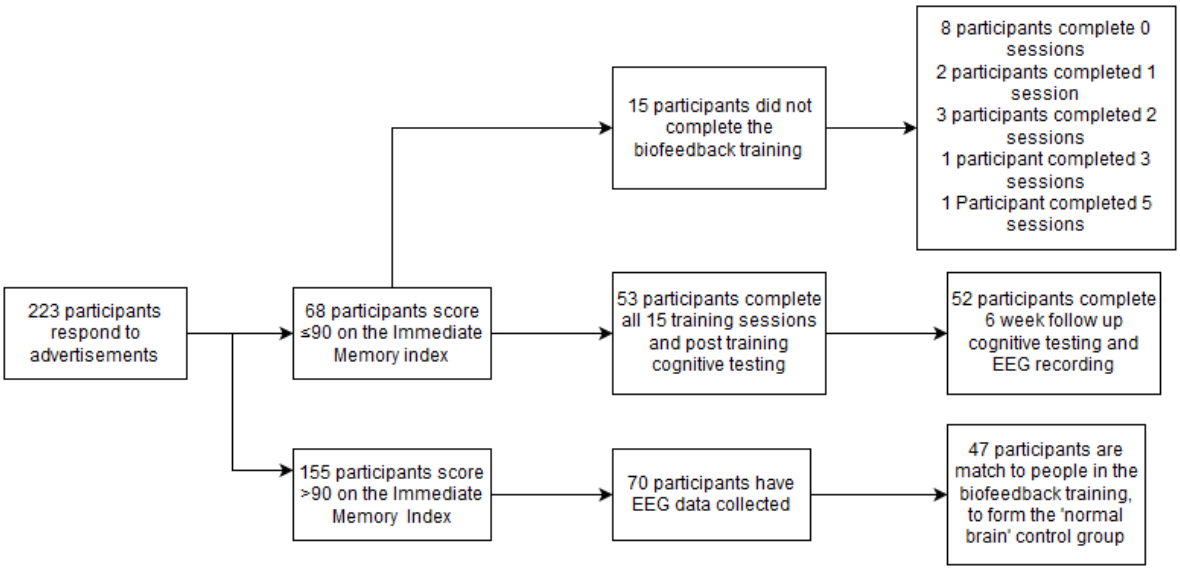


Figure 5-3: Recruitment of participants into biofeedback training

Baseline Characteristics

Baseline characteristics of volunteers

Volunteers were predominantly recruited through placing advertisements in the free local community newspaper, the Star ©. Approximately 100 people were recruited through this method. Eighty people were recruited through the Brain Health Research Centre database, a list of people held by the Brain Health Research Centre who are predominantly free of neurological disease who agree to be contacted to take part in research being carried out at the Centre. Approximately 10 people were recruited through actively contacting community groups such as Rotary and Lions clubs. The remainder were recruited advertising on posters displayed on community notice boards, word

of mouth, and flyers distributed at community events such as the Brain Health Research Centre Brain Day.

The mean age of volunteers who presented for screening was 65.2 years old. Ages ranged from 40 to 93 years old. The mean years of education was 15.2 years. 112 were screened using the RBANS A form and 111 were screened using the RBANS B form.

The mean scores on the RBANS indices at screening are shown below in table 5-1.

Table 5-1: Mean RBANS index scores for all screened volunteers

RBANS index	Mean Score	Range (min, max)
Immediate Memory	98.4	53, 129
Visuospatial	108.5	53, 136
Language	101.6	60, 132
Attention	103.3	72, 150
Delayed Memory	101.3	40, 127
Sum of Index scores	513.2	322, 651
Total	103.5	55, 148

The volunteers as a group scored high on the visuospatial index compared to the rest of the indices. Participants also tended to score highly in the attention index, with no participant scoring below 72 on that index. The lowest possible score in the indices is 40, which was scored in the delayed memory index by two people. The mean score on the final two trials 2-back test was 51.5%.

Analysis of RBANS subgroups

112 volunteers were randomised to RBANS A at baseline, and 111 were randomised to RBANS B. Table 5-2 below shows the score in each RBANS subtest and index for the volunteers in each group.

Table 5-2: RBANS scores for all screened volunteers separated by RBANS form

	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Age	64.9 (10.45)	65.5 (10.28)
Number of Women (%)	77 (68.8%)	65 (58.6%)
Years of Education	15.3 (2.70)	15.2 (2.47)
List Learning	26.7 (5.13)	27.7 (4.63)
Story Learning	15.0 (3.83)	17.4 (3.25)
Figure Copy	18.9 (1.45)	18.5 (1.64)
Line Orientation	17.4 (2.46)	17.4 (3.01)
Picture Naming	9.5 (0.73)	9.7 (0.95)
Semantic Fluency	22.8 (4.95)	19.7 (4.60)
Digit Span	10.6 (2.20)	10.7 (2.57)
Coding	45.9 (10.08)	44.8 (9.73)
List Recall	5.5 (2.28)	6.1 (2.25)
List Recognition	19.1 (1.41)	19.2 (1.30)
Story Recall	7.8 (2.65)	9.5 (2.35)
Figure Recall	14.4 (4.14)	14.4 (3.42)
Immediate Memory Index	94.4 (14.67)	102.2 (13.57)
Visuospatial Index	109.5 (14.87)	107.5 (15.46)
Language Index	104.1 (11.81)	99.0 (10.36)
Attention index	103.8 (14.29)	102.8 (14.54)

	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Delayed Memory index	99.6 (14.68)	103.3 (13.92)
Sum of Indices	511.3 (50.00)	515.0 (44.92)
Total Scale Index	103.2 (14.08)	104.0 (13.92)
Average last two 2-back	52.0 (24.41)	50.5 (26.93)

The volunteers who were initially randomised to the RBANS form A performed worse on the List Learning, Story Learning and Story recall subtests. The volunteers on RBANS A also performed worse on the Immediate Memory index and Delayed memory index, and performed better on the Language index.

68 volunteers qualified to take part in the biofeedback training, by scoring below 90 on the Immediate Memory index. 42 qualified using the RBANS A form, and 26 qualified using the RBANS B form. The characteristics and baseline scores of those who qualified to take part in the biofeedback training, are presented in Table C-1 in appendix C1.

Among people who qualified to take part in the study, the differences between the RBANS scores tends to be smaller than between versions A and B among the whole cohort. Importantly the difference in the immediate memory index between versions A and B among participants who qualified for the training was smaller than for the cohort as a whole. However, people on version A did score less on average on the immediate memory index. The people randomised to RBANS A scored higher in the visuospatial index than people on RBANS B, and this difference was bigger than that seen in the whole cohort.

Baseline characteristics of Volunteers in the 'normal brain' controls

70 volunteers who scored above 90 on the immediate memory index of the RBANS had EEG recordings taken. After the matching procedure described above, 47 volunteers were matched to the participants in the biofeedback training. Fifteen of these completed RBANS form A and 32 completed RBANS form B. The baseline characteristics of these participants is listed in Table C-2 in Appendix C1.

The 'normal brain' controls had more years of education on average than participants in the biofeedback trial. As would be expected from the screening procedure, the 'normal brain' controls scored high on the immediate memory and delayed memory indices, scoring 107.9 and 107.1 respectively.

Seven participants were ejected from the subsequent analysis on account of not having a match in the 'normal brain' controls. Two participants were from the broadband feedback group, three participants were from the narrow band feedback group and two participants were from the placebo feedback group.

Reasons for non-completion of the trial

Fifteen people took part in the screening test, and qualified to take part in the biofeedback training, but either chose not to participate or only completed a few sessions of biofeedback before pulling out of the study. This is shown by the recruitment flow diagram in Figure 5-3 above. Of these, two had pulled out for supervening medical reasons, although these did not meet our exclusion criteria. Four cited the time commitment as being excessive, one objected to the use of the EEG gel. The rest did not cite a reason for pulling out of the trial, or were lost to follow up.

Baseline characteristics of participants in the trial

Of the 53 people who completed all 15 biofeedback sessions, 33 were screened on RBANS A and 20 were started on RBANS B. Table 5-3 below shows the baseline characteristics of the 54 participants who completed all 15 sessions of the biofeedback training.

Table 5-3: RBANS index scores for 53 participants who completed all 15 training sessions

	Group total	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Age	67.8 (10.18)	67.9 (9.99)	67.8 (10.50)
Number of Women (%)	22 (41.5%)	13 (39.4%)	9 (45.0%)
Years of Education	14.1 (2.43)	14.3 (2.33)	13.7 (2.55)
List Learning	22.5 (4.82)	22.7 (4.94)	22.1 (4.58)
Story Learning	12.5 (2.90)	12.0 (2.84)	13.4 (2.78)
Figure Copy	18.3 (1.72)	18.4 (1.87)	18.3 (1.41)
Line Orientation	16.9 (2.42)	17.2 (2.44)	16.5 (2.29)
Picture Naming	9.4 (0.85)	9.2 (0.95)	9.6 (0.58)
Semantic Fluency	18.6 (4.23)	19.7 (4.23)	16.9 (3.65)
Digit Span	10.1 (2.02)	9.9 (1.84)	10.6 (2.22)
Coding	39.5 (9.37)	39.8 (7.96)	39.1 (11.30)
List Recall	4.0 (2.20)	4.2 (2.22)	3.7 (2.17)
List Recognition	18.3 (1.85)	18.5 (1.69)	18.1 (2.07)
Story Recall	6.2 (2.64)	5.9 (2.51)	6.7 (2.78)
Figure Recall	12.0 (4.50)	12.7 (4.44)	11.0 (4.40)
Immediate Memory Index	80.9 (9.37)	80.2 (9.70)	82.0 (8.70)
Visuospatial Index	104.1 (15.16)	105.6 (15.12)	101.7 (14.91)
Language Index	95.5 (10.17)	96.7 (10.81)	93.4 (8.6)
Attention index	95.8 (12.33)	95.3 (11.70)	96.7 (13.25)

	Group total	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Delayed Memory index	88.7 (14.39)	90.1 (13.99)	86.5 (14.77)
Sum of Indices	465.0 (39.49)	467.8 (39.42)	460.3 (39.15)
Total Scale Index	90.2 (9.98)	90.9 (9.94)	89.0 (9.92)
Average last two 2-back	43.6 (24.65)	46.5 (25.18)	38.8 (22.92)

The participants who completed the study tended to score much lower in the immediate memory index and the delayed memory index than the cohort as a whole, which is not surprising given the selection criteria. The participants also scored lower on the other three indices to a lesser extent, indicating that the visuospatial, language and attention indices are somewhat, but not totally independent of the memory indices.

The difference between the test scores from participants who were randomised to Form A compared the Form B were small compared to the difference in scores in the cohort as a whole. There was a large difference in the semantic fluency scores, with participants randomised to form A scoring three more points higher on average. There was also a large difference in the figure recall scores, with participants on Form A scoring a point higher on average than Form B. The largest difference in index scores was in the language index, with participants on Form A scoring four points higher than on Form B.

Baseline characteristics after Randomisation

Table 5-4 below shows the demographic distribution of participants into each group.

Table 5-4: Baseline characteristics after randomisation

	Broadband Feedback Mean (SD)	Narrowband Feedback Mean (SD)	Placebo Feedback Mean (SD)
Age	70.8 (12.1)	66.7 (9.77)	66.0 (7.43)
Number of Women (%)	8 (44.4%)	7 (41.1%)	7 (38.9%)
Years of Education	14.2 (2.29)	13.1 (2.49)	14.9 (2.18)
Number on Form A	10	10	12

The broadband feedback group was on average older than the other two groups. The number of women in each group in nearly identical, as the randomisation procedure designed. The narrowband feedback group has less years of formal education than the other groups. The placebo group has more participants who were originally randomised to Form A.

The distribution of age and years of education are shown in the box plots in Figures 5-4 & 5-5 respectively.

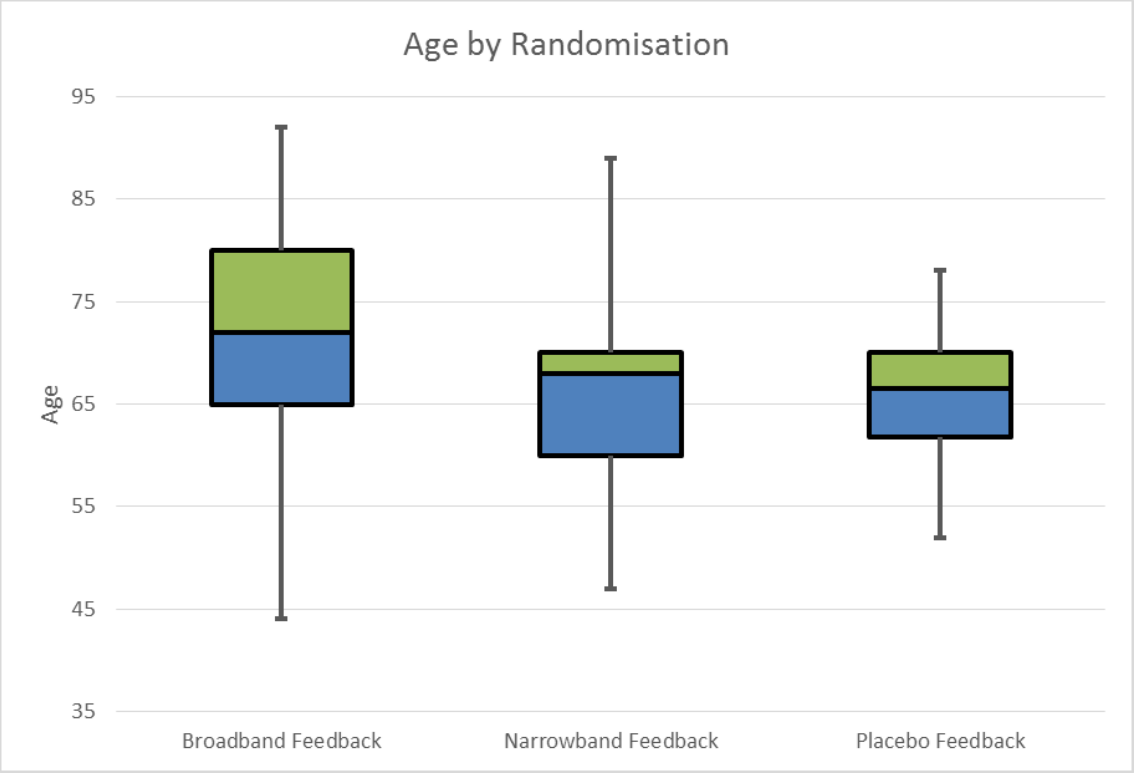


Figure 5-4: Boxplot of age by group after randomisation

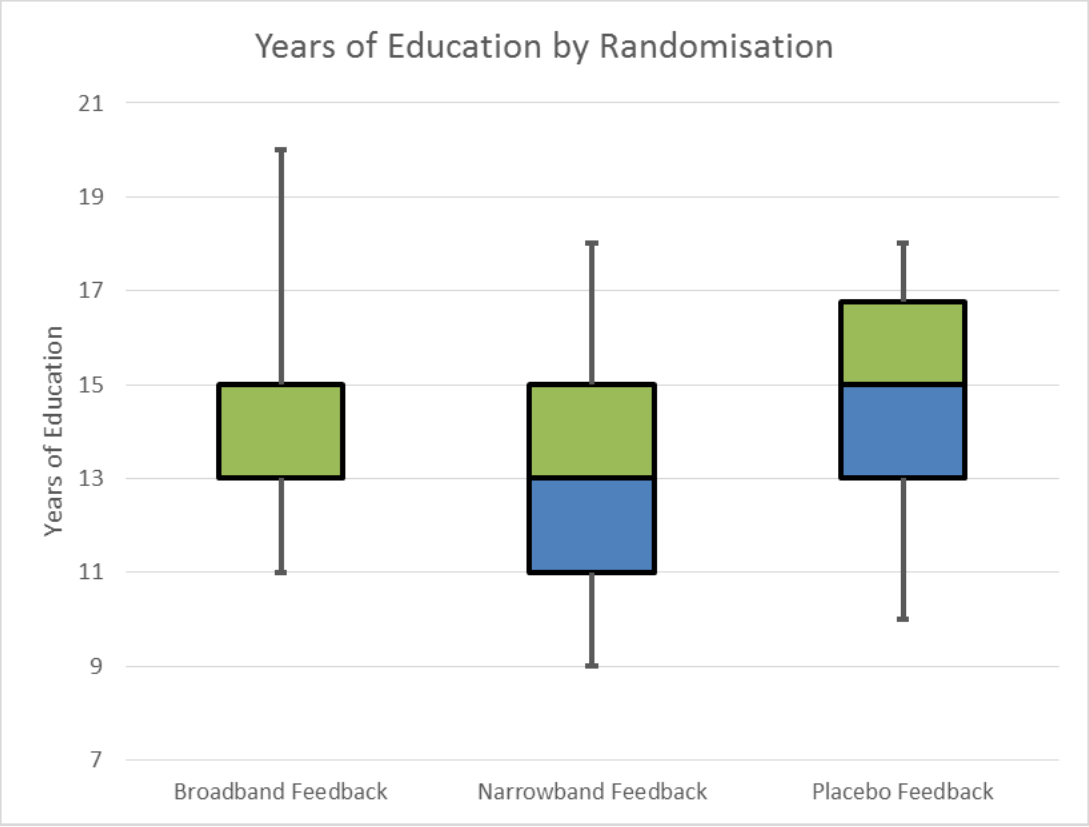


Figure 5-5: Years of education by group after randomisation

There was a smaller range of ages in the placebo feedback group, and a much wider distribution of ages in the broadband feedback group. The mean years of education in the broadband feedback group appears to be raised by an outlier (1 person had 20 years of formal education). There was no statistically significant difference in age, or years of education between the groups.

Baseline Cognitive Scores in each group

Table 5-5 below shows the scores for the initial RBANS test and the initial 2 back test separated out by group.

Table 5-5: Baseline RBANS score by group after randomisation

	Broadband Feedback Group Mean (SD)	Narrowband Feedback Group Mean (SD)	Placebo Feedback Group Mean (SD)
List Learning	21.3 (5.8)	22.6 (4.22)	23.6 (3.89)
Story Learning	12.2 (2.90)	12.9 (2.53)	12.5 (3.17)
Figure Copy	17.8 (1.93)	18.9 (1.26)	18.3 (1.67)
Line Orientation	17.2 (2.09)	17.1 (2.69)	16.5 (2.41)
Picture Naming	9.3 (0.80)	9.5 (1.04)	9.3 (0.67)
Semantic Fluency	18.1 (4.71)	18.6 (3.98)	19.2 (3.88)
Digit Span	9.8 (1.50)	10.2 (2.34)	10.3 (2.11)
Coding	34.4 (9.85)	43.9 (7.89)	40.5 (7.56)
List Recall	3.4 (2.52)	4.2 (1.98)	4.4 (1.92)
List Recognition	17.8 (2.48)	18.8 (1.11)	18.6 (1.50)
Story Recall	5.4 (2.41)	6.6 (2.63)	6.5 (2.69)
Figure Recall	11.4 (5.37)	12.6 (3.34)	12.1 (4.42)
Immediate Memory Index	79.8 (9.91)	81.5 (8.38)	81.5 (9.59)

	Broadband Feedback Group Mean (SD)	Narrowband Feedback Group Mean (SD)	Placebo Feedback Group Mean (SD)
Visuospatial Index	102.7 (14.11)	108.1 (14.17)	101.8 (16.31)
Language Index	94.8 (13.09)	95.2 (9.90)	96.3 (6.31)
Attention index	91.3 (7.93)	100.5 (12.67)	95.9 (13.88)
Delayed Memory index	84.4 (18.68)	91.4 (11.91)	90.4 (9.96)
Sum of Indices	453.1 (49.12)	476.7 (26.80)	465.8 (35.05)
Total Scale Index	87.1 (12.34)	93.0 (6.99)	90.6 (8.78)
Average last two 2-back	35.2 (22.4)	47.8 (26.03)	52.0 (26.15)

In most instances, the randomisation has resulted in the cognitive scores being evenly distributed between the groups. The narrowband feedback group has a higher score in the visuospatial index than the other two groups, mostly due to a higher performance in the figure copy sub test. The broadband feedback group has a lower baseline score in the delayed memory index, but also a wider distribution of score. The difference between the delayed memory index score between the broadband and narrowband feedback groups was not significant ($t_{29.1}$=-1.285, p=0.209), nor was the difference between the broadband feedback group and the placebo feedback group ($t_{25.9}$=-1.158, p=0.255).

Comparison of EEG characteristics between participants and 'normal brain' controls

There was no significant difference in the current density between the participants in the trial and the 'normal brain' controls. Images voxel with the highest magnitude difference in connectivity in each band can be found in Figure C-1 in appendix C2.

No significant changes were found at the p=0.05 level in the connectivity of the DMN. Images presented in Figure C-2 in appendix C2 represent changes which appear when the p value is set to p=0.12. The images below show where the changes are.

Because there were no significant changes found, only general comments can be made about the direction of change, rather than commenting on the specific changes in specific locations. Overall, the participants have reduced connectivity in the theta band, and increased connectivity in the alpha 2 and beta 1 bands. The other bands have a mixture of increased and decreased connectivity. However, in the delta, alpha 1 and beta 3 bands, the majority of connections have higher connectivity.

Mixed Model Analysis of RBANS Index Scores

Primary Result- Immediate Memory index score

The final mixed model contained the index scores for 53 participants at baseline, 53 participants at immediate follow up and 52 participants at 6 week follow up, as one person in the placebo group dropped out after immediate follow up. Time point and assigned group were entered as fixed variables.

Figure 5-6 below demonstrates the change in the immediate memory index at each time point in each group.

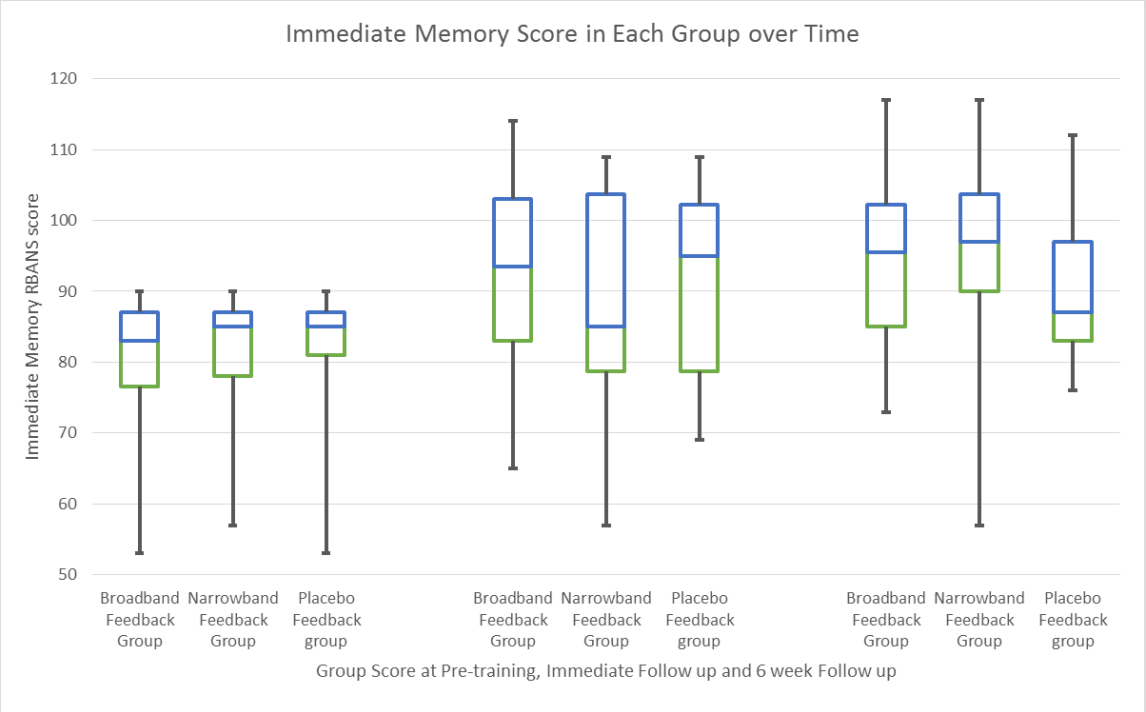


Figure 5-6: Boxplot showing Immediate Memory Index score by randomisation at pre-training, immediately post-training, and at 6 week follow up

The mixed model analysis found a significant first order effect with respect to time ($F_{2, 52.736}$=39.712, p<0.001) but didn't find a significant first order effect with respect to randomisation ($F_{2, 53.153}$=0.072, p=0.931). No significant second order effect was found for a Randomisation*Time interaction ($F_{4, 52.724}$=1.162, p=0.338).

Post hoc pairwise comparisons revealed significant differences between time points within groups, but no significant changes between groups within time points. Within the broadband feedback group, there was a significant difference between pre training and immediate post training immediate memory index score (difference= 11.7 points, p=0.001) and between the pre training and 6 week follow up score (difference =15.3, p<0.001). There was no significant difference between the immediate follow up and the 6 week follow up training.

Within the narrow band feedback group, there was a significant difference between the pre training and the immediate follow up immediate memory index score (difference =7.9, p=0.019), and there was also a significant difference between the pre training score and the 6 week follow up score

(difference =12.4, p<0.001). There was no significant difference between the immediate follow up and the 6 week follow up score.

Within the placebo group, there was a significant difference between the pre training and the immediate follow up immediate memory score (difference = 9.5, p=0.004) and a significant difference between the pre training and the 6 week follow up score (difference =8.725, p=0.001). No significant difference was found between the immediate follow up and the 6 week follow up score.

Secondary Results

Delayed Memory

The final mixed model contained the index scores for 53 participants at baseline, 53 participants at immediate follow up and 52 participants at 6 week follow up, as one person dropped out after immediate follow up. Time point and assigned group were entered as fixed variables.

Figure 5-7 below demonstrates the change in the delayed memory index at each time point in each group.

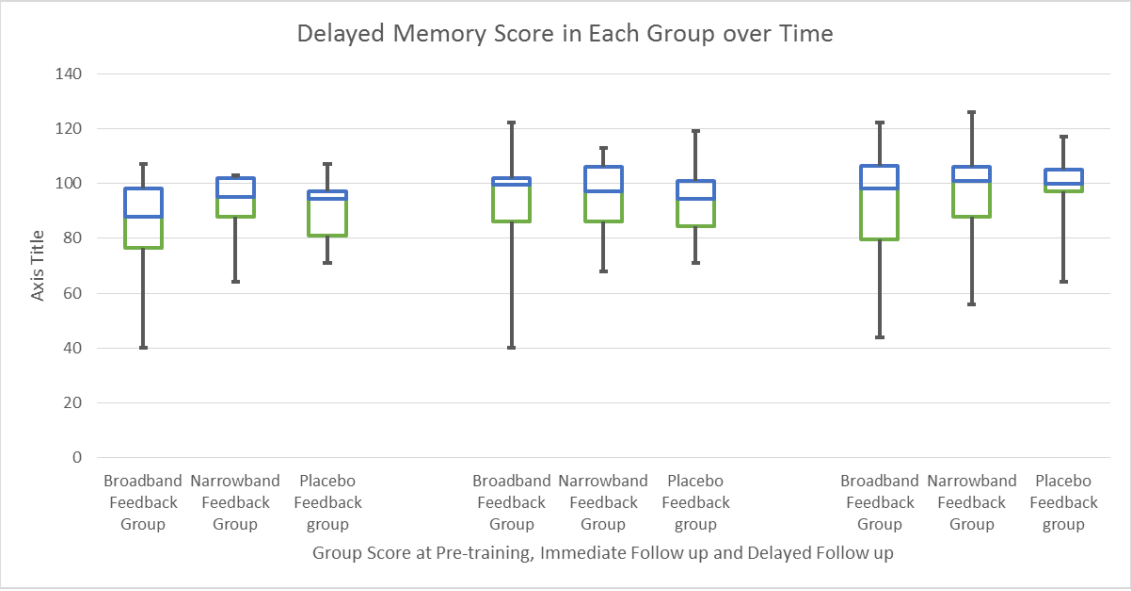


Figure 5-7 Boxplot showing Delayed Memory Index score by randomisation at pre-training, immediately post-training, and at 6 week follow up

The mixed model analysis found a significant first order effect on delayed memory with respect to time ($F_{2, 52.679}$=12.825, p<0.001). There was no first order effect with respect to randomisation ($F_{2,}$

$_{53.078}$=0.729, p=0.487). There was no significant second order effect for a Randomisation*Time interaction.

Post hoc analyses revealed that similarly to the immediate memory scores, there were significant differences between time points within groups; however there were no significant differences between groups within time points.

For the broadband feedback group, there was a significant difference between the pre training delayed memory score and the immediate follow up delayed memory score (difference=7.3, p=0.002). There was also a significant difference between the pre training score and the 6 week follow up score (difference=7.056, p=0.012). However, there was no significant difference between the scores of the immediate follow up and the 6 week follow up.

For the narrowband feedback group, there was no significant difference between the pre training delayed memory score and the immediate follow up delayed memory score (difference=2.5, p=0.294). Nor was there a significant difference between the scores of the immediate follow up and the 6 week follow up. However, there was also a significant difference between the pre training score and the 6 week follow up score (difference=6.4, p=0.025).

For the placebo training feedback group, there was no significant difference between the pre training and immediate follow up delayed memory score (difference=2.5, p=0.265). There was a significant difference between the pre training and the 6 week follow up score (difference=8.4, p=0.004). There was no significant difference between the immediate post training and 6 week follow score.

Visuospatial index

The mixed model analysis found a significant first order effect for time ($F_{2, 52.720}$=3.658, p=0.033). There were no other significant first order or second order effects.

Post hoc analysis revealed that in the broadband feedback group there was a significant difference between the immediate follow up and the 6 week follow up visuospatial scores (difference =-7.1, p=0.011). There was also a difference between the pre training and immediate post training visuospatial score in the narrowband feedback group (difference =8.412, p=0.006). No significant changes were found for the placebo feedback group.

Language index

The mixed model analysis found a significant first order effect for time ($F_{2, 52.625}$=5.853, p=0.005). There were no other significant first order or second order effects.

Post hoc analysis demonstrated a significant difference between the pre training Language score and the 6 week follow up score in the broadband feedback group (difference=6.2, p=0.007). There was also a significant difference between the pre training and the 6 week follow up score in the narrowband feedback group (difference=-4.8, p=0.037). No significant differences were found for the placebo group.

Individual Analysis by Group

Broadband feedback group

Baseline characteristics

Table C-3 in Appendix C3 shows the baseline scores of the participants in the broadband feedback group. Participants who started on RBANS A had similar scores to the participants who started on RBANS B on the baseline indices.

Comparison to the 'normal brain' controls at baseline

There were no significant differences in the current density between the participants in the broadband feedback group and their matched controls. Images showing the voxel with the highest level of changes can be seen in Figure C-3 in appendix C4.

There were no significant differences in the connectivity of the default mode network compared to the 'normal brain' controls. Images showing the highest magnitude of changes are given in Figure C-

6 in appendix C5 (p=0.383). As with the cohort as a whole, there was a trend toward lower connectivity in the theta band and higher connectivity in the alpha 1, and alpha 2 bands.

Immediate Follow up Cognitive Scores

In table 5-6 below are the immediate follow up cognitive scores for the RBANS and the 2 Back test for the broadband feedback group. The average change from the baseline score is given in the second column. Most of the change from baseline was small compared to the standard deviation of the baseline score. However the immediate memory index score increased in magnitude greatly, by 11.7 points (p=0.001). The delayed memory index score had also increased in magnitude, but the change was not as large, increasing by 7.3 points (p=0.002).

Table 5-6: RBANS scores and change from baseline at immediate follow up in the broadband feedback group

	Score Mean(SD)	Change from Baseline
List Learning	23.4 (6.16)	2.1
Story Learning	14.4 (3.56)	2.2
Figure Copy	16.7 (2.38)	-1.1
Line Orientation	16.9 (2.66)	-0.3
Picture Naming	9.7 (0.56)	0.4
Semantic Fluency	18.5 (5.52)	0.4
Digit Span	10.0 (2.03)	0.2
Coding	35.6 (10.43)	1.2
List Recall	5.2 (2.65)	1.7
List Recognition	18.3 (2.53)	0.5
Story Recall	6.9 (3.05)	1.6
Figure Recall	10.3 (4.94)	-1.1
Immediate Memory Index	91.5 (14.33)	11.7

	Score Mean(SD)	Change from Baseline
Visuospatial Index	97.0 (17.51)	-5.7
Language Index	97.8 (10.50)	3.0
Attention index	94.1 (12.55)	2.7
Delayed Memory index	91.8 (20.61)	7.3
Sum of Indices	472.2 (54.02)	19.1
Total Scale Index	92.3 (13.7)	5.2
Average last two 2-back	31.1 (15.08)	-4.0

The scores of the immediate follow up and change from baseline separated by initial RBANS form is given in Table C-6 in appendix C6. There were two major differences between those who started on form A and those who started on form B. The change in the immediate memory score was very high on those who started on form A, at 16.1 points higher at follow up, compared to those who started on form B, who scored only 6.5 points higher at follow up. Similarly, those who started on form A scored 10.3 points higher in the delayed memory index at follow up, compared to those who started on form B who scored 3.6 points higher at follow up.

Changes in Current Density from Baseline to Immediate Follow Up

No significant changes were found in the current density map from baseline to immediate follow up. Diagrams illustrating the voxel with the highest magnitude change can be found in Figure C-9 in appendix C7.

Changes in Connectivity of the Default Mode Network from Baseline to Immediate Follow up

No significant changes in the connectivity of the default mode network was found using 11 regions of interest. Diagrams showing changes in connectivity at the most statistically significant value (p=0.408) can be found in Figure C-13 in appendix C8. Bands not shown in appendix C8 have no changes at this level of significance.

Overall, there appears to be a trend toward decreased connectivity in the delta band, beta 1 band, and a trend toward increased connectivity in the theta band. This pattern is a reversal of the trends shown in the comparison to the 'normal brain' cohort.

Change in the Activity and Connectivity Indices in the in-Training Data.

The average correlation coefficient for phase lagged synchronisation between the PCC and the Parahippocampal gyrus in the beta 1 band over time differed significantly from 0 (r=0.158, 95%CI 0.052-0.262, p=0.005). There was a slight tendency for the connectivity in this band to increase as the number of sessions increased. The graph in Figure 5-8 below shows the change in beta 1 connectivity over time for each individual in this group. Graphs of the changes in other measured indices are given in Figure C-16 to C-21 in appendix C9.

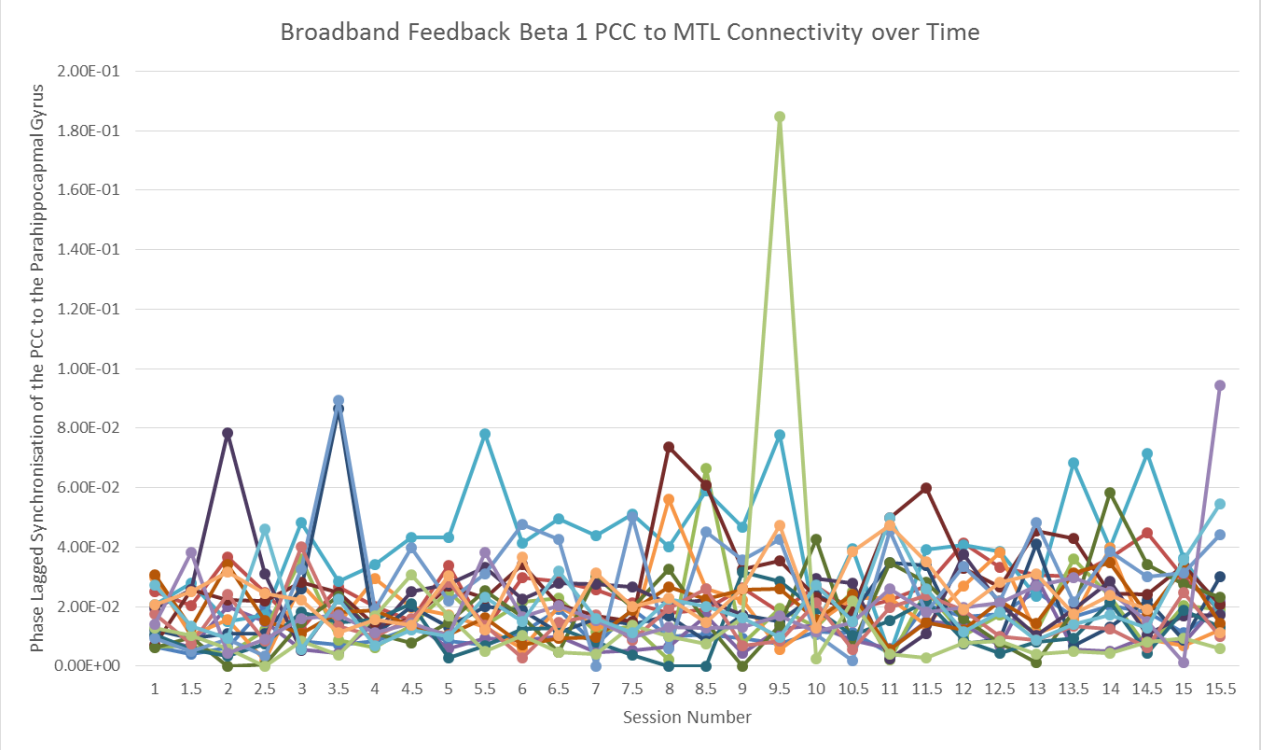


Figure 5-8: Individual trends in phase lagged synchronisation during training in the beta 1 band in the broadband feedback group

Figure 5-9 below shows the average change in the connectivity in the beta 1 band in the Broadband feedback group (β=0.0004).

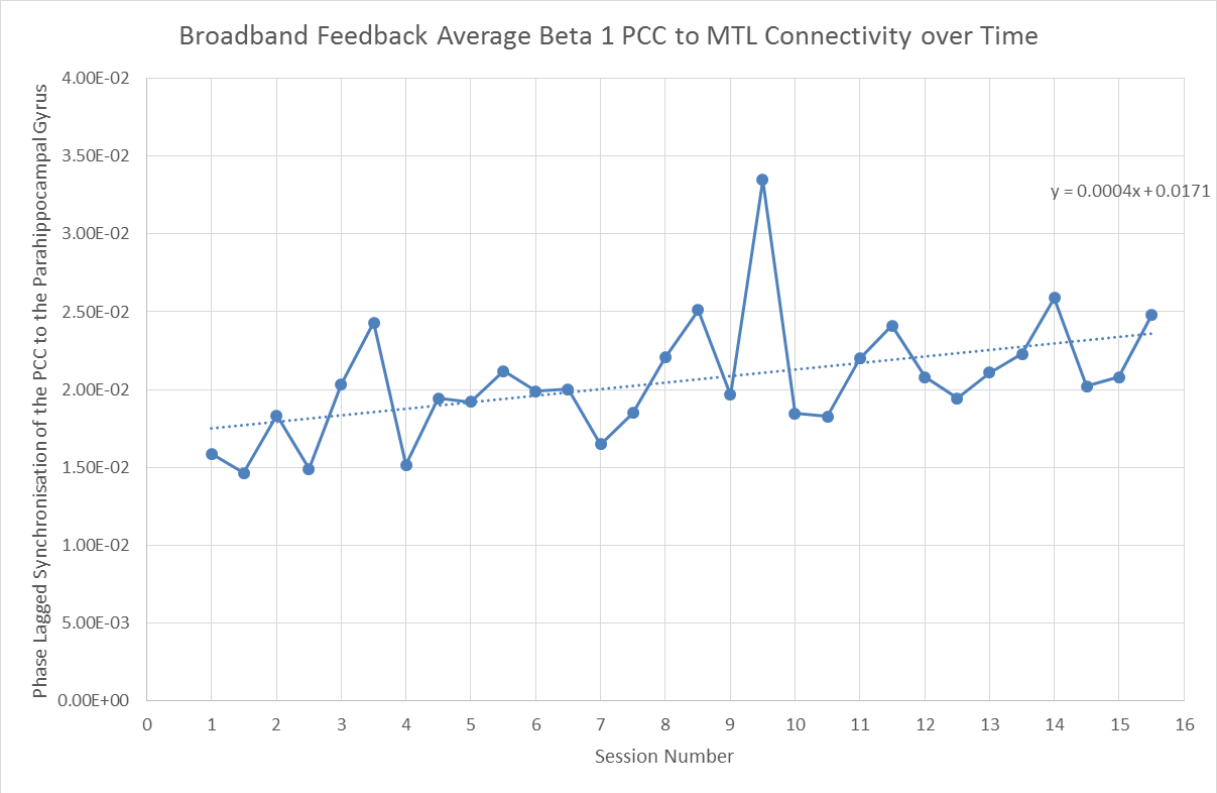


Figure 5-9 Group trends in phase lagged synchronisation during training in the beta 1 band in the broadband feedback group

Within Session change

No significant within session change in current density was found in any of the theta, alpha 1, alpha 2 or beta 1 band.

A significant increase was found in the within session alpha 1 connectivity (p=0.004) and alpha 2 connectivity (p=0.002) indices. The other within session connectivity indices were non-significant.

Interview data

Six people in the broadband feedback group said that they experienced some memory benefit from the training. Of these people, two had an increase of more than 10 points in the immediate memory index between the pre training test and the immediate follow up test. Of the 12 people who said they did not receive any memory benefit from the training, there was an improvement of 10 or more points in the immediate memory index in nine people. One person noted excessive tiredness as an adverse effect.

6 Week Follow up cognitive scores

Table 5-7 below shows the average score in the RBANS cognitive indices and subtests scored at the 6 week follow up session, and the change in the score from the baseline. Table C-9 in appendix C10 shows the change in the RBANS subtests and indices separated by whether the participants started on RBANS form A or B

Table 5-7 RBANS score and change from baseline at 6 week follow up in the Broadband feedback group

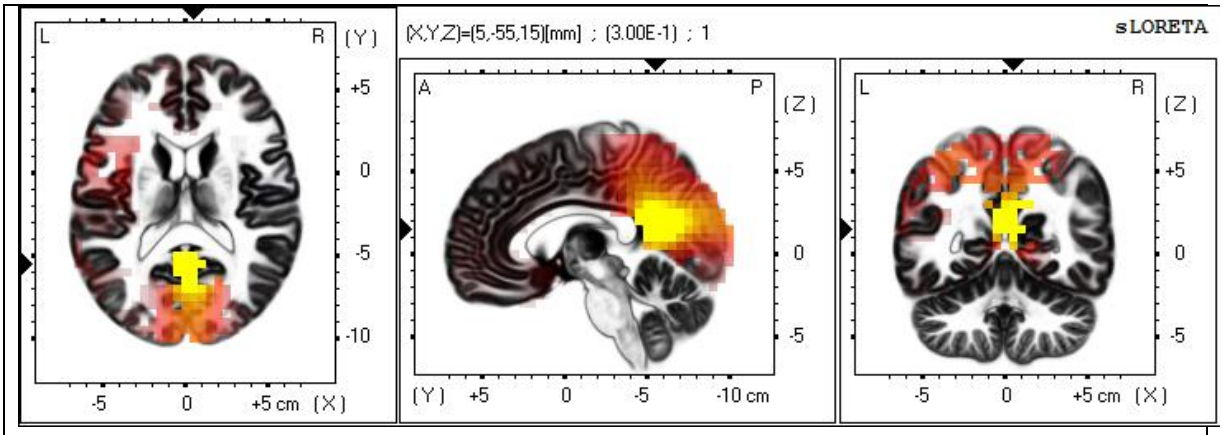
	Mean (SD)	Difference from Baseline
List Learning	24.2 (5.60)	2.9
Story Learning	15.4 (3.55)	3.2
Figure Copy	17.8 (1.50)	0.1
Line Orientation	17.3 (2.28)	0.1
Picture Naming	9.6 (0.50)	0.3
Semantic Fluency	19.4 (5.37)	1.3
Digit Span	9.6 (1.98)	-0.2
Coding	38.2 (9.88)	3.8
List Recall	4.3 (2.87)	0.9
List Recognition	18.4 (2.19)	0.6
Story Recall	7.3 (3.25)	1.9
Figure Recall	11.7 (5.62)	0.3
Immediate Memory Index	95.1 (11.52)	15.3
Visuospatial Index	104.1 (10.66)	1.4
Language Index	101.0 (9.61)	6.2
Attention index	95.8 (11.33)	4.4
Delayed Memory index	91.5 (21.22)	7.1

	Mean (SD)	Difference from Baseline
Sum of Indices	487.5 (45.22)	34.4
Total Scale Index	96.2 (11.96)	9.1
Average last two 2-back	40.9 (20.23)	5.7

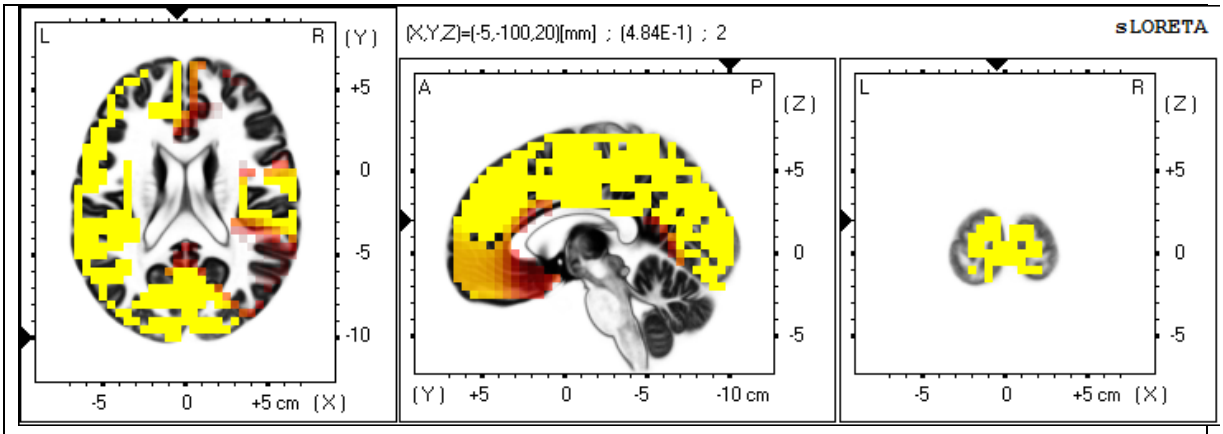
There was a large magnitude change in the immediate memory index of 15.3 points (p<0.001). This was caused by large changes mainly in the story memory score in comparison to the standard deviation. There was a moderate change in the delayed memory index at 7.1 points (p=0.012), and in the language with 6.2 change (p=0.007)

Changes in Current Density at 6 week follow up compared to baseline

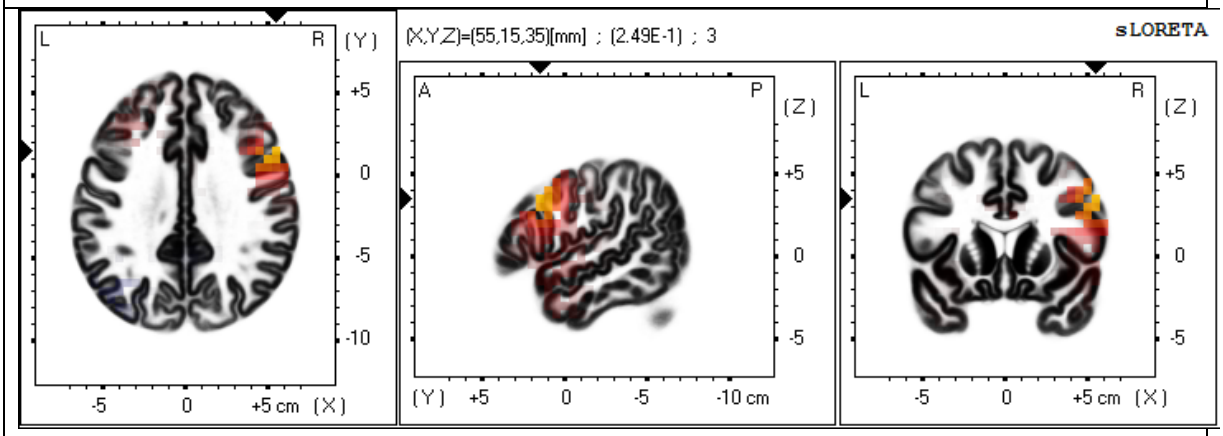
The images in figure 5-10 below show the changes in the current density comparing the 6 week follow up resting state recording to the baseline resting state. These changes were statistically significant (p=0.0428). Red and yellow areas represent areas of increased activity at the 6 week follow up compared to baseline and blue regions indicate areas of decreased activity compared to baseline.



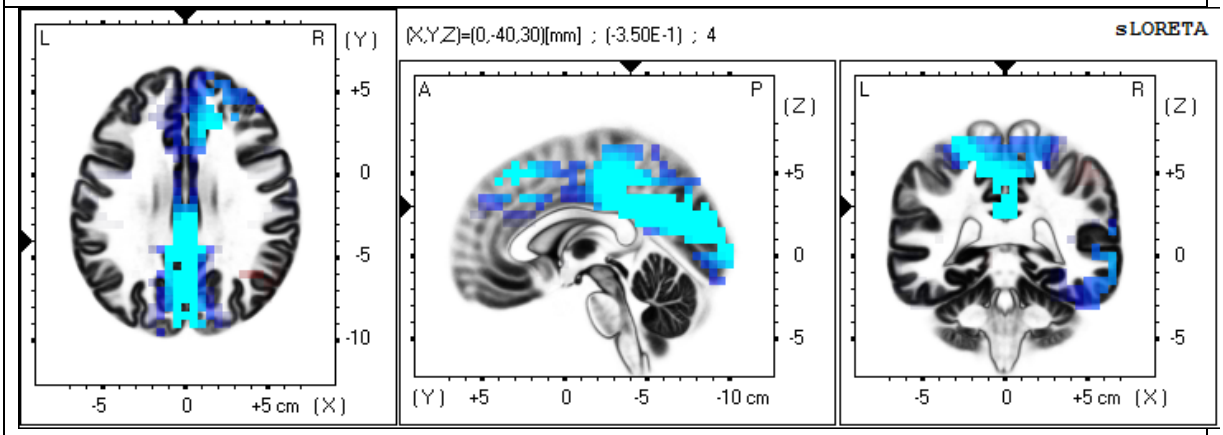
Delta band



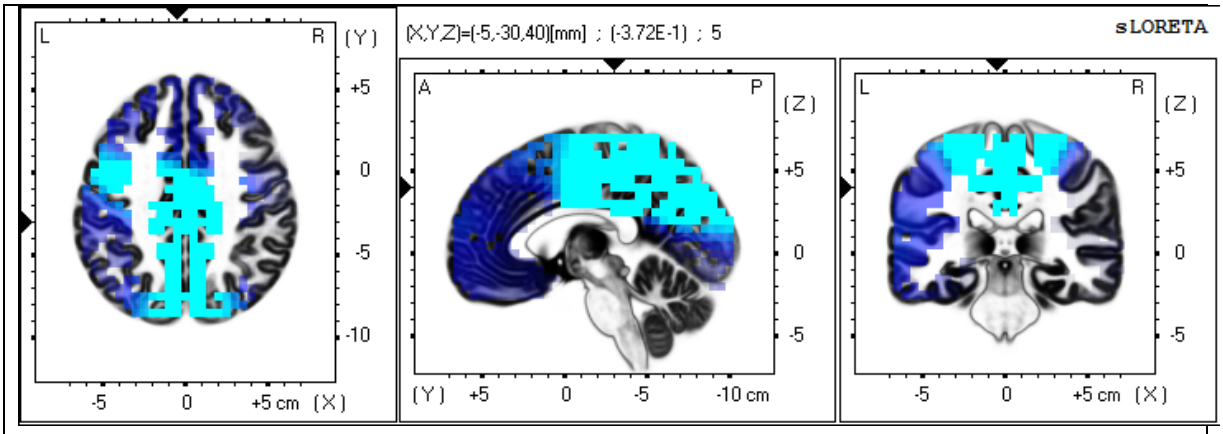
Theta band



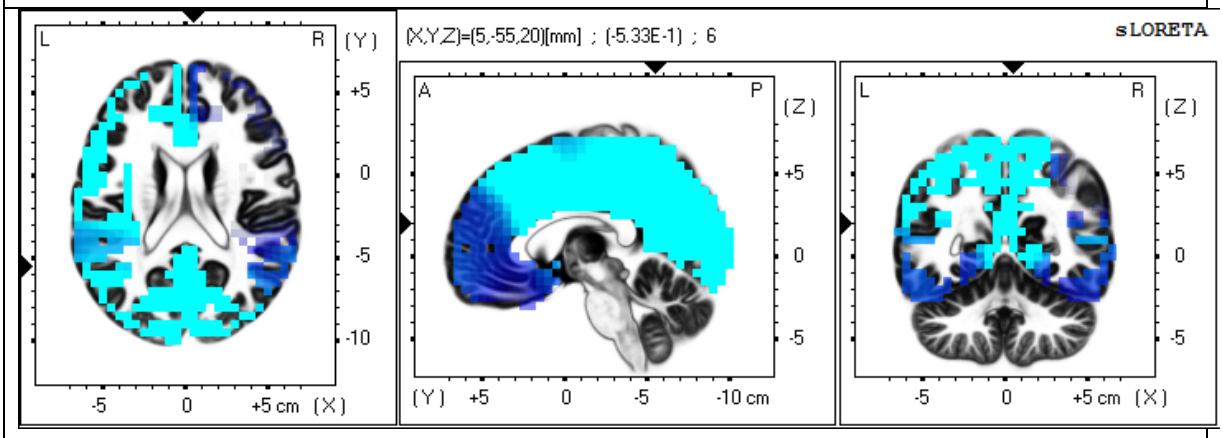
Alpha 1 band



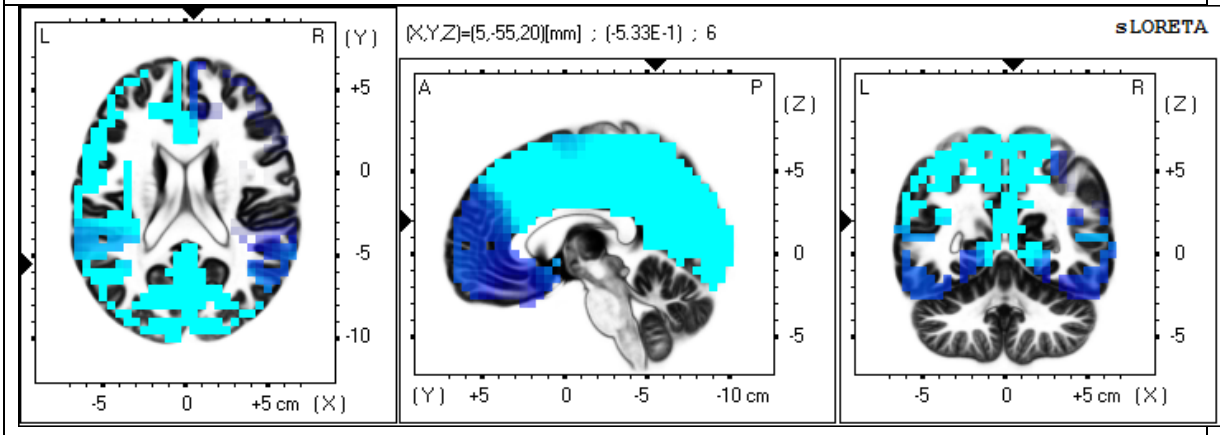
Alpha 2 band



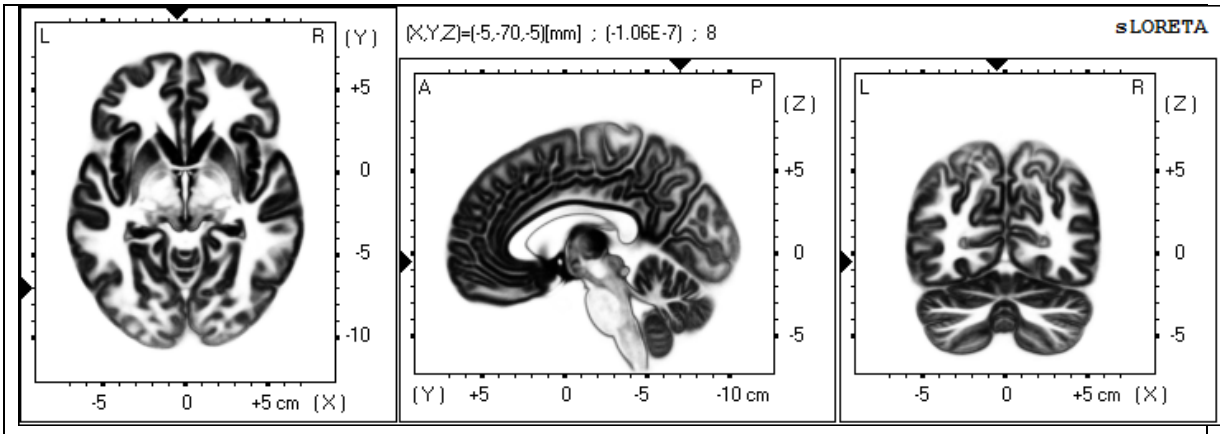
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure 5-10: Current density maps showing the change in resting state current density between 6 week follow up and pre-training recordings in the broadband feedback group

Broadly, there wass increased activity in the low frequency bands, the delta, theta and alpha1 bands. There was decreased activity in higher frequency bands, the alpha 1, beta 1, beta 2 and beta 3 bands. No significant changes were found for the omega band. The change was roughly centred around the PCC in each of the bands, apart from the alpha 1 band, in which the change was centred on the right frontal gyrus.

Changes in the connectivity of the DMN at 6 week follow up

There was no significant change found in the connectivity of the DMN found at 6 week follow up compared to the pre-training resting state recording. Images with the highest magnitude changes (p=0.681) can be found in Figure C-35 in appendix C11.

Changes in the Resting state indices

There was no significant trend identified in either the current density of the PCC or the phase lagged synchronisation of the PCC to the parahippocampal gyrus in the resting state data, including the pre training time point, sessions 8, 12 and the session 15 time point. Therefore, the average of those points were taken in each band for both the activity index and the connectivity index, and this average was compared to the session 16 point using a repeated t-test. No significant change between the average activity during the training and the activity at the 16 week follow up was found.

A significant change was found in the connectivity index between the average of the training period resting state recordings and the 6 week post training recording in the theta band, alpha 1 band and beta 1. The phase lagged synchronisation of the PCC to the parahippocampal gyrus was 0.083 units higher in the theta band at the 6 week follow up (t_{17}=2.855, p=0.011), 0.148 units higher in the alpha 1 band (t_{17}=3.842, p=0.001), and 0.026 units higher in the beta 1 band (t_{16}=2.813, p=0.012). The alpha 2 resting state connectivity index changes were not significant. Figure 5-11 to 5-13 below shows the change in the indices over time.

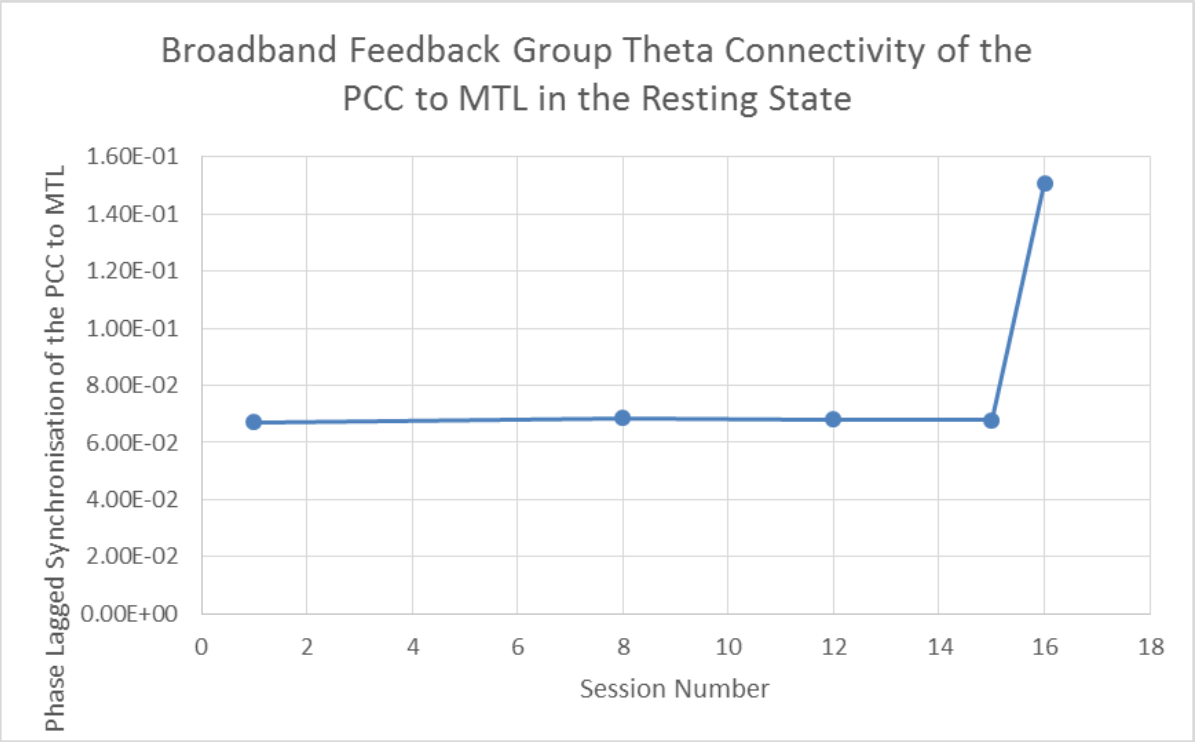


Figure 5-11: Change in the group level theta band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the broadband feedback group.

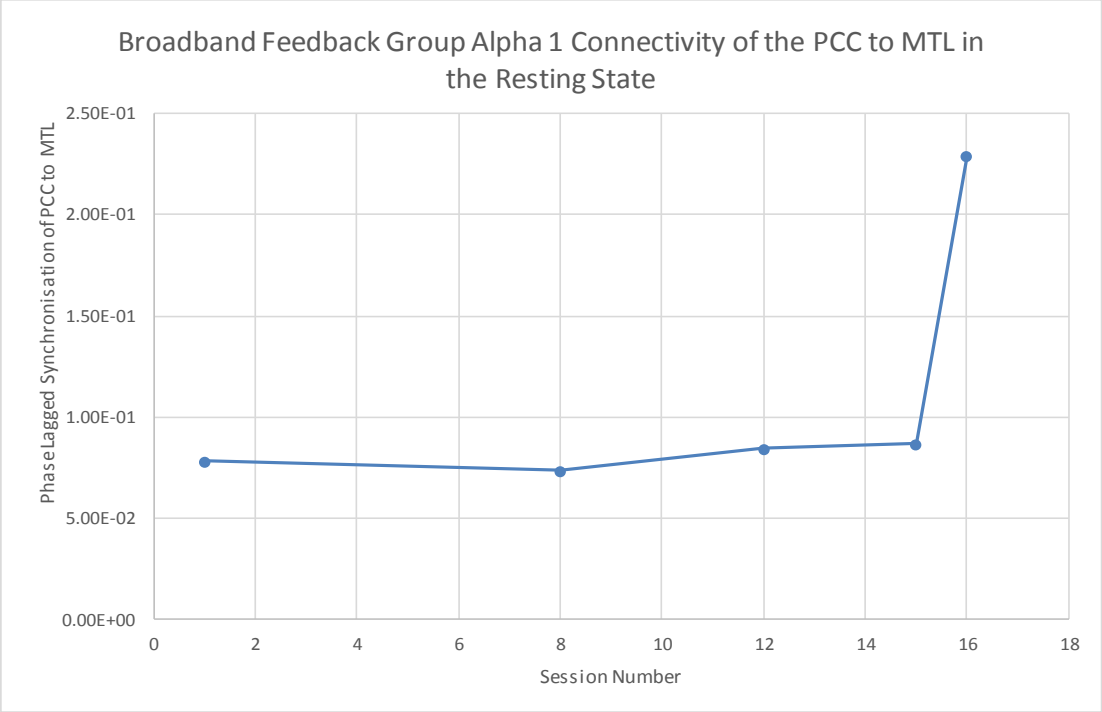


Figure 5-12:Change in the group level Alpha 1 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the broadband feedback group.

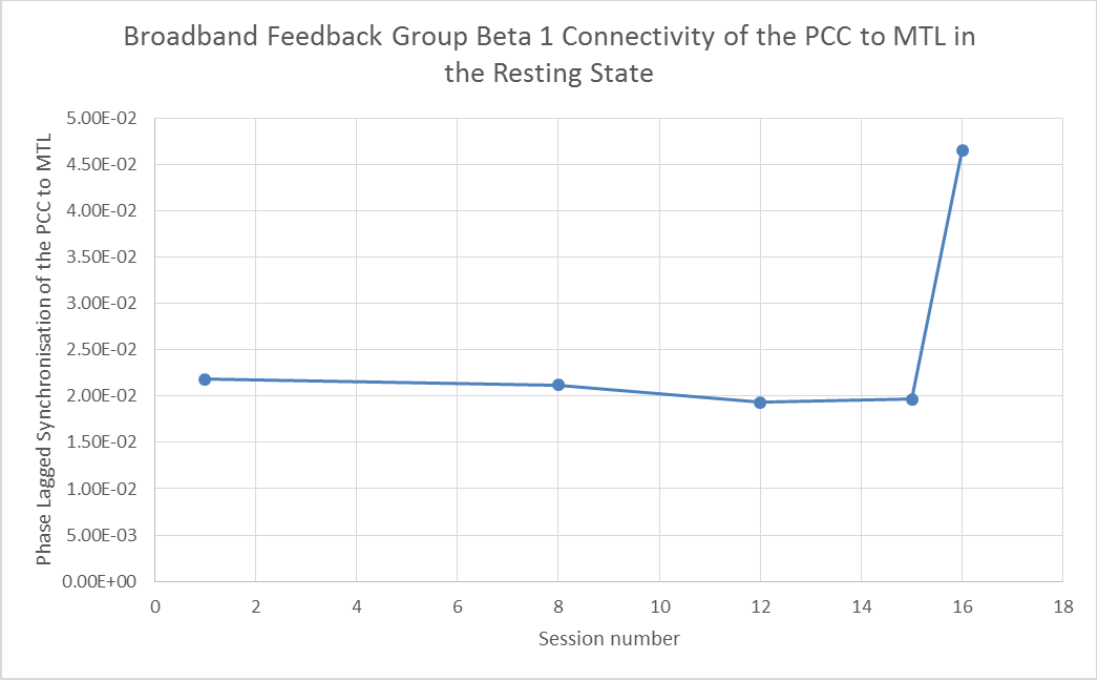


Figure 5-13: Change in the group level beta 1 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the broadband feedback group.

Narrowband Feedback group

Baseline characteristics

Table C-4 in appendix C3 shows the baseline scores of the participants in the narrowband feedback group. Participants who started on RBANS B scored higher on the Attention index when compared to participants who started on RBANS A. Other index scores were broadly similar.

Comparison to the 'normal brain' controls at baseline

There were no significant differences in the current density between the participants in the narrowband feedback group and their matched controls. Images showing the voxel with the highest level of changes can be seen in Figure C-3 in appendix C4.

No significant changes were found in the connectivity of the default mode network between participants in the narrowband biofeedback group and the 'normal brain' controls (p=0.085). These differences mostly follow the pattern seen in the cohort as a whole (alpha 1 and alpha 2 connectivity is mostly up). However, there was higher connectivity in the theta band in the participants then the 'normal brain' controls, in contrast to the cohort as a whole which has lower connectivity in the theta band, as shown in the images in Figure C-7 in appendix C5.

Immediate Follow up Cognitive Scores

In table 5-8 below are the immediate follow up scores on the RBANS for the narrowband feedback group and the change from baseline. The changes of moderate to large magnitude were in the immediate memory index, where participants scored 7.9 points higher at immediate follow up than they did at baseline (p=0.019), and in the visuospatial index where participants score 6.5 points lower than they did at baseline (p=0.006).

Table 5-8 RBANS scores and change from baseline at immediate follow up in the narrowband feedback group

	Score Mean (SD)	Change from Baseline
List Learning	24.1 (4.48)	1.5
Story Learning	14.6 (4.60)	1.7
Figure Copy	22.0 (14.81)	3.1
Line Orientation	16.5 (2.55)	-0.6
Picture Naming	9.6 (0.59)	0.2
Semantic Fluency	19.4 (3.90)	0.8
Digit Span	9.2 (2.78)	-1
Coding	43.2 (8.00)	-0.7
List Recall	4.3 (2.35)	0.1
List Recognition	18.1 (2.37)	-0.6
Story Recall	8.0 (3.11)	1.4
Figure Recall	12.5 (3.27)	-0.1
Immediate Memory Index	89.5 (15.64)	7.9
Visuospatial Index	101.5 (10.64)	-6.5
Language Index	97.9 (10.32)	2.6
Attention index	96.4 (13.92)	-4.1
Delayed Memory index	93.9 (14.31)	2.5
Sum of Indices	479.1 (34.78)	2.4
Total Scale Index	93.7 (9.43)	0.6
Average last two 2-back	49.3 (22.52)	5.6

Appendix C6 table C-7 shows the scores at immediate follow up and change from baseline separated by whether the participants started of Form A or Form B. There was a striking difference between the changes in scores of participants who started on Form A compared to Form B. Participants who started on Form A scored 14.5 points higher at follow up, but the participants who started on Form B scored four points lower at follow up. Also, participants who started on Form A scored one point lower on the Language index at follow up, compared to participants who started on Form B scored nine points higher on the Language index at follow up.

Changes in Current Density from Baseline to Immediate Follow Up

No significant changes were found in the current density map from baseline to immediate follow up. Diagrams illustrating the voxel with the highest magnitude change can be found in figure C-10 in appendix C7.

Changes in Connectivity of the Default Mode Network from Baseline to Immediate Follow up

No significant changes in the connectivity of the default mode network was found using 11 regions of interest. Diagrams showing changes in connectivity at the highest magnitude of change (p=0.163) can be found in Figure C-13 in appendix C8. Bands not shown in appendix C8 have no changes at this level of significance.

Overall, there was a trend toward decreased connectivity in the delta band, beta 1 band, beta 2 band, beta 3 band and omega band. It would appear to be a reversal of the trends seen in the comparison to the 'normal brain' controls; however this was only concentrated in higher frequency bands, rather than alpha and theta bands.

Change in the Activity and Connectivity Indices in the in-Training Data.

In three of the activity indices, the correlation coefficient differed significantly from 0, but none of the changes in the connectivity indices were statistically significant. Graphs for the remaining indices is given in Figure C-22 to C-26 appendix C9. Figure 5-14 shows the change in theta activity in the PCC for each participant (r=0.229, 95%CI 0.115-0.343, p=0.001). Figure 5-15 shows the average change in theta activity over time in the narrowband feedback group (β=0.0349). There was a tendency for the

theta activity to increase over time with the training.

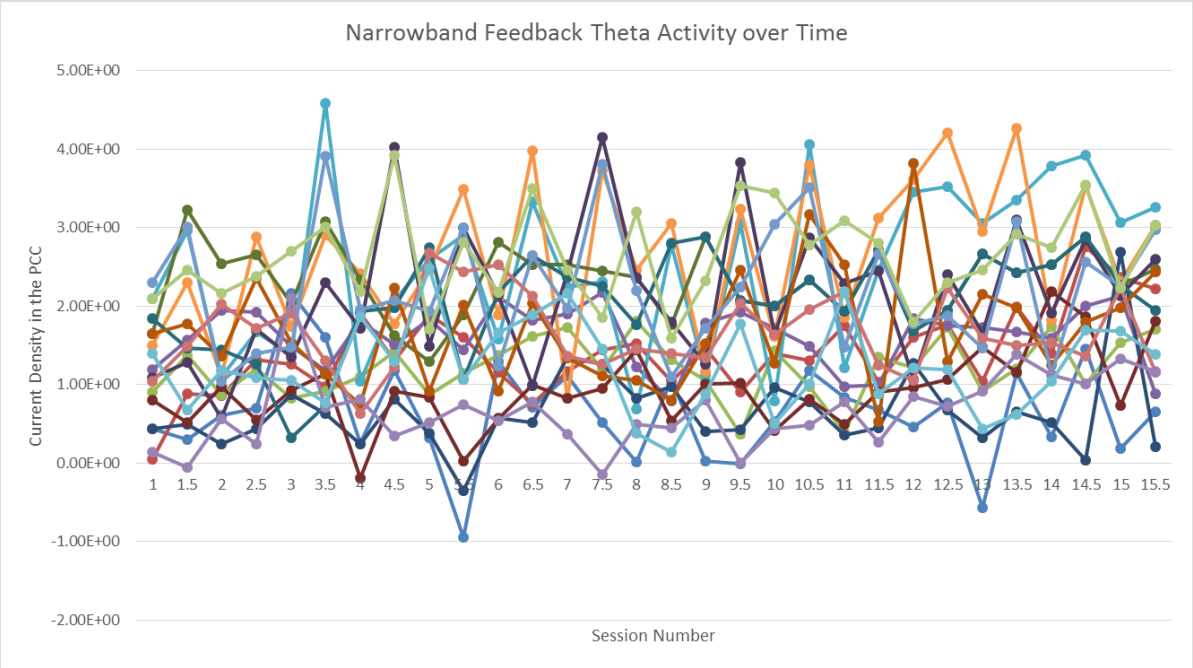


Figure 5-14: Individual level changes in the theta current density of the PCC in the training state in the narrowband feedback group

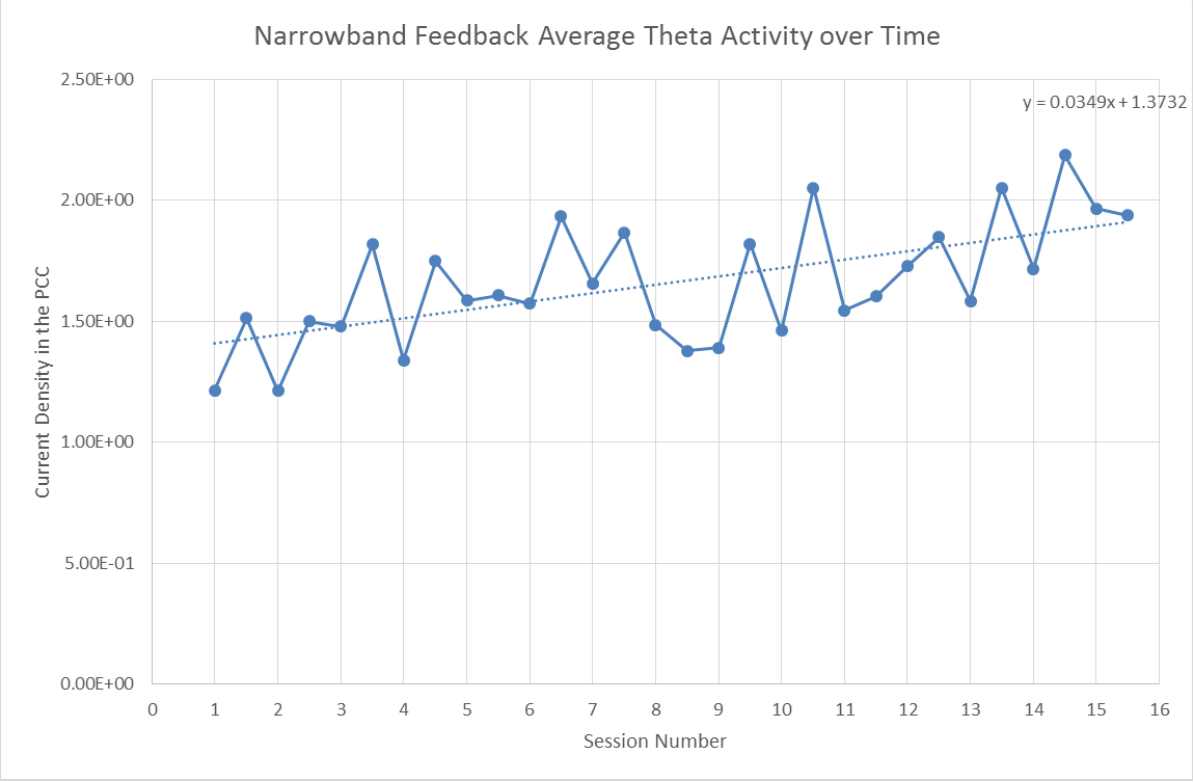


Figure 5-15 Group level changes in the theta current density of the PCC in the training state in the narrowband feedback group

The graph in Figure 5-16 shows the change in Alpha 1 activity in the PCC for each participant(r=0.210, 95%CI 0.082-0.337, p=0.003). Figure 5-17 shows the average change in Alpha 1 activity over time in the narrowband feedback group (β=0.0323). There was a tendency for the alpha 1 activity to increase over time as the number of sessions increase. The average activity also seems to spike at the end of each session, and decrease before the beginning of the next session.

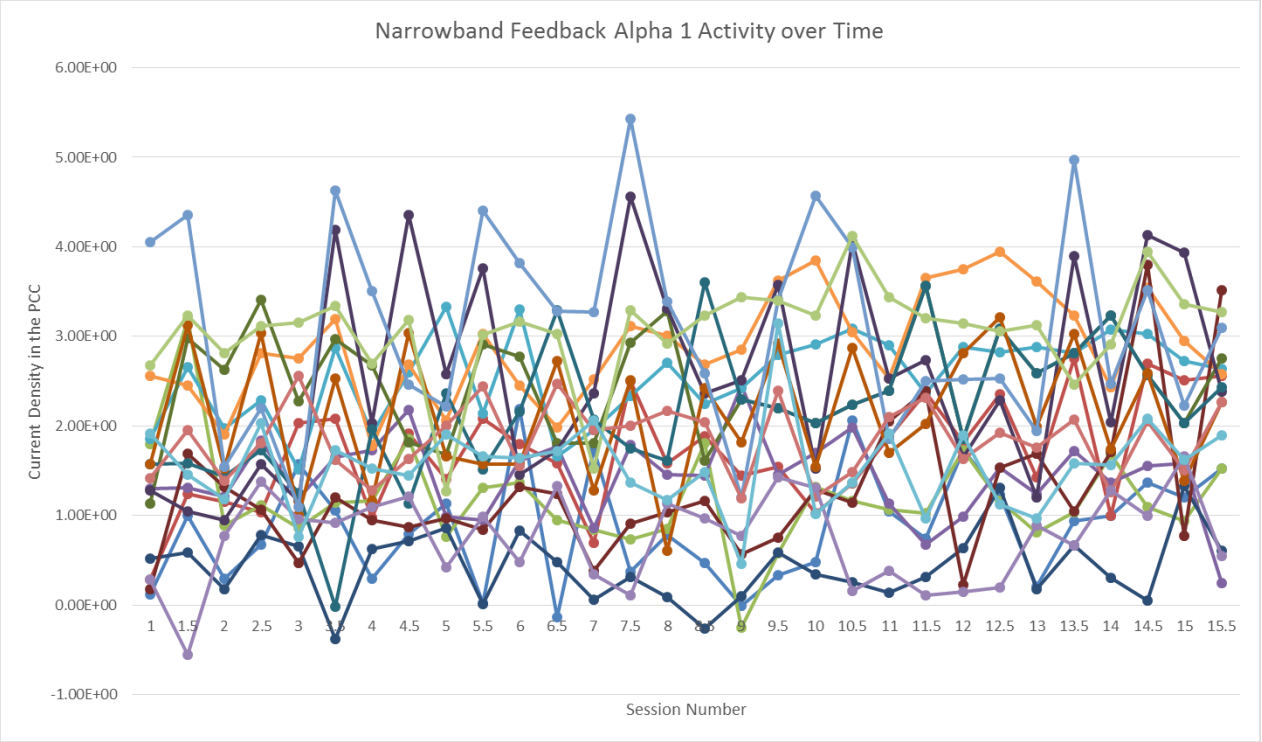


Figure 5-16 Individual level changes in the alpha 1 current density of the PCC in the training state in the narrowband feedback group

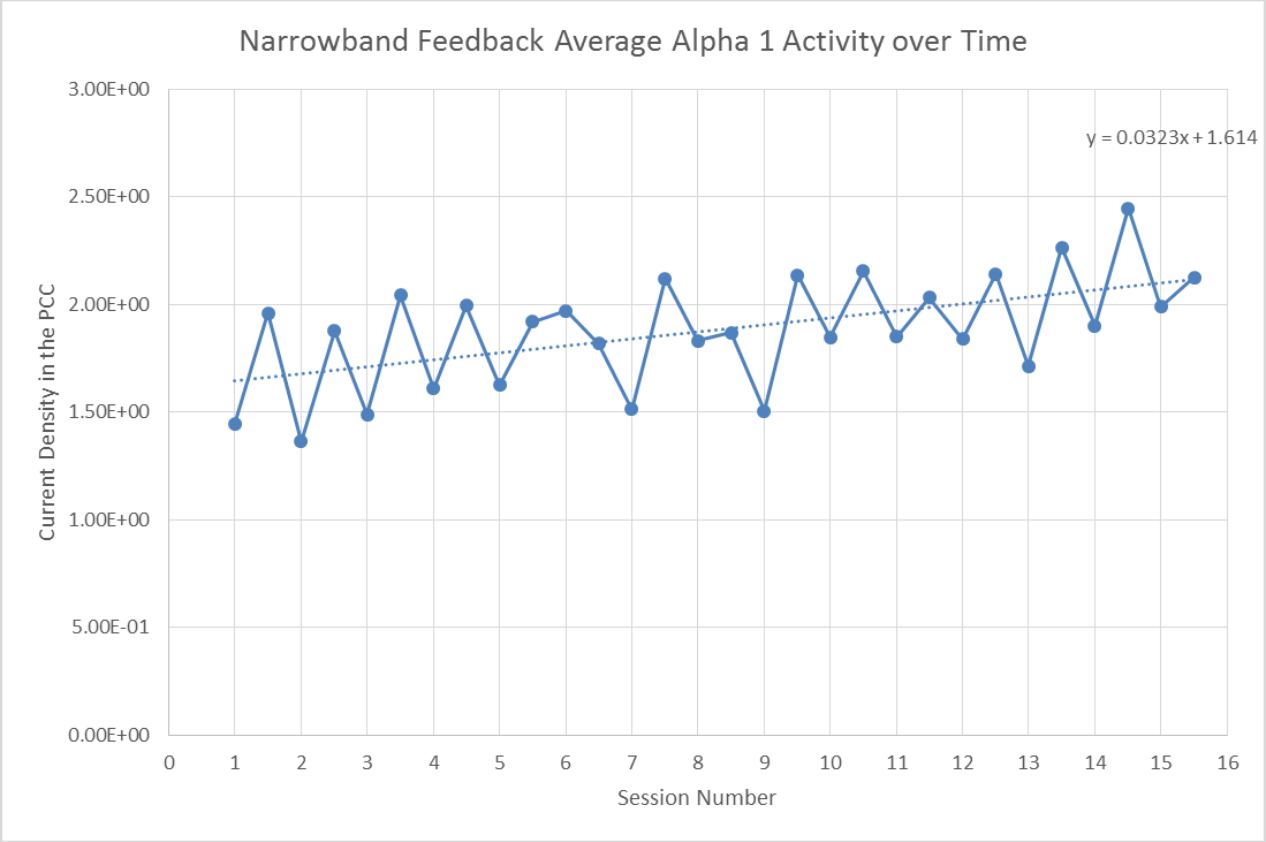


Figure 5-17 Group level changes in the alpha 1 current density of the PCC in the training state in the narrowband feedback group

Figure 5-18 shows the change in Beta 1 activity in the PCC for each participant(r=0.230, 95%CI 0.131-0.328, p<0.001). Figure 5-19 shows the average change in Beta 1 activity over time in the narrowband feedback group (β=0.0229). There was a tendency for the beta activity to increase slightly over time.

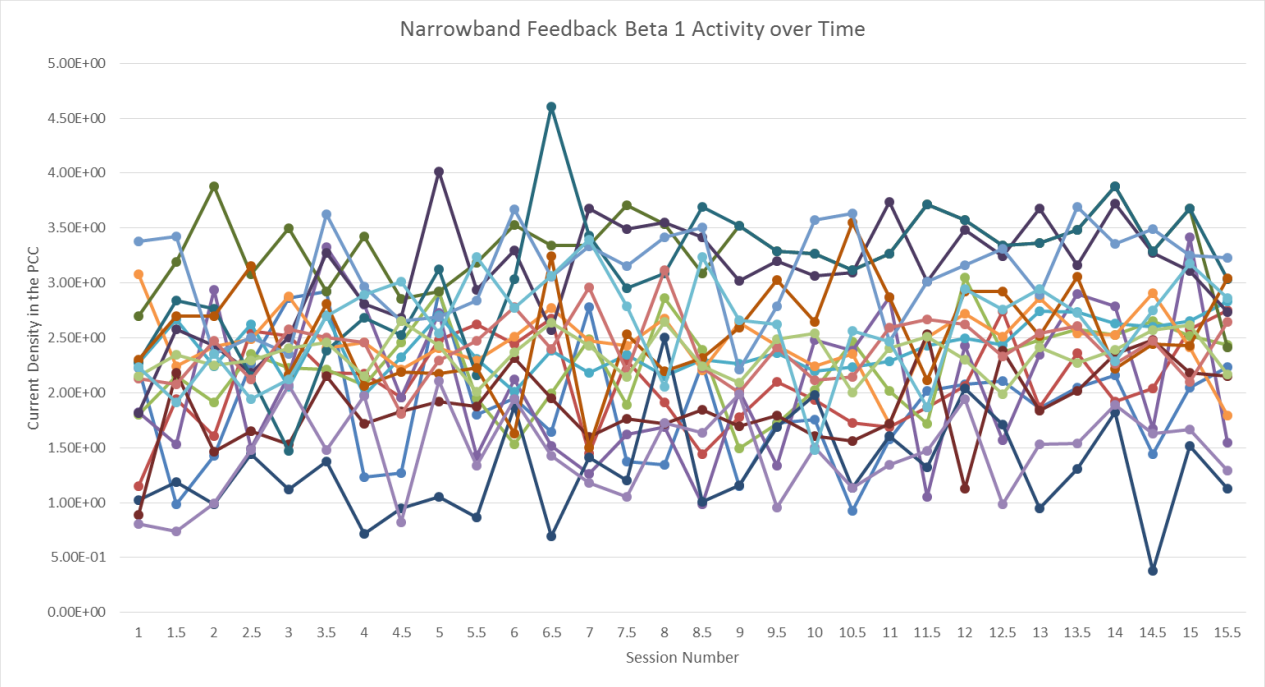


Figure 5-18: Individual level changes in the beta 1 current density of the PCC in the training state in the narrowband feedback group

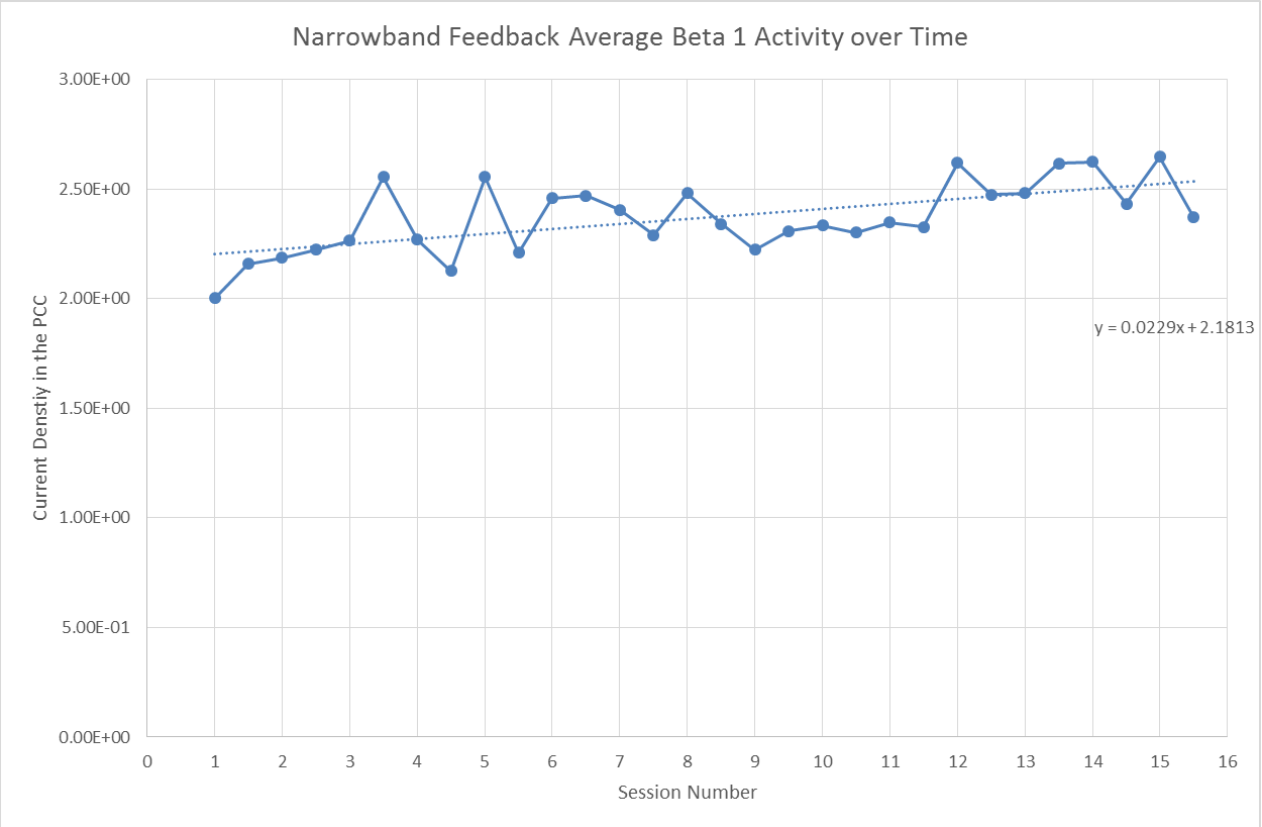


Figure 5-19 Group level changes in the beta 1 current density of the PCC in the training state in the narrowband feedback group

Within session change

A significant increase was found in within session alpha 1 current density (p=0.001). No other significant within session change was found in the current density of the other bands.

No significant within session change in connectivity indices was found in any of the theta, alpha 1, alpha 2 or beta 1 band.

Interview data

There were four people who said they experienced some memory benefit from the biofeedback training. Of these people, one experienced an increase of more than 10 points in the immediate memory index between the pre training test and the immediate follow up score. Of the 13 people who said they received no benefit from the training, seven had a more than 10 point increase in their immediate memory scores. Two people experienced excessive tiredness as a result of taking part in the biofeedback training.

6 Week Follow Up Cognitive Scores

Table 5-9 below shows the average score in the RBANS cognitive indices and subtests scored at the 6 week follow up session, and the change in the score from the baseline for the narrowband feedback group. Table C-10 in Appendix C10 shows the change in the RBANS subtests and indices separated by whether the participants started on RBANS form A or B

Table 5-9 RBANS score and change from baseline at 6 week follow up in the narrowband feedback group

	Mean (SD)	Difference from Baseline
List Learning	24.3 (5.00)	1.7
Story Learning	16.6 (3.38)	3.7
Figure Copy	17.6 (2.12)	-1.4
Line Orientation	16.9 (2.30)	-0.2
Picture Naming	9.6 (0.48)	0.2
Semantic Fluency	19.9 (4.31)	1.2

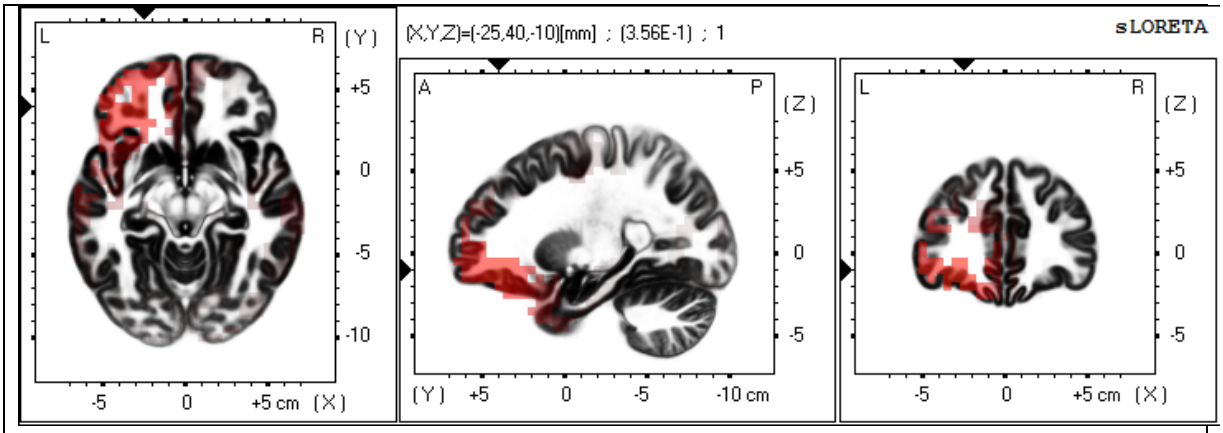
	Mean (SD)	Difference from Baseline
Digit Span	10.3 (2.24)	0.1
Coding	46.1 (8.31)	2.2
List Recall	4.5 (2.85)	0.3
List Recognition	18.5 (1.75)	-0.3
Story Recall	9.1 (2.36)	2.4
Figure Recall	14.2 (2.46)	1.6
Immediate Memory Index	93.9 (13.14)	12.4
Visuospatial Index	99.6 (13.05)	-8.4
Language Index	100.1 (8.56)	4.8
Attention index	103.4 (11.74)	2.9
Delayed Memory index	97.8 (15.84)	6.4
Sum of Indices	495.8 (33.59)	19.1
Total Scale Index	98.3 (8.63)	5.2
Average last two 2-back	52.8 (25.26)	9.1

In the narrowband feedback group there was a large magnitude increase in the immediate memory index, with a change of 12.4 points ($p<0.001$). This was mostly caused by a large magnitude change in comparison to the standard deviation, in the story memory score. There was a moderate magnitude decrease in the visual spatial index, with participants scoring 8.4 points less at the 6 week follow up than at baseline, although this was not statistically significant. There was also a moderate increase in the delayed memory index, of 6.4 points ($p=0.025$).

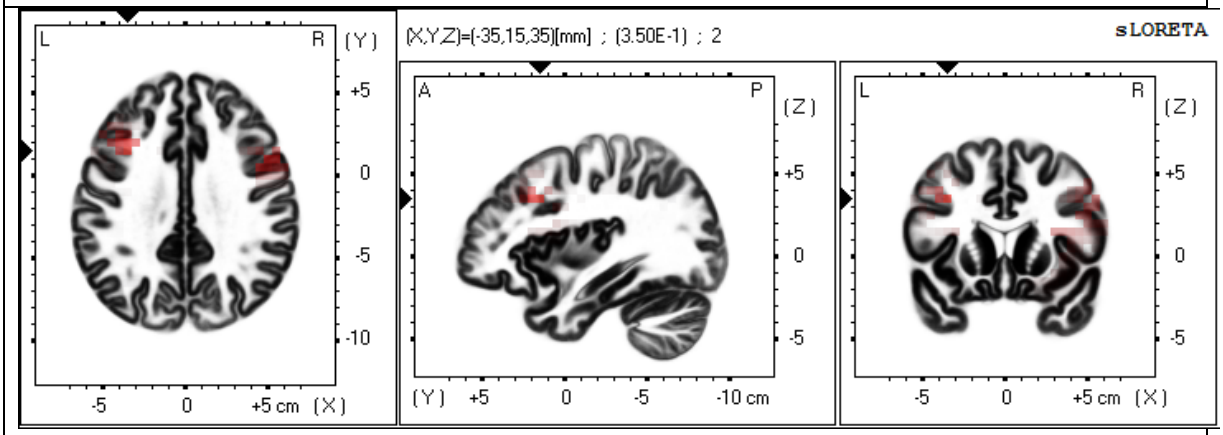
Changes in Current Density at 6 week follow up compared to baseline

Figure 5-20 below shows the changes in the current density in the narrow band feedback group, comparing the 6 week follow up recording with the baseline recording. These changes were statistically significant as $p=0.046$. Red and yellow areas represent areas of increased activity at the 6

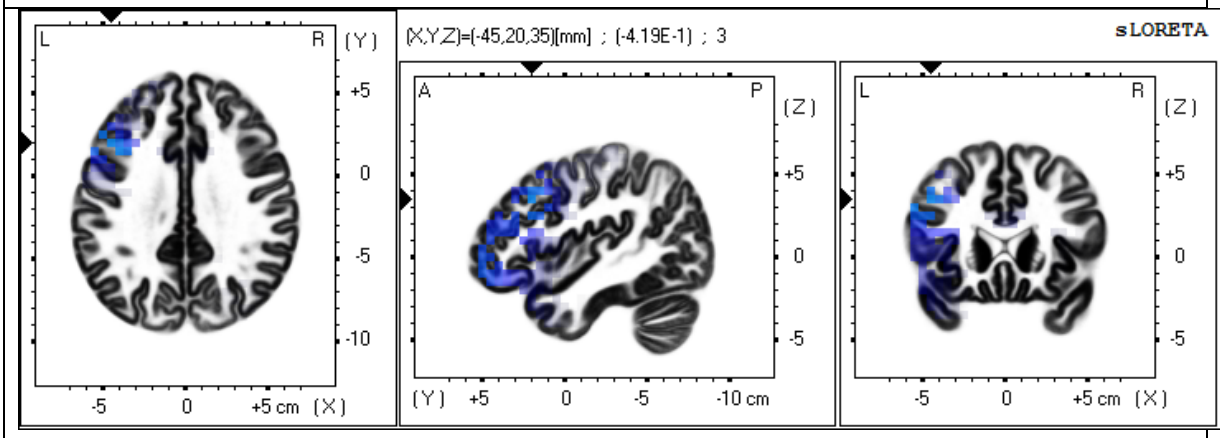
week follow up compared to baseline and blue regions indicate areas of decreased activity compared to baseline.



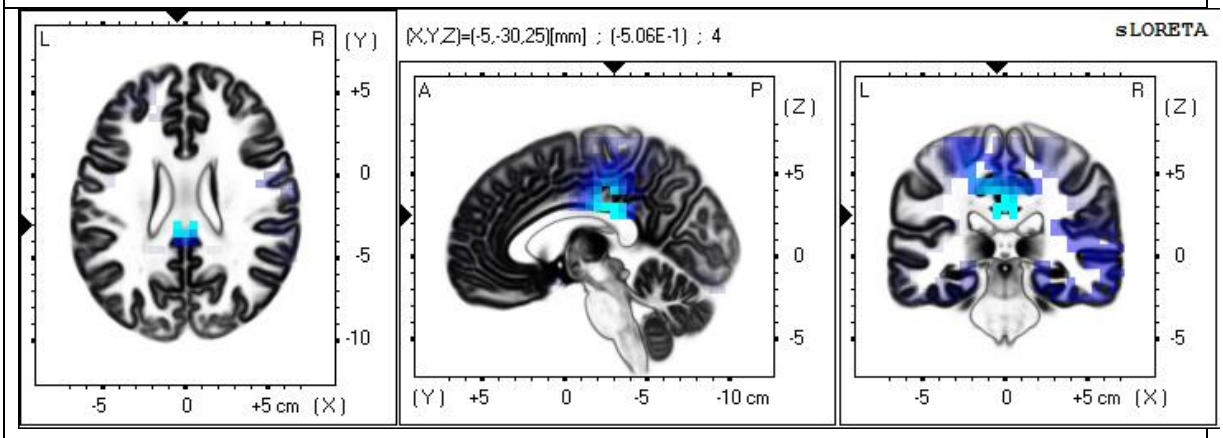
Delta band



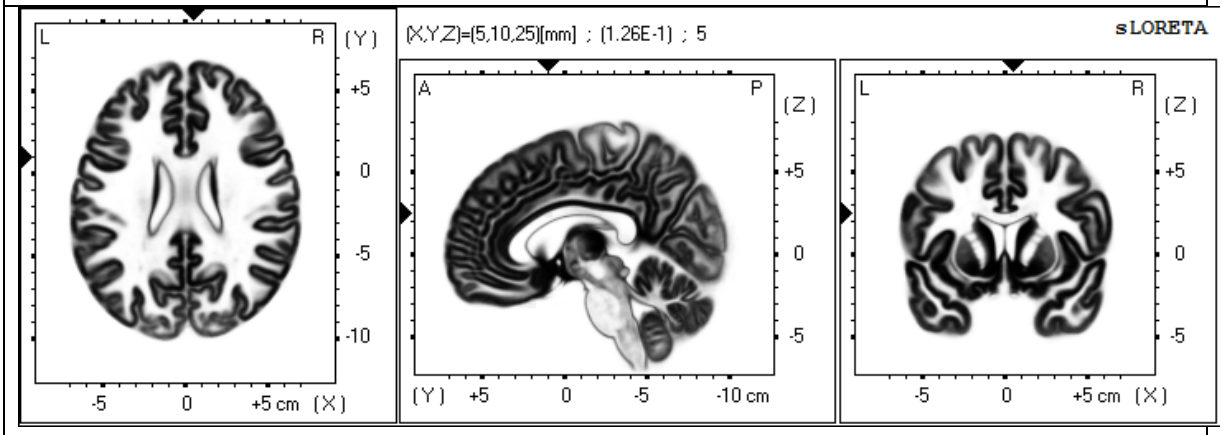
Theta band



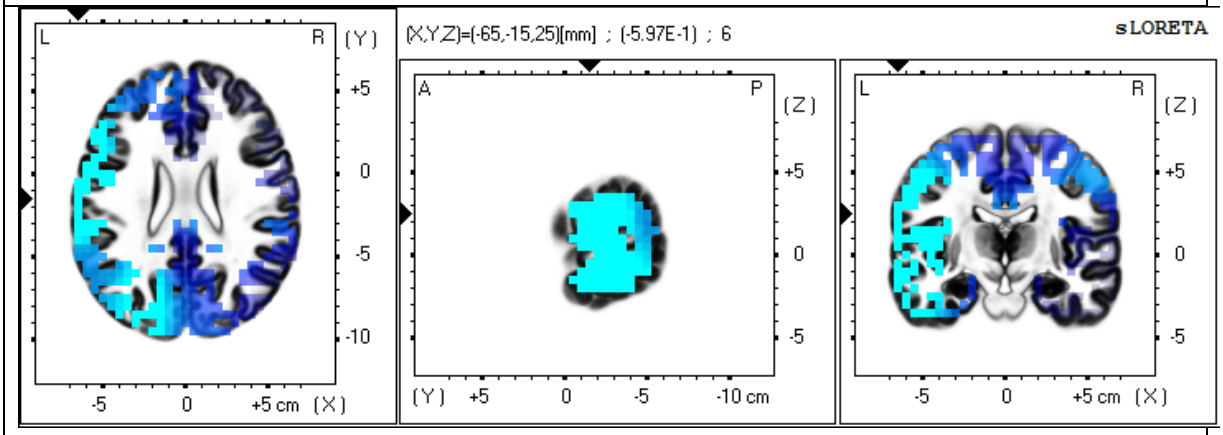
Alpha 1 band



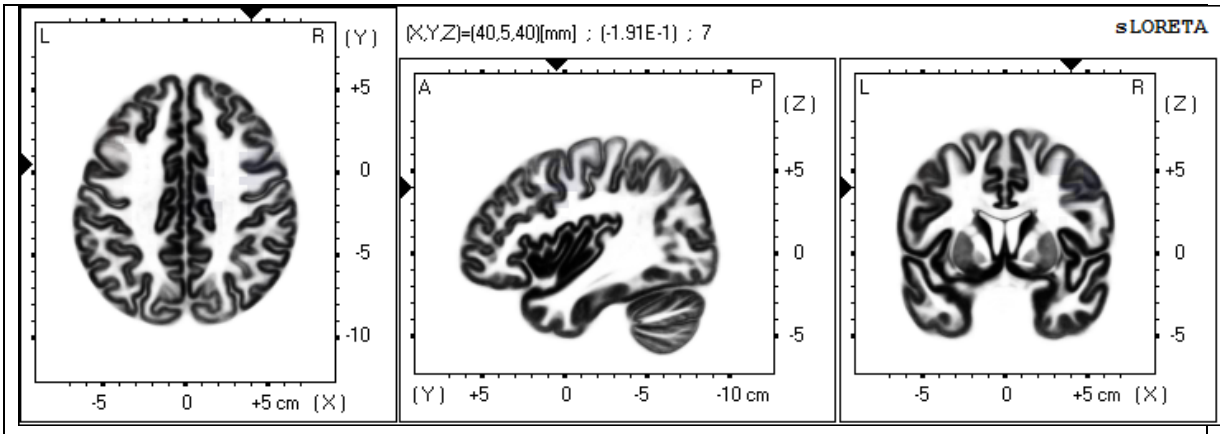
Alpha 2 band



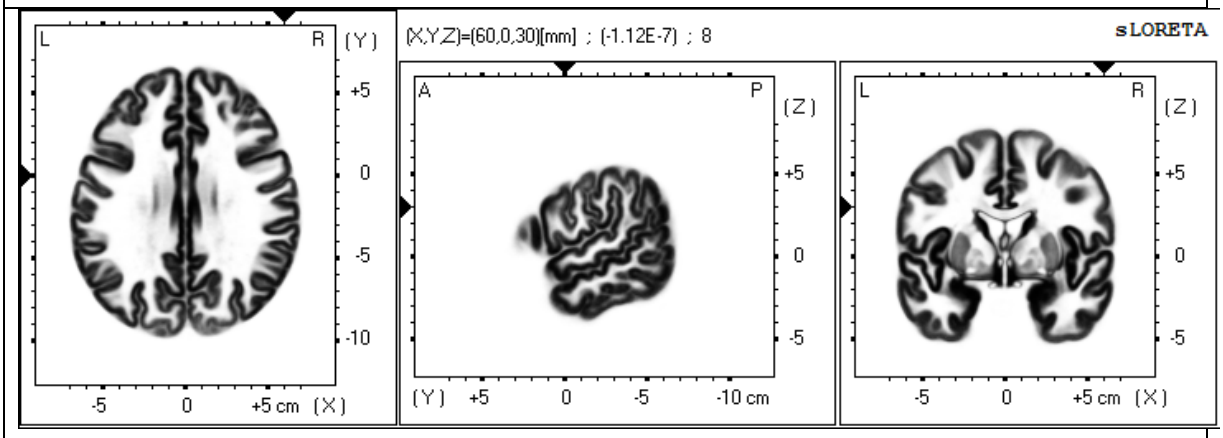
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure 5-20 Current density maps showing the change in resting state current density between 6 week follow up and pre-training recordings in the narrowband feedback group

There were significant increases in activity in the delta band and theta bands, and significant decreases in activity in the alpha 1, alpha 2 and beta 2 bands. No significant changes were found for the beta 1, beta 3 and omega bands. Changes in activity were mostly centred on the left frontal lobe, except for the decrease in activity in the alpha 2 band, which was centred on the superior part of the PCC and the anterior part of the posterior cingulate gyrus.

Changes in the connectivity of the DMN at 6 week follow up

There was no significant changes found in the connectivity of the DMN found at 6 week follow up compared to the pre-training resting state recording. Images with the highest significance changes (p=0.32) can be found in Figure C-36 in appendix C11.

Changes in the Resting state indices

There was no significant trend identified in either the current density of the PCC or the phase lagged synchronisation of the PCC to the parahippocampal gyrus in the resting state data. The average of the first four resting state recordings were therefore compared to the 6 week follow up resting state recording.

There was no significant difference in the activity index between the averages of the resting state recordings in the training period compared to the 6 week follow up.

A significant difference was found in the beta 1 band and alpha 2 band for the connectivity index. The phase lagged synchronisation was 0.113 units higher in the alpha 2 band at the 6 week follow up recording compared to the average of the first four measurement (t_{16}=3.188, p=0.006) and 0.0295 units higher in the beta 1 band(t_{16}=4.24, p=0.001) . No other significant change in the resting state indices were found. Figure 5-21 and 5-22 below shows the change in the index over time.

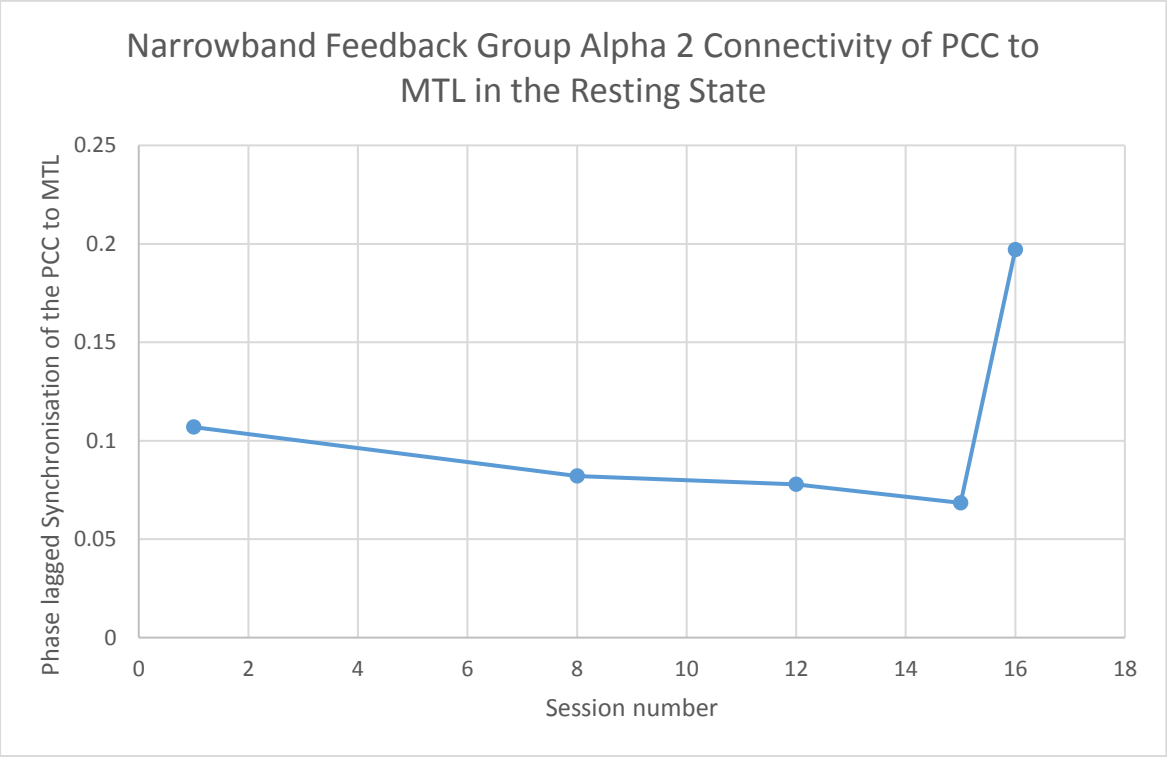


Figure 5-21: Change in the group level alpha 2 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the narrowband feedback group.

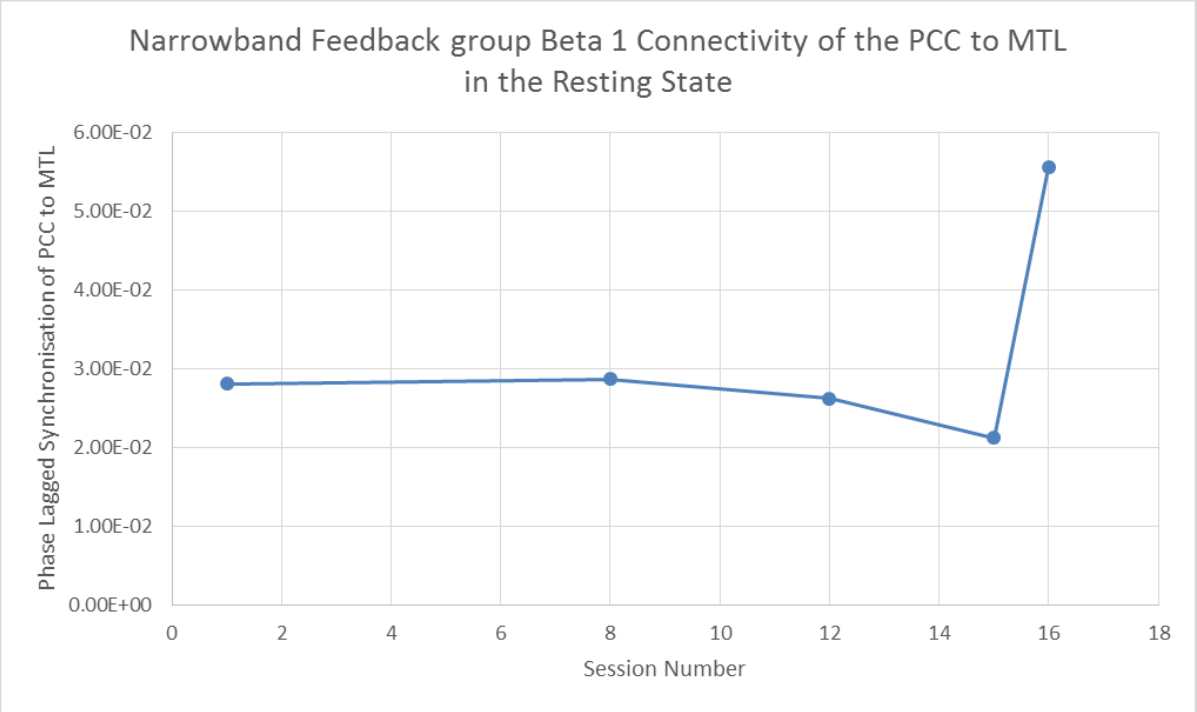


Figure 5-22 Change in the group level beta 1 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the narrowband feedback group.

Placebo Feedback group

Baseline Characteristics

Table C-5 in Appendix C3 shows the baseline scores of the participants in the placebo feedback group, and the baseline scores separated by initial RBANS form. Participants who started on RBANS B scored higher on the Immediate Memory Index than participants who started on RBANS A. Participants on RBANS B also scored lower in the visuospatial index, and in the delayed memory index.

Comparison to the 'normal brain' controls at baseline

There were no significant differences in the connectivity between the participants in group 1 and their matched controls. Images showing the voxel with the highest level of changes can be seen in Figure C-5 in appendix C4.

There were no significant differences in the connectivity of the default mode network compared to the 'normal brain' controls. Images showing the highest significance of changes are given in Figure C-8 in appendix C5 (p=0.64). As with the cohort as a whole, there was a trend toward lower

connectivity in the theta band. However, the alpha 1 band has a trend toward lower connectivity in the participants, compared to the cohort as a whole. The alpha 2 band have more connections that were lower in the participants compared to the participants as a whole.

Immediate Follow up Cognitive Changes

Table 5-10 below shows the cognitive scores at immediate follow up in the placebo group and the changes from baseline. The immediate memory index score was 9.5 points higher at immediate follow up than at baseline (p=0.004). No other changes of moderate to large magnitude were observed in this group.

Table 5-10 RBANS scores and change from baseline at immediate follow up in the placebo feedback group

	Score Mean (SD)	Change from Baseline
List Learning	25.1 (3.54)	1.6
Story Learning	14.8 (4.54)	2.3
Figure Copy	17.9 (2.09)	-0.4
Line Orientation	15.9 (4.07)	-0.7
Picture Naming	9.9 (0.23)	0.6
Semantic Fluency	20.3 (3.93)	1.1
Digit Span	10.5 (2.63)	0.2
Coding	42.4 (6.77)	1.9
List Recall	4.2 (2.04)	-0.2
List Recognition	18.3 (1.59)	-0.3
Story Recall	8.2 (2.74)	1.7
Figure Recall	13.4 (3.64)	1.3
Immediate Memory Index	91.0 (13.04)	9.5
Visuospatial Index	99.0 (19.30)	-2.8

	Score Mean (SD)	Change from Baseline
Language Index	99.8 (8.51)	3.6
Attention index	98.3 (13.11)	2.4
Delayed Memory index	92.9 (12.37)	2.6
Sum of Indices	481.1 (39.69)	15.2
Total Scale Index	94.3 (10.44)	3.7
Average last two 2-back	52.9 (22.22)	1.0

Table C-8 in appendix C6 shows the immediate follow up score and the changes from baseline in the placebo group separated out by whether participants started on Form A or Form B. Participants who started out on Form A scored 16.1 points higher in the immediate memory index at follow up, compared to participants who started out on Form B who scored 3.7 points lower at follow up. Participants who started out on Form A scored 1.9 points higher at follow up on the Language index, compared to participants who start out on Form B who scored 6.8 points higher. Also, participants who started out on Form A scored 5.2 points higher on the delayed memory index and 6.4 points higher on the total index, compared to participants who started on Form B who scored 2.7 points lower and 1.7 points lower on the delayed memory and total index scores respectively.

Changes in Current Density from Baseline to Immediate Follow Up

No significant changes were found in the current density map from baseline to immediate follow up. Diagrams illustrating the voxel with the highest magnitude change can be found in Figure C-11 in appendix C7.

Changes in Connectivity of the Default Mode Network from Baseline to Immediate Follow up

No significant changes in the connectivity of the default mode network was found using 11 regions of interest. Diagrams showing changes in connectivity at the most statistically significant value

(p=0.307) can be found in Figure C-14 in appendix C8. Bands not shown in appendix C8 have no changes at this level of significance.

In this group, there was a trend toward higher connectivity in the theta band, and the omega band, and no changes seen in other bands. This does indicate a reversal of the trend seen in the theta band, but the result was not replicated across multiple bands as it was in the broadband feedback group.

Change in the Activity and Connectivity Indices in the in-Training Data

No significant changes in any of the measured connectivity or activity indices were found. The graphs showing the individual changes in activity and connectivity over time are given in Figure C-27 to C-34 in Appendix C9.

Interview data

Five people in the placebo feedback group said they experienced some benefit from the biofeedback training. Of these three experienced an improvement of more than 10 points in the immediate memory score between the pre-training test and the immediate follow up score. Of the 13 people who said they did not experience any benefit from the biofeedback training seven experienced an increase of more than 10 points in the immediate memory index. Three people in the placebo feedback group experienced excessive tiredness as a result of doing the biofeedback training.

Within Session Change

A significant increase was found in within session theta (p=0.001), alpha 1 current density (p<0.001), and alpha 2 bands (p=0.006). No other significant within session change was found in the current density of the other bands.

No significant within session change in connectivity indices was found in any of the theta, alpha 1, alpha 2 or beta 1 band.

6 Week Follow Up Cognitive Scores

Table 5-11 below shows the average score in the RBANS cognitive indices and subtests scored at the 6 week follow up session, and the change in the score from the baseline for the placebo feedback group. Table C-11 in Appendix C10 shows the change in the RBANS subtests and indices separated by whether the participants started on RBANS form A or B

Table 5-11 RBANS scores and change from baseline at 6 week follow up in the placebo feedback group

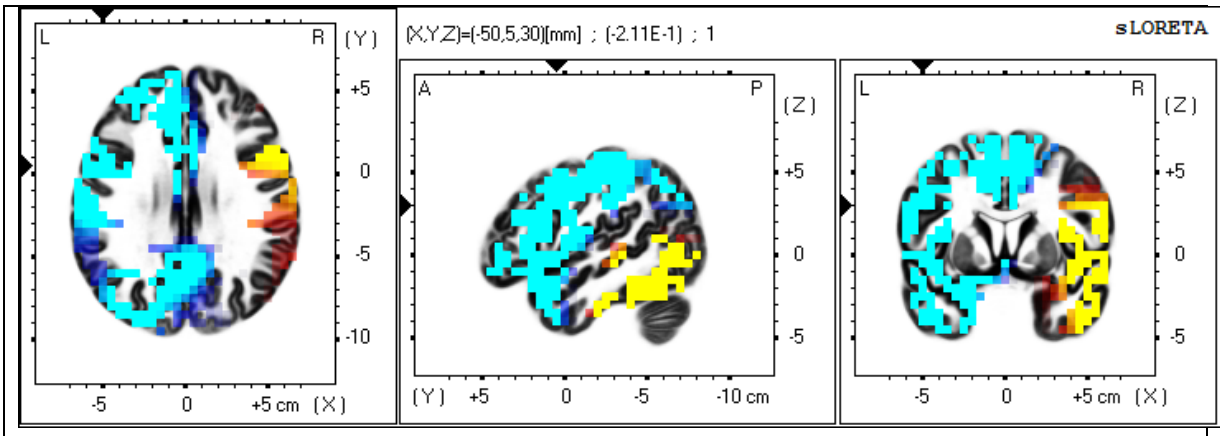
	Mean (SD)	Difference from Baseline
List Learning	25.5 (3.73)	1.9
Story Learning	14.4 (4.07)	1.9
Figure Copy	17.8 (2.12)	-0.5
Line Orientation	16.3 (3.59)	-0.3
Picture Naming	9.8 (0.38)	0.5
Semantic Fluency	19.5 (3.40)	0.4
Digit Span	10.4 (2.35)	0.1
Coding	44.1 (8.54)	3.6
List Recall	4.9 (1.71)	0.5
List Recognition	19.2 (1.16)	0.7
Story Recall	7.7 (2.40)	1.2
Figure Recall	13.1 (4.28)	0.9
Immediate Memory Index	90.2 (10.66)	8.7
Visuospatial Index	99.5 (17.41)	-2.3
Language Index	98.0 (5.58)	1.7
Attention index	100.5 (15.44)	4.6
Delayed Memory index	99.2 (10.76)	8.8
Sum of Indices	487.5 (44.16)	21.7

	Mean (SD)	Difference from Baseline
Total Scale Index	96.3 (11.87)	5.7
Average last two 2-back	56.4 (24.79)	4.4

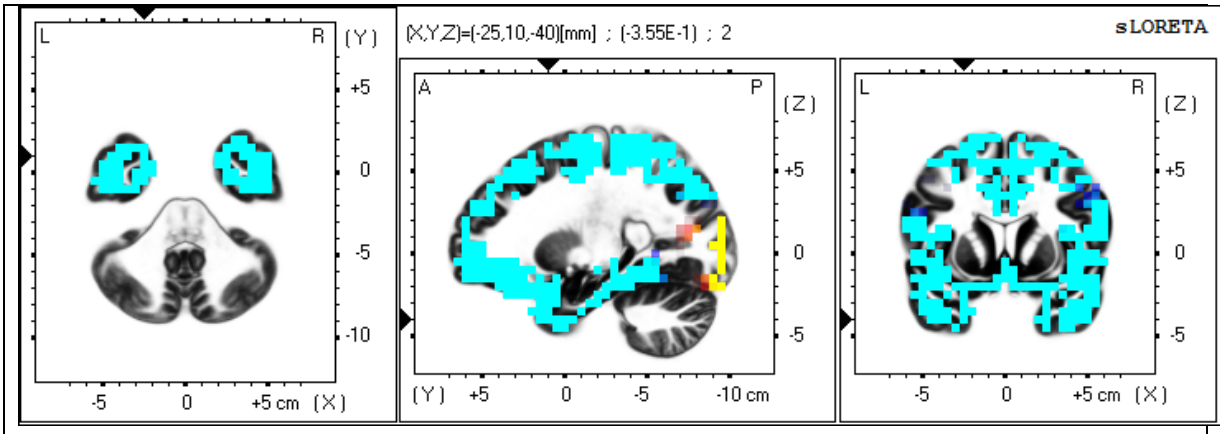
There was a moderate increase of 8.7 points in the immediate memory index at the 6 week follow up test compared to the pre training test (p=0.001). There was also a moderate increase in the delayed memory index of 8.8 points (p=0.004).

Changes in Current Density at 6 week follow up compared to baseline

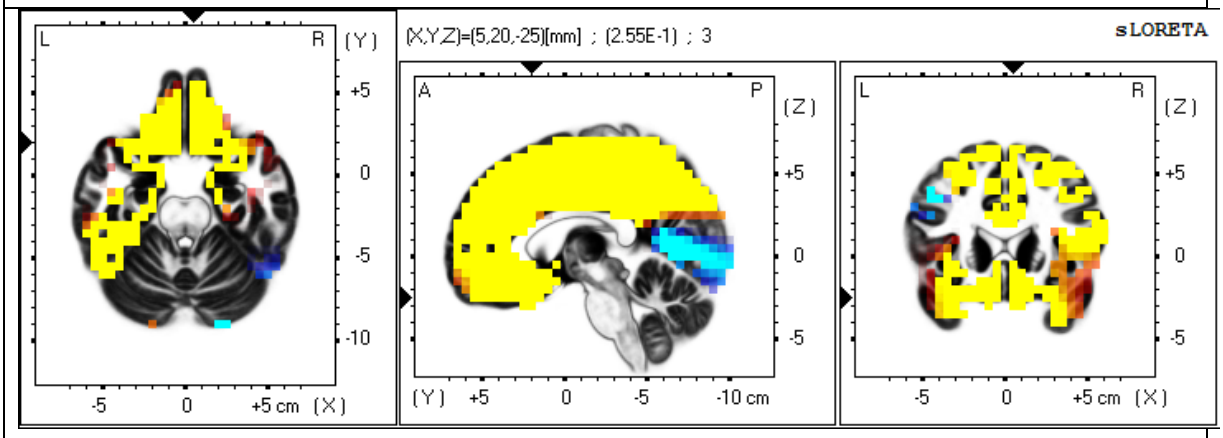
The images in figure 5-23 below show the changes in the current density in the placebo feedback group at 6 week follow up compared to the baseline resting state recording. These changes were significant (p=0.049). Red and yellow areas represent areas of increased activity at the 6 week follow up compared to baseline and blue regions indicate areas of decreased activity compared to baseline.



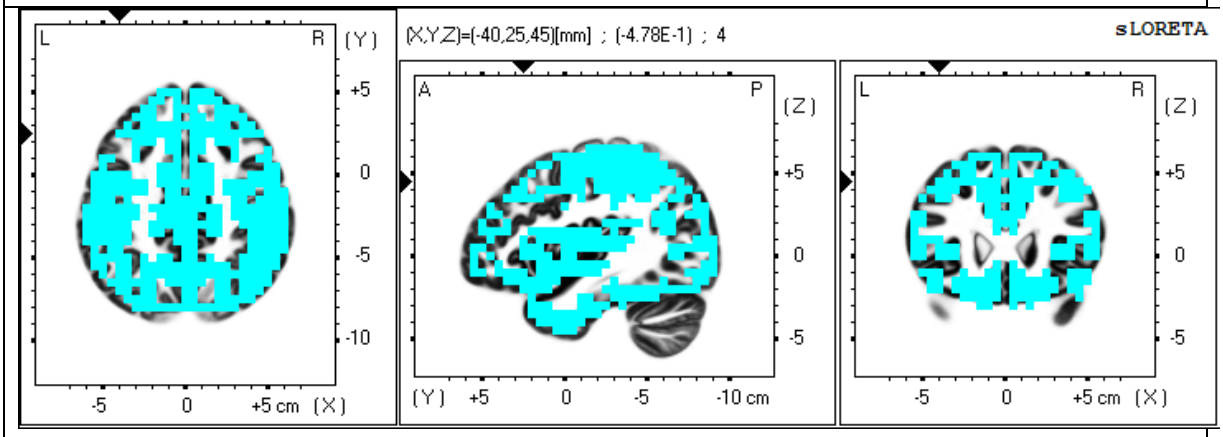
Delta band



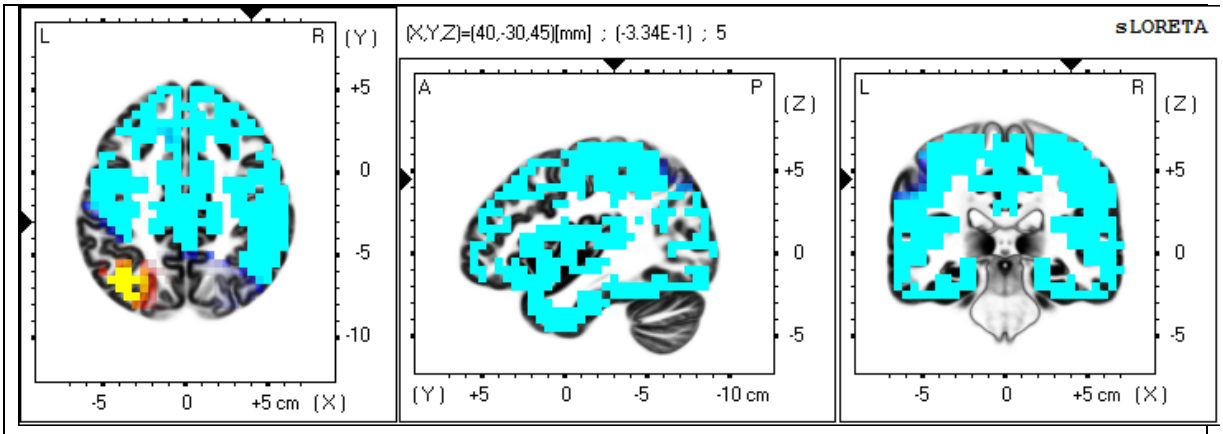
Theta band



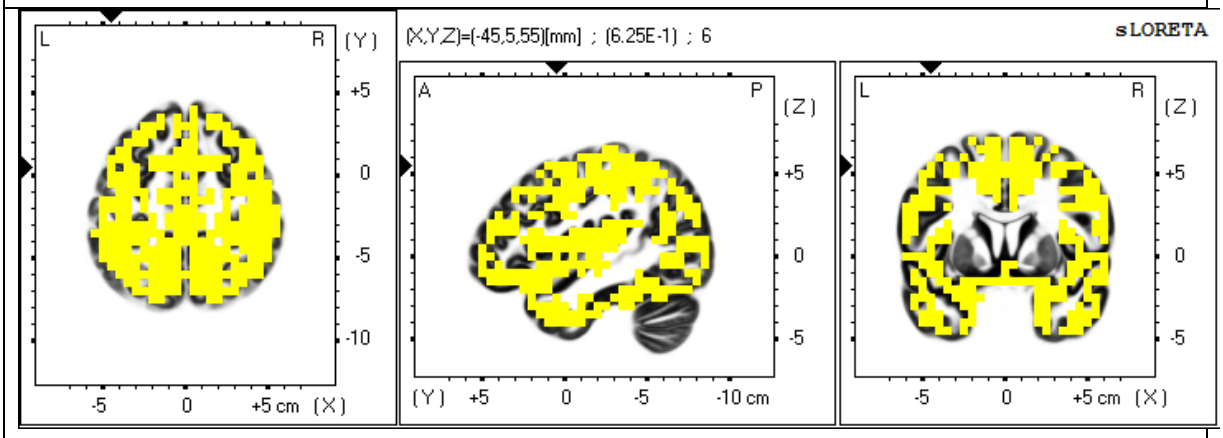
Alpha 1 band



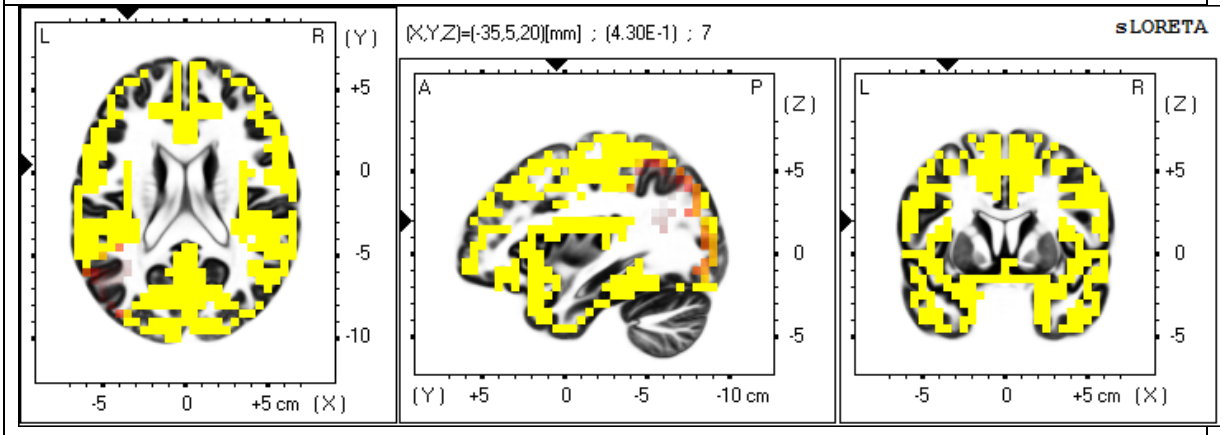
Alpha 2 band



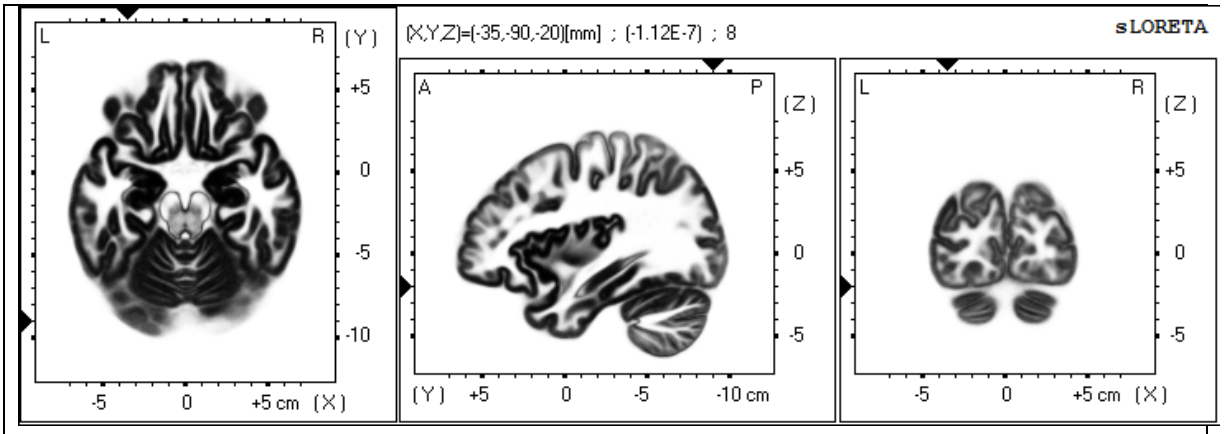
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure 5-23 Current density maps showing the change in resting state current density between 6 week follow up and pre-training recordings in the placebo feedback group

The changes were more mixed than with the other groups, and there is a lot less definition to the images, because the changes in the placebo group were only significant at a low threshold of change. There was mixed changes in activity in the delta, theta, alpha 1 and beta 1 bands. There was a pure decrease in activity in the alpha 2 band and pure increases in activity in the beta 2 and beta 3 bands. No significant changes were found in the omega band.

Changes in the connectivity of the DMN at 6 week follow up

There was no significant changes found in the connectivity of the DMN found at 6 week follow up compared to the pre-training resting state recording. Images with the highest significance changes (p=0.088) can be found in Figure C-37 in appendix C11.

Changes in the Resting state indices

There was no significant trend identified in either the current density of the PCC or the phase lagged synchronisation of the PCC to the parahippocampal gyrus in the resting state data. The 6 week follow up recording was then compared to the average of the first four recordings.

There was no significant difference in the activity index between the average of the first four resting state recordings and the 6 week follow up recording.

A significant change in the connectivity index in the theta band and the alpha 2 band between the average of the first four resting state recordings and the 6 week follow up recording. The phase

lagged synchronisation was 0.031 units higher in the theta band in the 6 week follow up recording (t_{16}=3.369, p=0.004) and 0.06 units higher in the alpha 2 band (t_{16}=3.105, p=0.007). No other significant changes in the connectivity indices were found. Figures 5-24 and 5-25 below shows the change in the index over time.

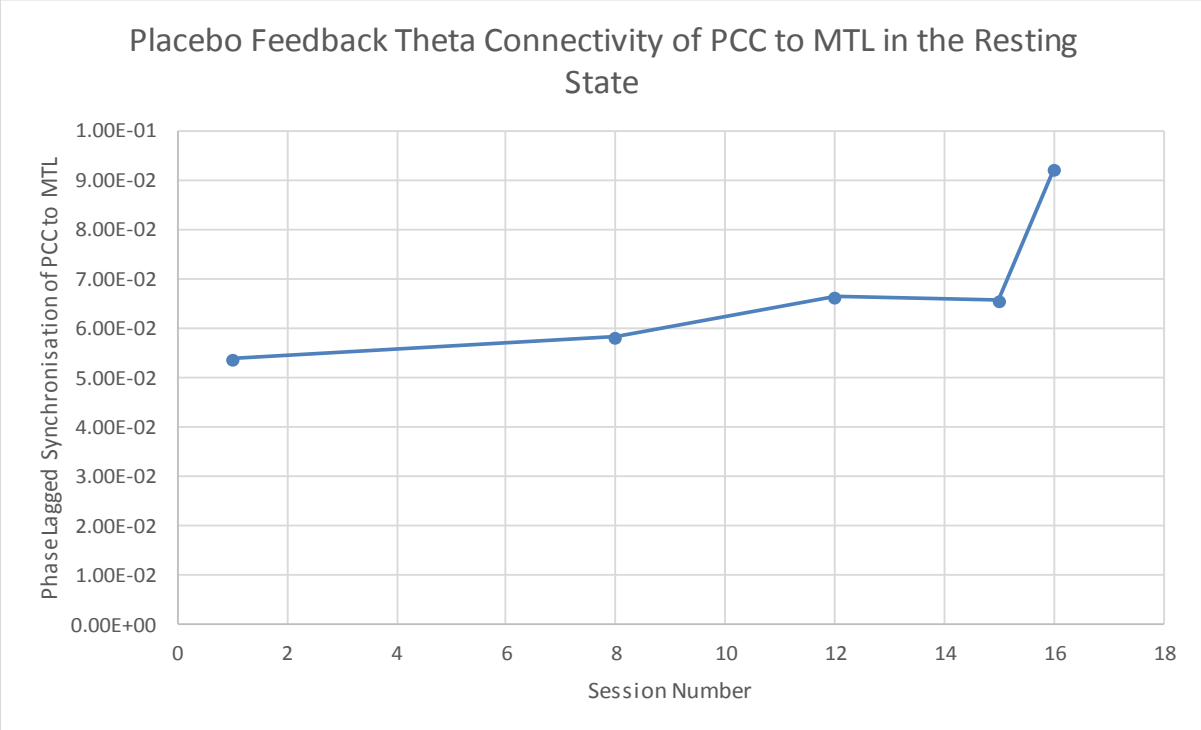


Figure 5-24 Change in the group level theta 1 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the placebo feedback group.

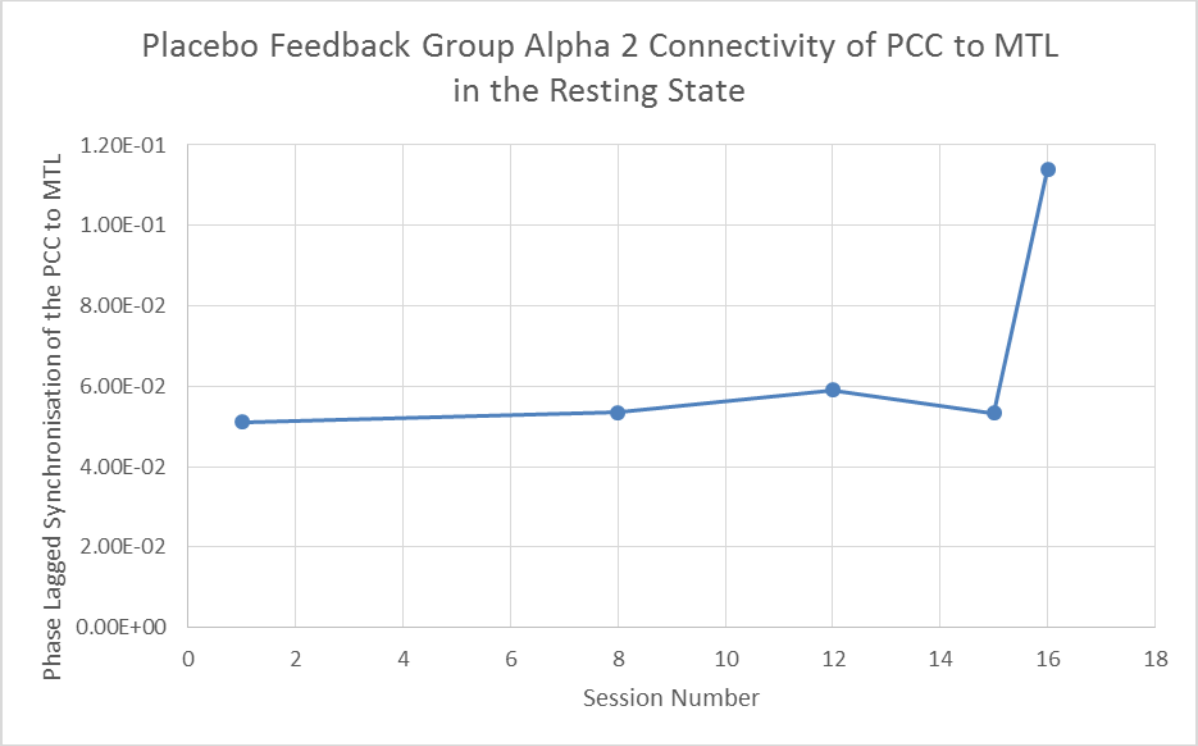


Figure 5-25: Change in the group level alpha 2 band phase lagged synchronisation between the PCC and the parahippocampal gyrus in the resting state over time in the placebo feedback group.

Chapter 6 Exploratory Analyses

Aim

The aim of this chapter is to describe the results of secondary analyses conducted on the data of the randomised controlled trial. The design of the trial is described in chapter 5. These analyses are exploratory in nature, designed to generate hypotheses for future study. This corresponds to the 4th stated aim of the biofeedback trial in chapter 5, which was to identify EEG biomarkers using sLORETA which correlate to changes in memory that could be used to track progress in future biofeedback trials. In addition, there are some further analyses of the primary outcome presented to control for the emergent form effect on the RBANS As such, the results described below have been separated from the definitive results described in chapter 5.

Method of Analysis

Bivariate Correlation of EEG parameters and baseline cognitive scores

The bivariate correlation was carried out between the baseline immediate memory index and the baseline delayed memory index for both participants in the trial and the 'normal brain' comparison group with the following EEG parameters:

1) baseline current density of the PCC in four frequency bands (theta, alpha 1, alpha 2 , beta 1)
2) baseline connectivity measured by phase lagged synchronisation of the PCC to the left parahippocampal gyrus in four frequency bands (theta, alpha 1, alpha 2, beta 1)

This correlation was performed for all the participants and for all the 'normal brain' control EEGs. A Bonferroni correction was applied to test the significance.

Baseline Seed Based Connectivity analysis

Baseline connectivity of the PCC to the rest of the brain was also assessed. This was done by placing a seed point in the PCC, and searching for significant changes in the phase lagged synchronisation of the PCC with the other 6329 voxels modelled by the sLORETA program. This was calculated for the 47 participants in the trial who had 'normal brain' matches and their matches separately. The

connectivity maps for the participants were then compared to the connectivity maps for the 'normal brain' matches, using the permutation technique described in chapter 3.

Seed Based Analysis by Group

The change in connectivity of the PCC between the baseline EEG and the immediate follow up resting state EEG was assessed. This was done by placing a seed point in the PCC and searching for significant changes with all the other voxels modelled by the sLORETA program. This was done for the immediate follow up and the baseline EEGs separately. Then a pairwise comparison of the immediate follow up and the baseline EEG was performed, using the permutation technique described in chapter three. This was calculated for each group separately. The sLORETA brain mapping program can then locate the voxels which have the greatest change in connectivity to the PCC.

This process was repeated for the 6 week follow up data.

Restricted Analysis of the Posterior Default Mode Network.

The default mode network has multiple functions, of which memory retrieval is just one (55). In order to assess for effects on parts of the default mode network specifically dedicated to memory, it was decided to restrict the connectivity analysis to nodes of the posterior default mode network (224). The locations and MNI coordinates of these nodes can be found in Table D-1 in Appendix D1. The phase lagged connectivity between the five nodes was assessed using the default mode connectivity analysis method given in chapter 3, but using five regions of interest instead of 11. This was done comparing the immediate post training EEG to the baseline resting state EEG, and also comparing the 6 week follow up EEG to the baseline EEG.

Correlation of Memory Change Scores to Changes in EEG Parameters

The immediate memory index score from the pre training test was subtracted from the immediate follow up score and the 6 week follow up score, and the immediate follow up score was subtracted from the 6 week follow up score. The same set of subtractions was performed for the delayed

memory index. These three change scores were then entered into a bivariate correlation matrix with two levels. The first level assessed the correlation between the change scores and the changes in the EEG indices that had demonstrated a significant change in chapter 5. These scores were the change in the in-training beta 1 connectivity index in the broadband feedback group, the change in the in-training beta 1, in-training alpha 1 activity, and in-training theta activity in the broadband feedback group, the difference between the 6 week post follow up alpha 1 connectivity and average connectivity in the broadband feedback group, the difference in 6 week follow up beta 1 connectivity and average connectivity in the narrow band feedback group, and the difference between 6 week follow up theta connectivity in the placebo group. This first level of analysis was performed separately for each of the randomisation groups.

The second level assessed all the EEG indices scores against the changes in the immediate memory and delayed memory scores. All 54 participants who completed the training were assessed together. We assessed these at the $p=0.05$ level, without adjusting for multiple comparisons, as this stage was a hypothesis generation stage.

A third level of correlation was included to bring complete the analysis of validity (138-140). This was done by correlating the change in the delayed and immediate memory scores to the change in the EEG characteristics. Specifically, the variables in the table D-2 in appendix D2 were correlated with each other. This was done in each of the broadband, narrowband, and placebo feedback groups separately to see if different exposure would result in a different relationships between EEG variables and cognitive outcomes.

This analysis results in a 6 (memory) by 24 (EEG) variable correlation matrix, every correlation with a significance of $p<0.05$ is reported here. However, consideration of appropriate significance thresholds would be required for validating potential correlations. The data for the participant in the placebo group who did not complete the 6 week follow up was not included in this analysis.

Analysis of Responders vs Non-Responders

An analysis was carried out comparing 'responders' who appeared to have a greater change in their memory score to 'non responders' who did not appear to improve after training. An arbitrary threshold of 10 points difference was applied to define responders and non-responders. In order to control for the form effect, the difference between the 6 week follow up score and the pre training score in the immediate memory index was used, as the difference between the forms was less at this time point. The responders in both the broadband and the narrowband feedback groups were then compared to non-responders with respect to the following variables:

- Baseline variables
    - Age
    - Sex
    - Years of education
    - Initial RBANS form
    - Baseline immediate memory score
    - Baseline delayed memory score
- EEG variables
    - Baseline current density in the PCC in the theta, alpha 1, alpha 2 and beta 1 bands
    - Baseline phase lagged synchronisation of the PCC in the theta, alpha 1, alpha 2 and beta 1 bands
    - Regression of change in current density in the PCC over time, for both the resting state and the in-training data, in the theta, alpha 1, alpha 2 and beta 1 bands
    - Regression of the change in the phase lagged synchronisation of the PCC to the parahippocampal gyrus over time, for both the resting state and the in-training data, in the theta 1, alpha 1, alpha 2 and beta bands

- Change in the phase lagged synchronisation of the PCC to the parahippocampal gyrus between the 6 week follow up resting state recording and the average of the other resting state recordings, in the theta, alpha 1, alpha 2 and beta 1 bands

This analysis was then repeated with the broadband and narrowband feedback groups separately.

The statistical significance of the differences found between the 'responders' group and the 'non responders' group was assessed using independent group t-tests.

Further Analyses of the Change in Immediate Memory score.

It is clear that there was a form effect which had a significant impact on the change in immediate memory index. In order to remove this effect, two additional exploratory analyses were planned, in order to see whether an effect in immediate memory would be found if the form effect were removed.

Stratified analysis

A mixed model was generated for people who started on form A and form B separately. The participants' group and time were entered as fixed effects. The model was unstructured, so that the broadest possible assumptions about the distribution of scores could be made. Any second order effect (a group*time interaction), in either the group A or group B would provide evidence for a genuine effect for biofeedback training.

Adjusted Analysis

We assumed that the difference between the changes in score of those who moved from form A to form B compared to those who moved from form B to form A was caused only difference between the forms. Therefore, a weighted average change in the placebo group was calculated using the following formula.

$$Weighted\ Average = \frac{n_B}{n_t}\Delta_a + \frac{n_A}{n_t}\Delta_b$$

Where n_t=total number of people in placebo group

n_A=Number of people in the placebo group who started on form A

n_B=Number of people in the placebo group who started on form A

Δ_A=Average change in score between the pre training and immediate follow up in the immediate memory index for participants who started on form A

Δ_B=Average change in score between the pre training and immediate follow up in the immediate memory index for participants who started on form B

The average change in score for those in form A was then compared to this weighted average to calculate the expected gain from starting on form A. This difference was labelled the adjustment for A. This was also done with the average change in score for those who started on form B, to produce the adjustment for B. The score for the immediate memory at immediate follow up was then adjusted, those who started on form A with the adjustment for form A, and those on form B with the adjustment for form B. 6 week follow up scores were not adjusted, as the changes from baseline comparing form A to form B were not largely different.

A mixed model was then generated from this adjusted data. Randomisation and time were entered as fixed effects. A second order interaction (a group*time effect) would provide evidence for a real effect of the biofeedback training.

Results

Correlation of Baseline EEG parameters with Baseline Cognitive Score

Bonferroni adjustment set a significance level of 0.003125. Table D-2 in Appendix D2 shows the Pearson correlation and p values for each of the correlations performed.

A significant correlation between the delayed memory index and the connectivity between the PCC and the parahippocampal gyrus in the theta band was found (r=-0.271, p=0.003). Figure 6-1 below shows a scatter graph of the delayed memory index scores against the phase lagged synchronisation of the connection. As the connectivity in the theta band increases, the delayed memory scores tend to decrease.

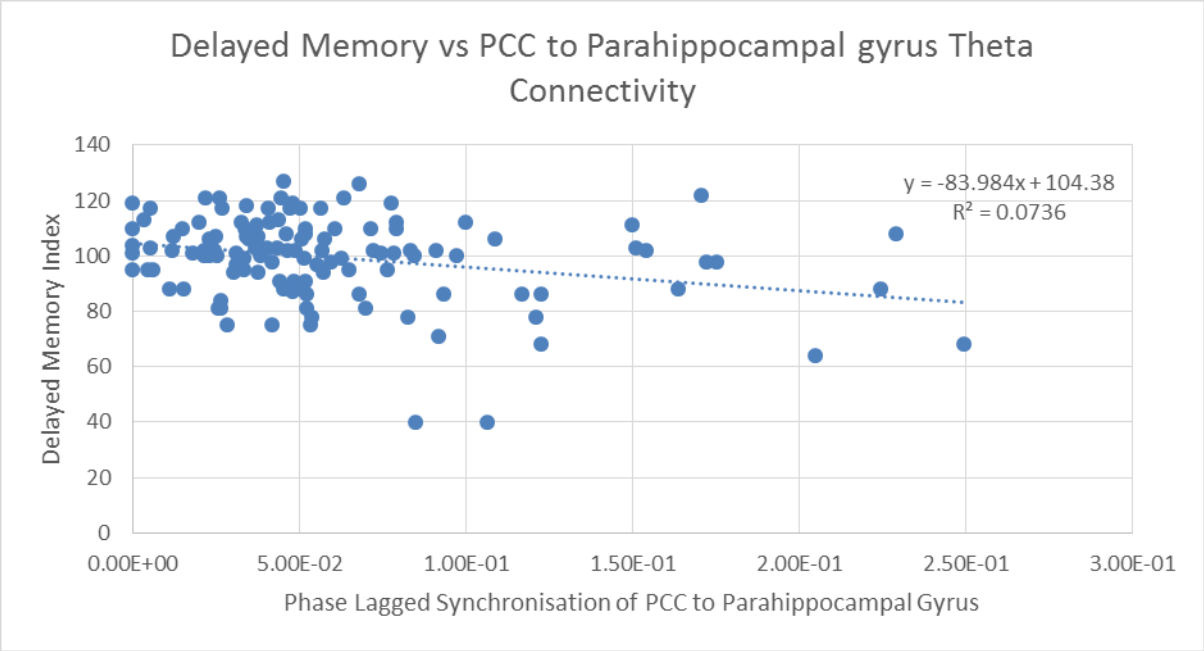


Figure 6-1 Scatterplot of score on the delayed memory index of all screened volunteers and the phase lagged synchronisation of the PCC to the parahippocampal gyrus

Seed point based Connectivity at Baseline

At baseline there were no statistically significant changes found in the connectivity of the PCC to the other parts of the brain in the participants when compared to the 'normal brain' controls. The images in Figure D-1 in Appendix D3 show the highest magnitude differences in connectivity (p=0.12)

Seed point based Connectivity Baseline to Immediate Follow Up

Broadband Feedback Group

In the broadband feedback group the change in one voxel in one frequency band was found to be significant ($p<0.0001$). The image showing this is presented in Figure 6-2 below.

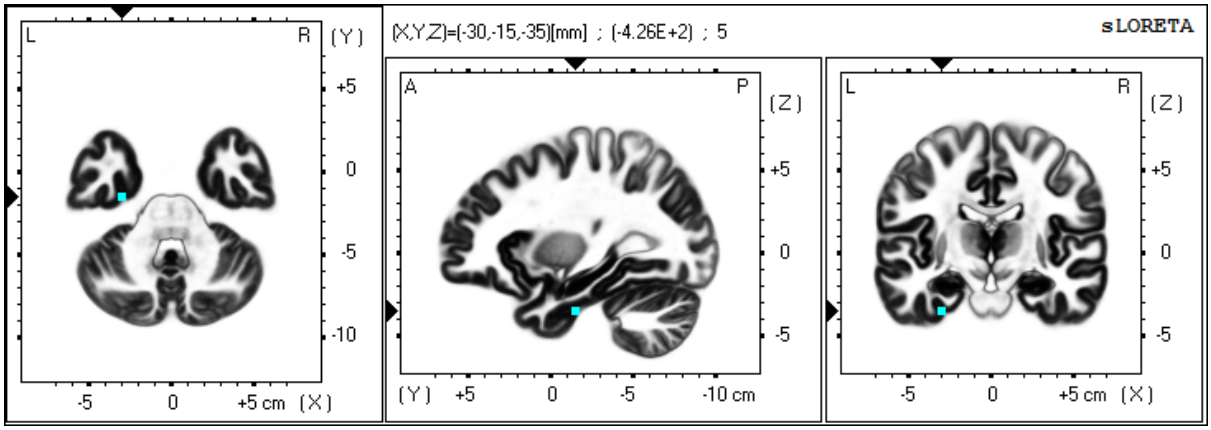


Figure 6-2: Map of PCC seed based phase lagged synchronisation changes from baseline to immediate follow up in the broadband feedback group. There was a voxel with a decrease in the left uncus

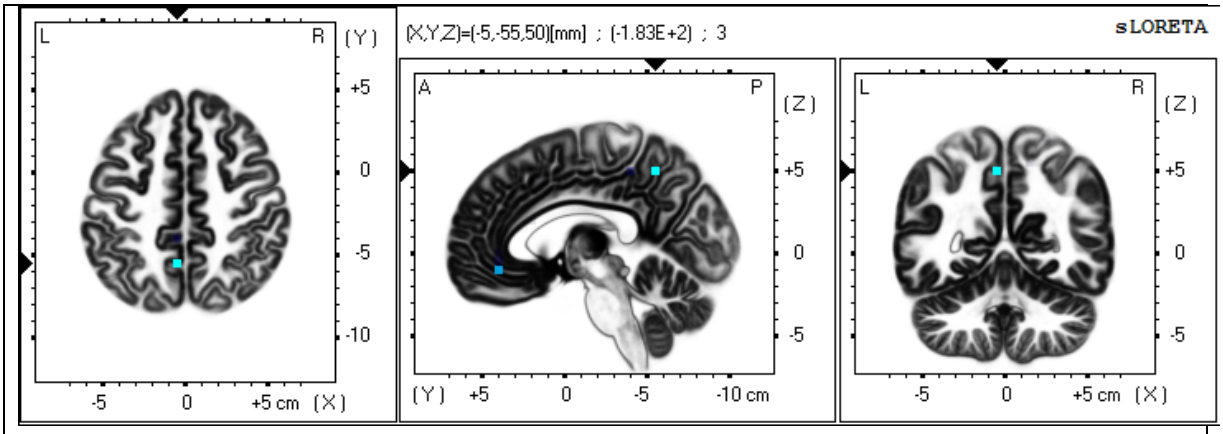
This voxel was located in the left uncus, a region of the medial temporal lobe. It shows significantly decreased connectivity with the PCC in the beta 1 band at immediate follow up compared to baseline. No other voxel in any other frequency band showed significant changes.

Narrowband Feedback Group

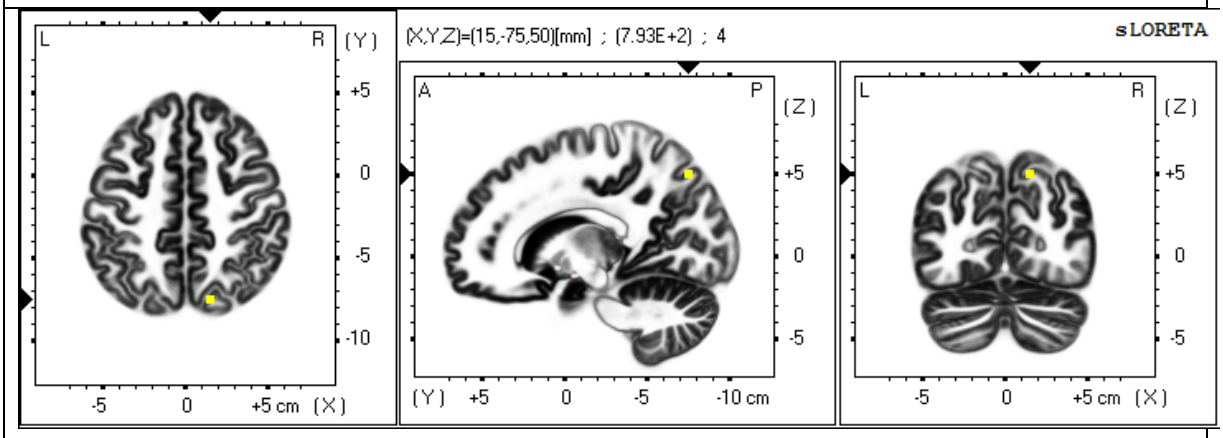
No significant changes in the PCC's connectivity were found compared to baseline. Figure D-2 in appendix D4 show the changes in connectivity at follow up compared to baseline at the $p=0.74$ level.

Placebo Feedback Group

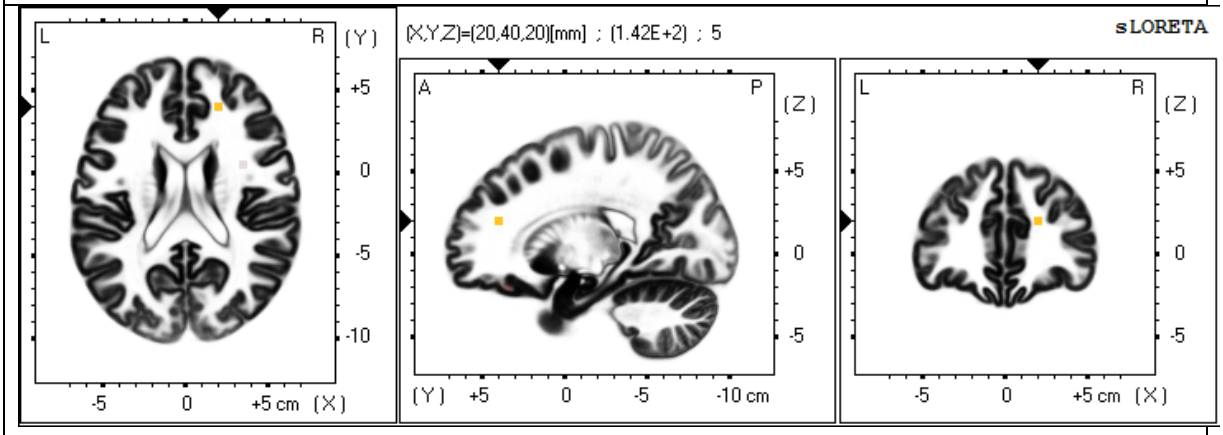
Significant changes in the connectivity of the PCC at immediate follow up compared to baseline were found. These changes are shown in the images in Figure 6-3.



Alpha 1 band



Alpha 2 band



Beta 1 band

Figure 6-3 Map of PCC seed based phase lagged synchronisation changes from baseline to immediate follow up in the placebo feedback group.

In the alpha 1 band, there were significant decreases in connectivity between the PCC and the precuneus, and the PCC and the Anterior Cingulate ($p<0.0001$). In the alpha 2 band there was a significant increase in connectivity between the PCC and the precuneus ($p<0.0001$). In the beta 1

band there was a significant increase in connectivity between the PCC and the Medial frontal Gyrus (p<0.0001).

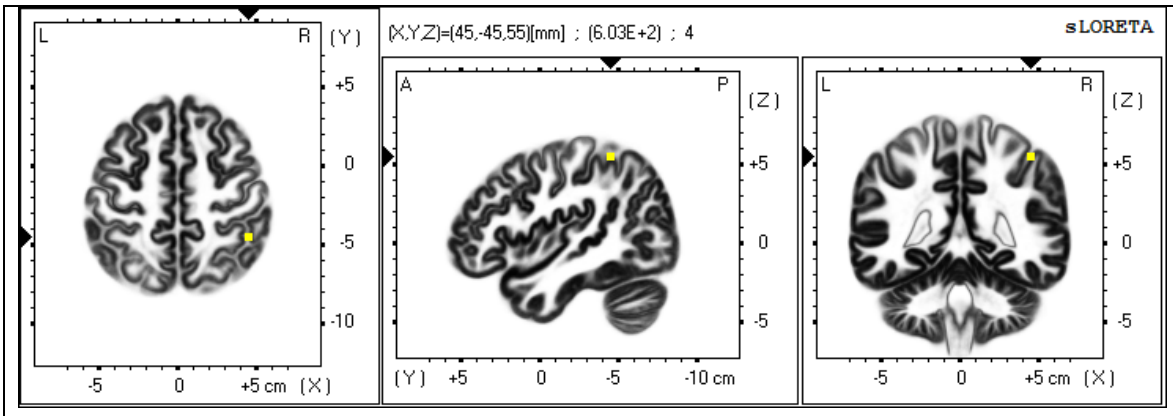
Seed based Connectivity Baseline to 6 week Follow Up

Broadband Feedback Group

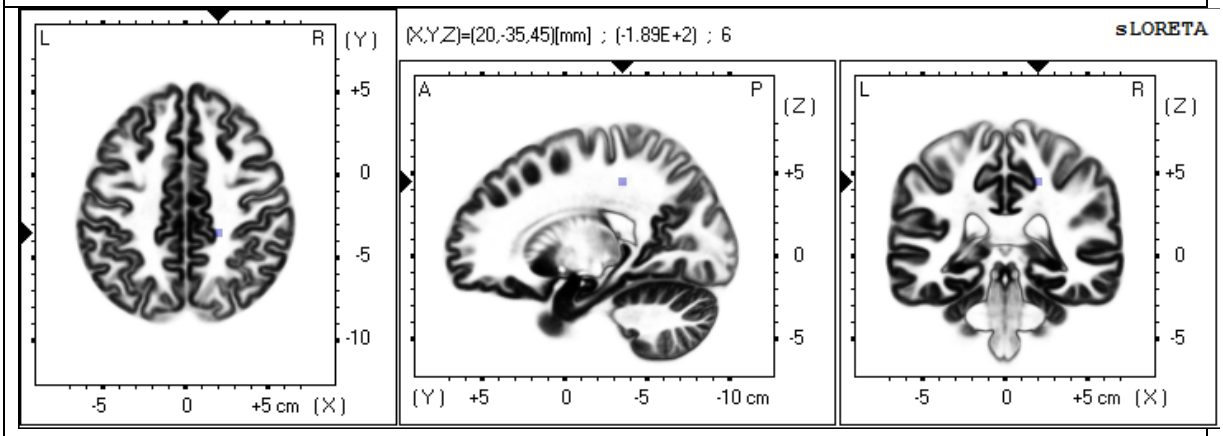
No significant changes were found in the connectivity changes were found in the broadband feedback group using the seed based modelling technique.

Narrowband Feedback Group

Significant changes were found in the narrowband feedback group in the alpha 2 and beta 2 bands (p<0.0001). Images showing the most significant voxels are show in the Figure 6-4 below. No other significant changes were found in other bands.



Alpha 2 band

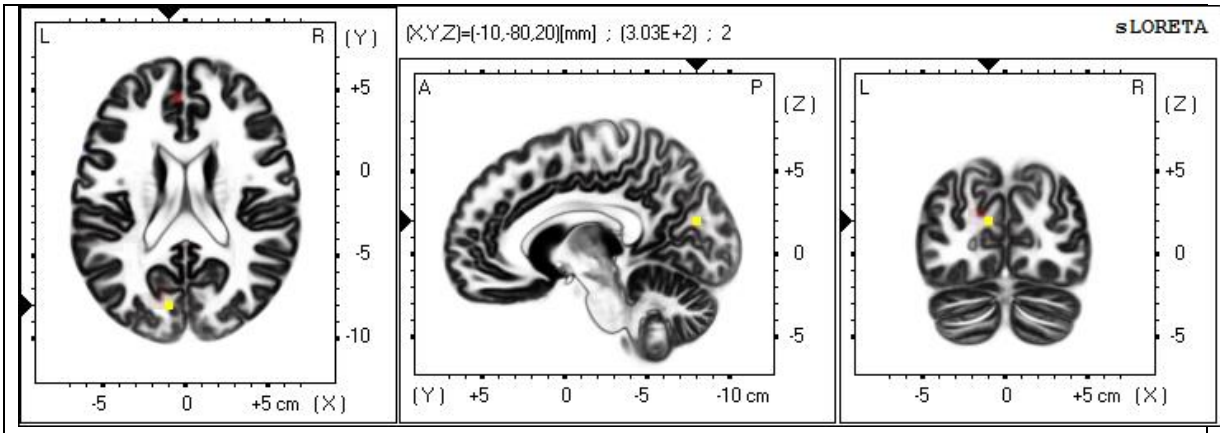


Beta 2 band

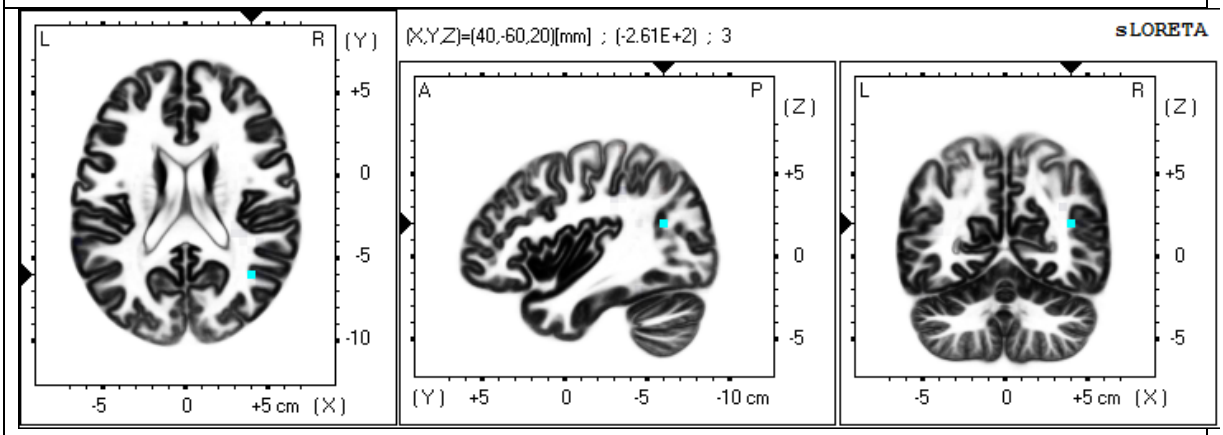
Figure 6-4 Map of PCC seed based phase lagged synchronisation changes from baseline to 6 week follow up in the narrowband feedback group.

Placebo Feedback Group

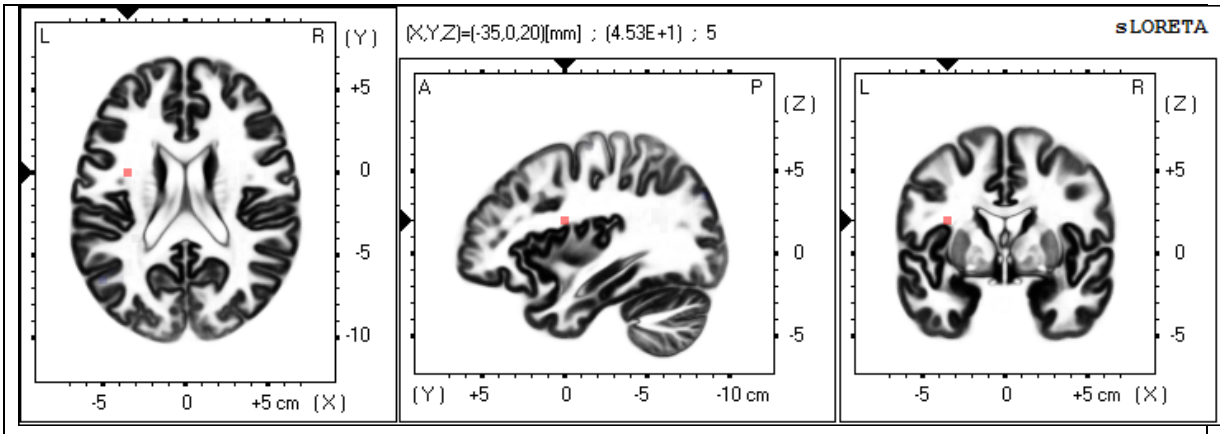
Significant changes were found in the theta, alpha 1 and beta 1 bands ($p<0.0001$). Images showing the most significant voxels are shown below. No other voxels in other bands were found to be significant. Changes are shown in figure 6-5 below.



Theta band



Alpha 1 band



Beta 3 band

Figure 6-5 Map of PCC seed based phase lagged synchronisation changes from baseline to 6 week follow up in the placebo feedback group.

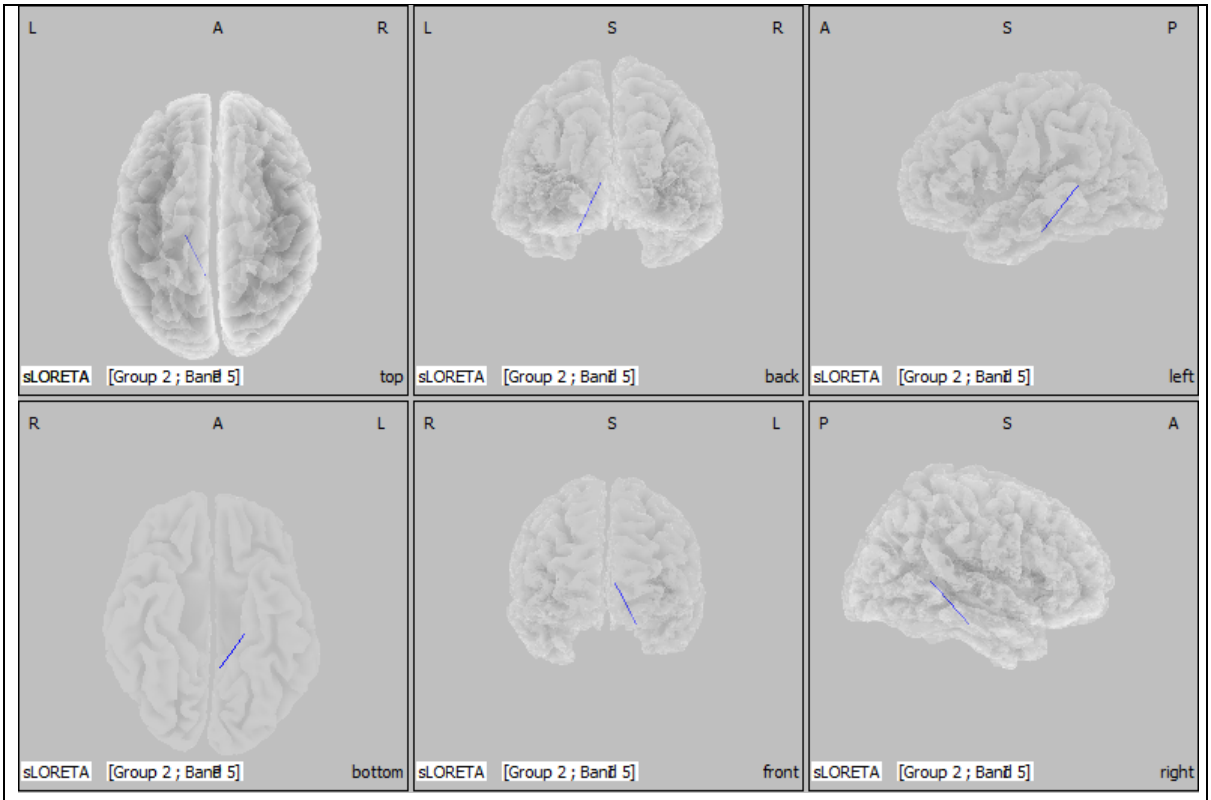
Posterior Default Mode Analysis

Broadband Feedback Group

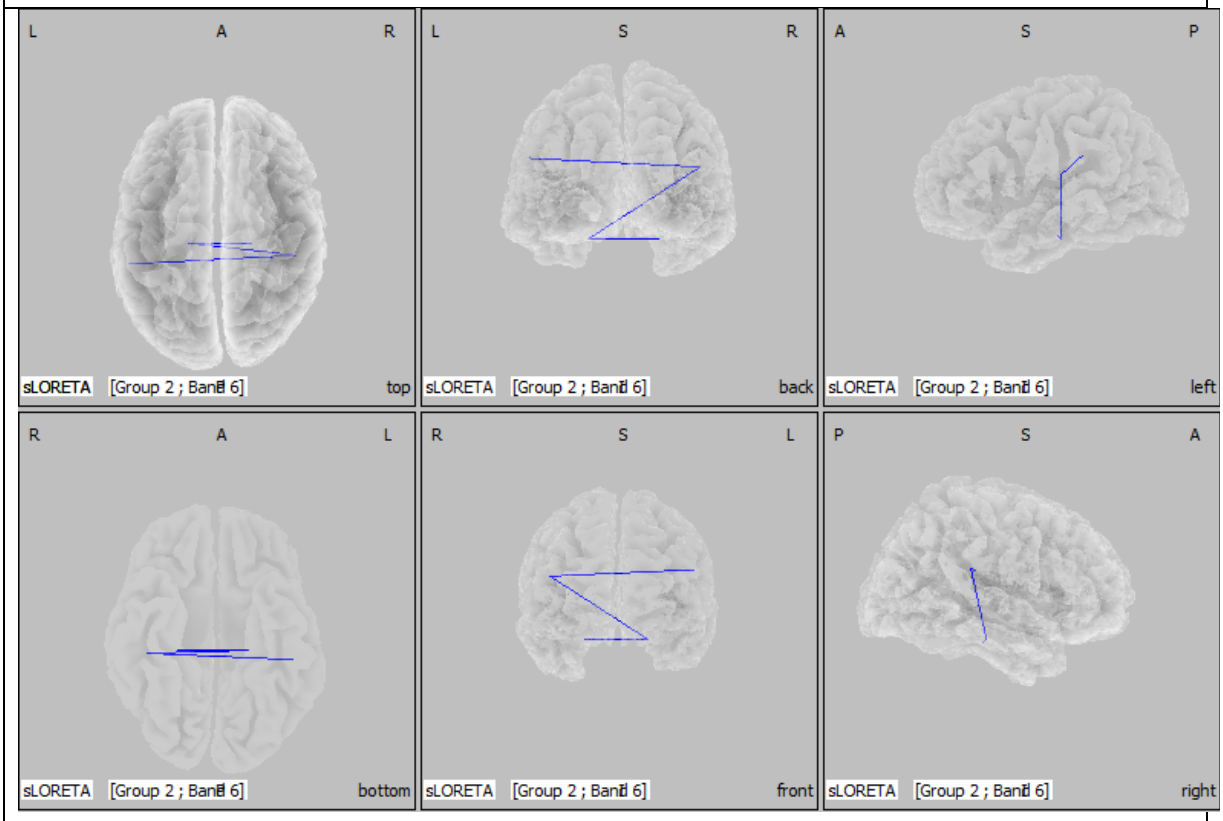
No significant changes in the connectivity of the posterior default mode network were found comparing the immediate follow up recording to the pre training recording. Images showing the changes in connectivity at the p=0.071 level are found in Figure D-3 in appendix D5.

Narrowband Feedback Group

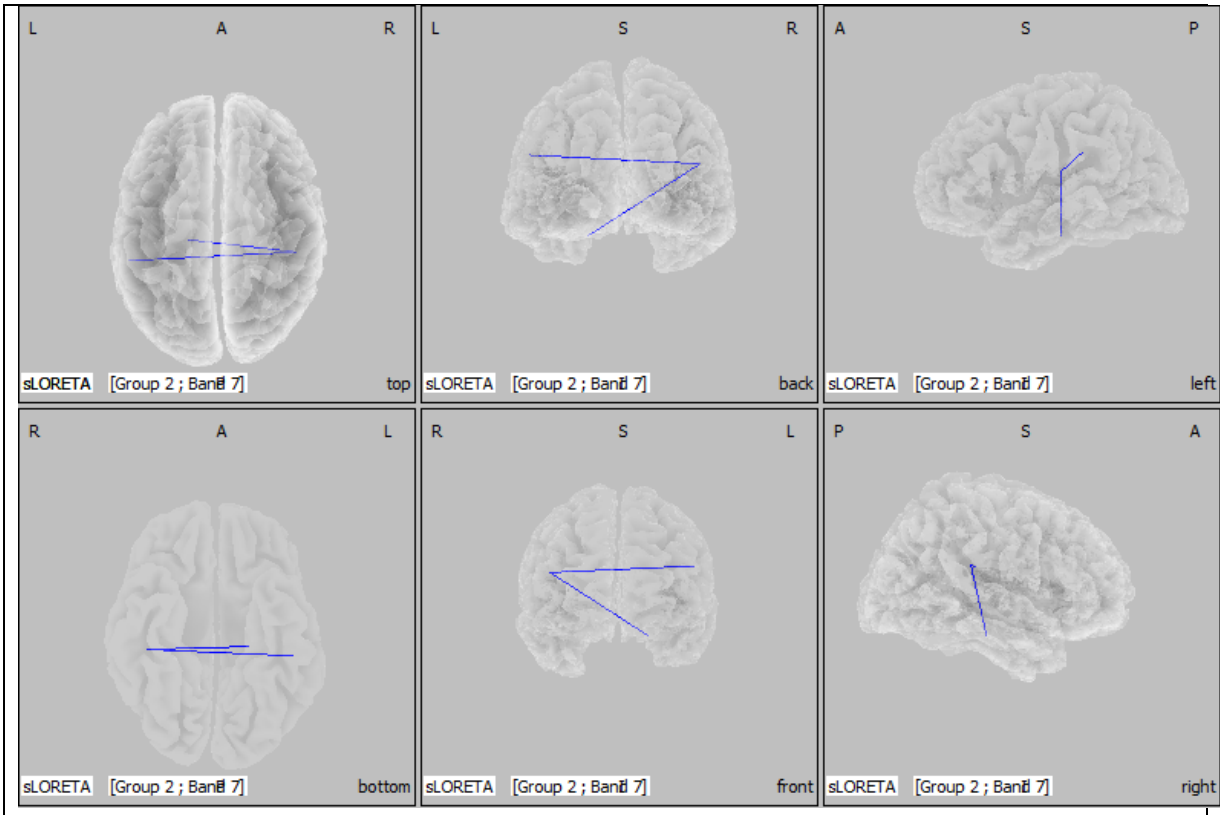
Significant changes were found in the connectivity of the posterior default mode network were found in this group. Images showing these changes (p=0.05) are found in Figure 6-6 below.



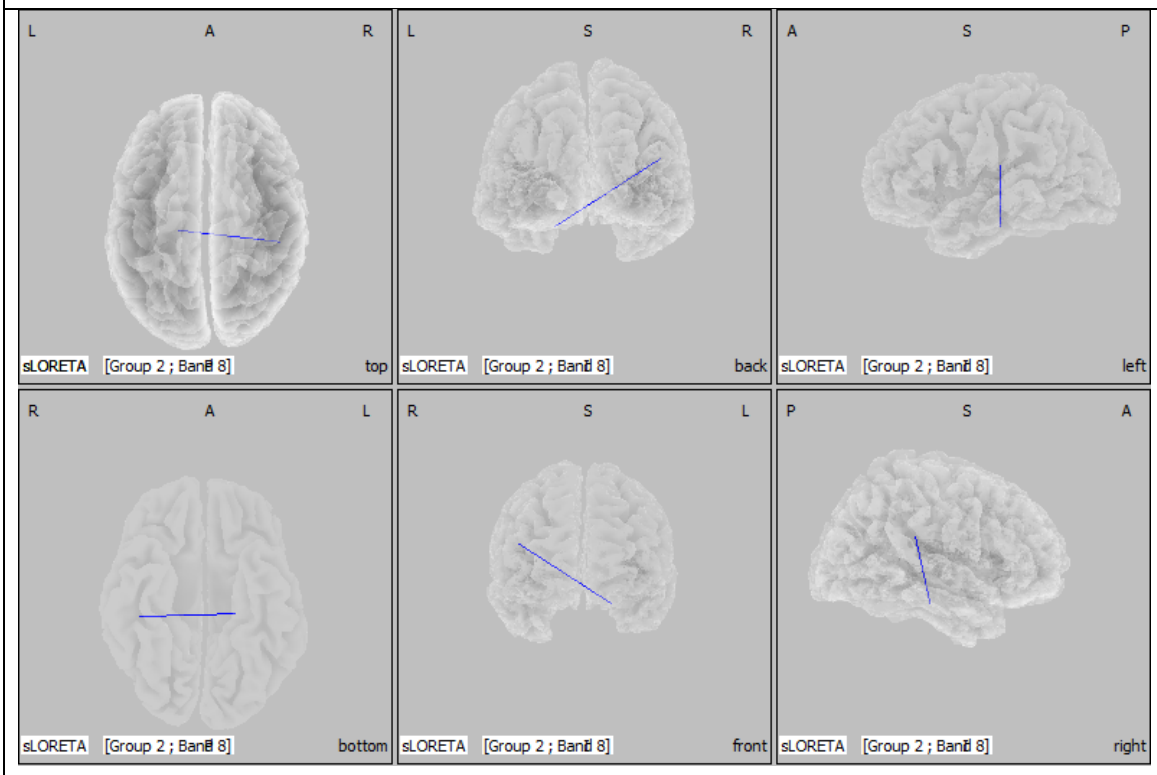
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure 6-6: Changes in the posterior default mode network phase lagged synchronisation from baseline to immediate follow up in the narrowband feedback group

There was a decrease in connectivity between posterior default mode nodes at immediate follow up compared to baseline in the beta 1, beta 2, beta 3 and omega bands. Most strikingly there was a decrease in connectivity between the PCC and the left parahippocampal gyrus.

Placebo Feedback Group

No significant changes in the connectivity of the posterior default mode network were found. Images showing the changes in connectivity at the p=0.471 level are found in figure D-4 in appendix D5.

Correlation of Change in Memory Scores and Change in EEG parameters

No significant correlations were found in at the first level of correlation analysis. This means that the changes in the electrical activity which were measured as significant compared to baseline were not correlated with the changes observed in the memory score.

At the second level of correlation analysis, three significant correlations were found. The first was a significant correlation between the resting alpha 1 activity and the difference between the 6 week follow up training score and the pre training score in the immediate memory index (r= -0.292, p=0.034). The second correlation that arose was between the resting connectivity in the beta 1 band and the difference between the immediate follow up and the pre training score in the immediate memory index (r=0.358, p=0.008). Finally the difference between the 6 week follow up resting state recording and average connectivity in the alpha 1 band correlated with the difference between the immediate follow up score and the pre training follow up in the immediate memory index.

The results of the third level of correlation analysis are separated out by participant group below.

Broadband Feedback group

Between Session measures

A significant correlation was found between the correlation coefficient of resting state theta phase lagged connectivity of the PCC to the MTL and the difference between the immediate follow up memory index and the pre-training memory index (β=0.647, p=0.004). A significant correlation was

also found between the correlation coefficient of resting state theta phase lagged connectivity of the PCC to the MTL and the difference between the 6 week follow up immediate memory index and the immediate follow up immediate memory index (β=-0.499, p=0.035).

A significant correlation was found between the correlation coefficient of resting state alpha 2 phase lagged connectivity of the PCC to the MTL and the difference between the 6- week follow up memory index and the pre-training immediate memory index (β=-0.499, p=0.035).

A significant correlation was found between the correlation coefficient of resting state theta phase lagged connectivity of the PCC to the MTL and the difference between the 6 week follow up and the immediate follow up delayed memory index (β=0.517, p=0.028).

Within Session measures

A significant correlation was found between the within session change of theta current density and the difference between the immediate follow up memory index and the pre-training immediate memory index (β=-0.552, p=0.018).

A significant correlation was found between the within session change of beta phase lagged synchronisation between the PCC and MTL and the difference between the 6 week follow up memory index and the pre-training delayed memory index (β=-0.495, p=0.037).

Narrowband Feedback Group

Between Session measures

A significant correlation was found between the correlation coefficient of training theta phase lagged connectivity of the PCC to the MTL and the difference between the 6- week follow up memory index and the immediate follow up immediate memory index (β=0.570, p=0.017).

A significant correlation was found between the correlation coefficient of resting state alpha 2 phase lagged connectivity of the PCC to the MTL and the difference between the 6- week follow up memory index and the immediate follow up delayed memory index (β=0.492, p=0.045). A significant correlation was found between the correlation coefficient of resting state alpha 2 phase lagged

connectivity of the PCC to the MTL and the difference between the 6- week follow up memory index and the pre training delayed memory index (β=0.812, p<0.001).

Within Session measures

A significant correlation was found between the within session change of alpha 2 current density and the difference between the immediate follow up memory index and the pre-training immediate memory index (β=-0.495, p=0.044). A significant correlation was also found between the within session change of alpha 2 current density and the difference between the 6 week follow up memory index and the pre-training immediate memory index (β=-0.672, p=0.003).

Placebo Feedback Group

Between Session measures

A significant correlation was found between the correlation coefficient of training theta phase lagged connectivity of the PCC to the MTL and the difference between the immediate follow up memory index and the pre-training immediate memory index (β=0.525, p=0.025).

A significant correlation was found between the difference in the alpha 2 connectivity in the 6 week follow up session and the average of the other sessions, and the difference between the 6 week follow up and the immediate follow up immediate memory index (β=-0.515, p=0.029).

Within Session measures

A significant correlation was found between the within session change of beta 1 current density and the difference between the immediate follow up memory index and the pre-training immediate memory index (β=-0.639, p=0.006). A significant correlation was also found between the within session change of beta 1 current density and the difference between the 6 week follow up memory index and the immediate follow up immediate memory index (β=-0.588, p=0.013).

A significant correlation was found between the correlation coefficient of training beta 1 phase lagged connectivity of the PCC to the MTL and the difference between the immediate follow up memory index and the pre-training immediate memory index (β=0.523, p=0.031). A significant correlation was found between the correlation coefficient of training beta 1 phase lagged

connectivity of the PCC to the MTL and the difference between the 6 week follow up memory index and the immediate follow up immediate memory index (β=0.579, p=0.015).

Responders vs Non-Responders

There were 12 people classified as responders in the broadband feedback group, 11 in the narrow band feedback group. For comparison, there were six participants classified as responders in the placebo feedback group. There were no significant differences found in the baseline variables, nor in the baseline EEG data.

There was a significant difference in the change in current density in the alpha 2 band between all the responders and the non-responders. The regression coefficient was 0.034 higher in the non-responders compared to the responders group (t_{33}=2.276, p=0.029). This indicates that the increase in the alpha 2 current density in the PCC was higher in the non-responders compared to the responders. No other significant differences were found in the EEG variables.

No significant difference was found between the responders and non - responders when analysis was restricted to either the broadband feedback group only or the narrowband feedback group only.

Further mixed model analyses of the change in immediate memory.

Stratified analysis

In the participants who started on form A, a significant first order effect with respect to time was found (p<0.001). No significant first order effect with respect to group was found (p=0.597). Furthermore, no significant second order effect was found (p=0.655 for a group*time interaction).

The post hoc testing showed that in all groups in group A, there was a significant difference in the immediate memory score within the group between the pre training and immediate post training session, and between the pre training and 6 week follow up score, but no difference was found between the immediate follow up score and the 6 week follow up score. See table 6-1 below for details

In the participants who started on form B, a significant first order effect was also found with respect for time ($p<0.001$). No significant first order effect was found with respect to group ($p=0.779$). Also, no significant second order effect was found ($p=0.231$ for a group*time interaction).

Post hoc testing in group B revealed that in the all of the groups, within each group there was no significant difference between the pre training and the immediate post training score. In the broadband feedback group there was a significant difference between the pre training and the 6 week follow up score but no significant difference between the immediate follow up and the 6 week follow up. In the narrow band feedback group, there was a significant difference between the pre training 6 week follow up, and a significant difference between the immediate follow up and the 6 week follow up. There were no significant differences between any time points in the placebo feedback group. See table 6-1 on the next page.

Table 6-1: Change in the immediate memory score stratified by Randomisation, and RBANS form

	Mean Difference Pre training to Immediate	Significance	Mean Difference Immediate follow up to 6 weeks follow up	Significance	Mean Difference Pre training to 6 week follow up	Significance
Broadband Feedback group A	16.1	<0.001	0.1	0.976	16.2	<0.001
Narrowband Feedback group A	14.5	<0.001	-2.1	0.507	12.3	<0.001
Placebo Feedback group A	16.1	<0.001	-5.8	0.068	10.3	0.002
Broadband Feedback group B	6.3	0.141	8.0	0.059	14.3	<0.001
Narrowband Feedback group B	-4.0	0.406	16.5	0.002	12.5	0.003
Placebo Feedback group B	-3.6	0442	9.3	0.057	5.7	0.135

Neither people who started on form A nor people who started on form B showed significant second order effects, suggesting that there was no significant treatment effect when using this form of analysis to adjust for the form effect.

Adjusted Analysis

A significant first order effect was found with respect to time ($p<0.001$). There was no significant first order effect with respect to group ($p=0.826$). No second order effect was observed ($p=0.255$ for a group*time interaction).

Post hoc analysis revealed that in the broadband feedback group there was a significant increase in the immediate memory score between the pre training and the post training scores. There was also significant differences between the pre training and the 6 week follow up score, and the immediate follow up and the 6 week follow up score. The narrow band feedback group did not have a significant change from pre training to immediate follow up, but did have a significant increase pre-training to 6 week follow up, and from immediate follow up to the 6 week follow up. The placebo feedback group had a significant increase from immediate follow up to 6 week follow up and from pre training to 6 week follow up, but no significant increase from pre training to immediate follow up. See table 6-2 below.

Table 6-2: Change in Immediate memory score after adjustment for RBANS form effect

	Mean Difference Pre training to Immediate	Significance	Mean Difference Immediate follow up to 6 weeks follow up	Significance	Mean Difference Pre training to 6 week follow up	Significance
Broadband feedback group	7.3	0.008	8.0	0.004	15.3	<0.001
Narrowband feedback group	1.7	0.528	10.7	<0.001	12.4	<0.001
Placebo feedback group	2.9	0.279	5.7	0.04	8.6	0.001

This would suggest that the maximum treatment effect, assuming there was no effect carried over past the cessation of training, was 4.4 points on the immediate memory index, seen in the broadband feedback group, adjusting for the form effect between form A and form B.

Analysis of Form Effect

In each graphs below, the group that started on form A increased between the pre training and immediate follow up immediate memory score, but did not have as marked an increase between the pre training and the 6 week follow up score. In contrast, the group that started on form B did not increase between the pre training and immediate follow up score, but had a more marked increase between the immediate follow up score and the 6 week follow up score. The graphs in Figure 6-7 to

6-9 corroborate the linear modelling findings described in chapter 5. This results in a difference emerging between the group that started on form A and the group that started on Form B at the immediate follow up time point, and the disappearance of this difference at the 6 week follow up time point. This pattern was present in both the active groups. The changes in the placebo group were of a lower magnitude, but in the same direction as that seen in the active groups. . This indicates some degree of test retest bias on top of the form effect.

The correlation coefficient of pretraining vs 6 week follow up immediate memory score of 0.552, indicating a moderate degree of correlation between the scores. Across the whole 52 participants who completed the 6 week follow up, the scores increased on average 10.4 points between the pre training score and the 6 week follow up. This indicates a moderately reliable increase in the immediate memory score in this situation.

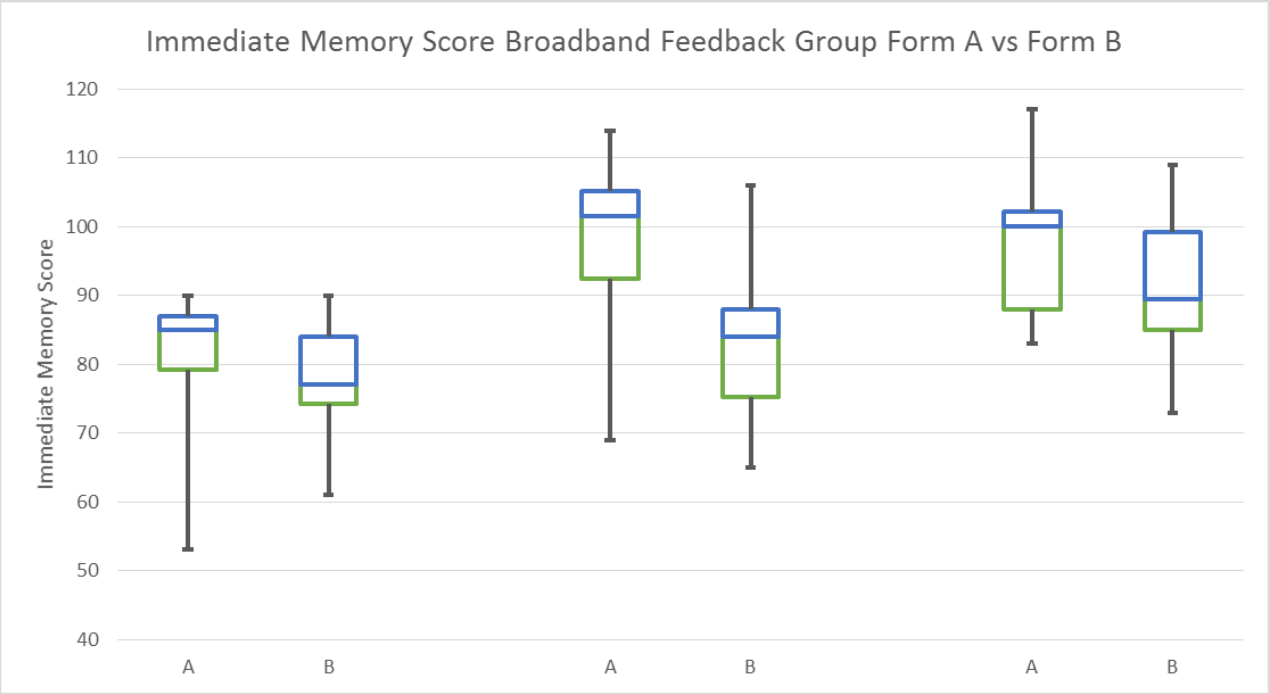


Figure 6-7: Boxplot of Immediate Memory score at pre-training, immediate follow up and 6 week follow up separated by RBANS form in the broadband feedback group

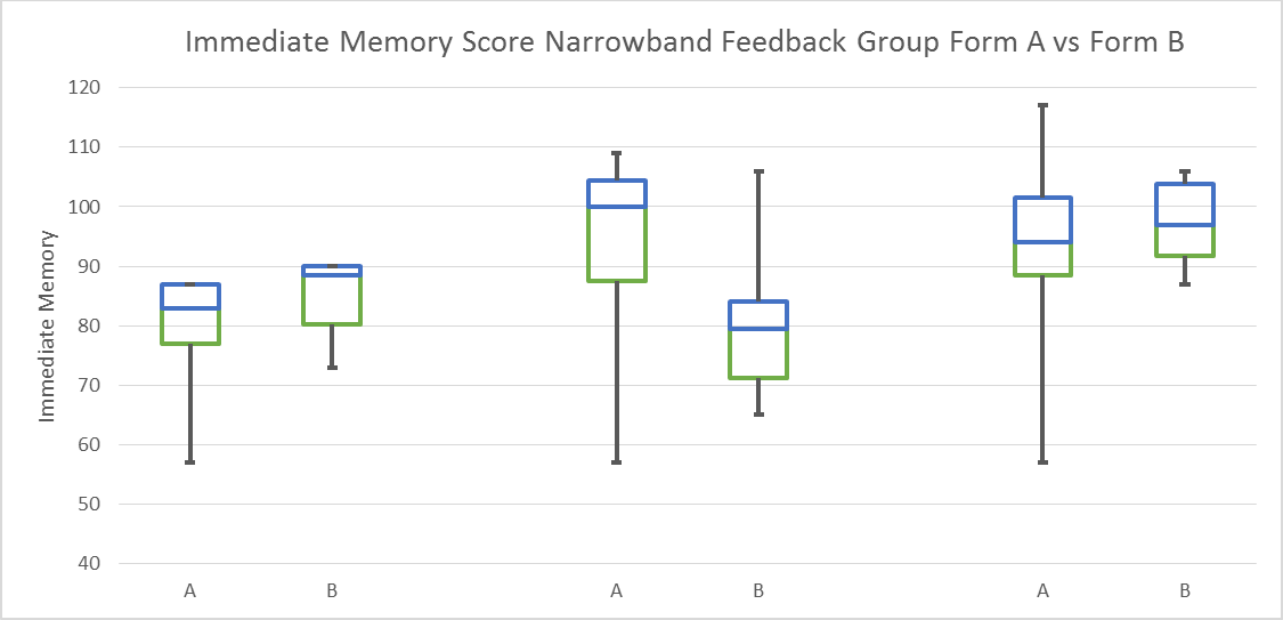


Figure 6-8 Boxplot of Immediate Memory score at pre-training, immediate follow up and 6 week follow up separated by RBANS form in the narrowband feedback group

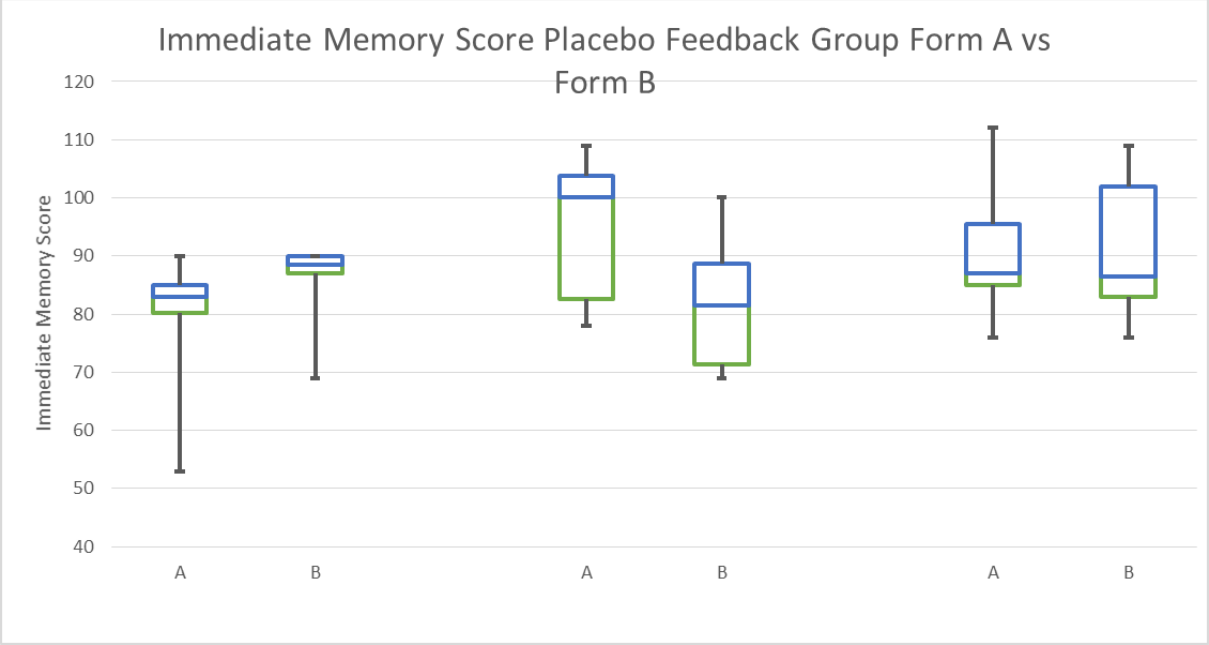


Figure 6-9 Boxplot of Immediate Memory score at pre-training, immediate follow up and 6 week follow up separated by RBANS form in the placebo feedback group

Chapter 7 Discussion

Key Results of the Randomised Controlled Trial

- 223 volunteers were screened to take part in the trial. 68 participants met the inclusion criteria, and 53 of these completed all 15 training sessions
- No significant randomisation*time effect was found for either the Immediate Memory Index or the Delayed Memory Index. All groups had similar scores at immediate follow up and 6 week follow up
- A significant increase in the Alpha 1 activity in the narrowband feedback group was detected, suggesting some electrophysiological training had occurred.
- A significant increase in Beta 1 connectivity occurred in the broadband feedback group, and a significant increase occurred in the theta activity and beta in the narrowband feedback group, indicating non-training specific EEG changes had also occurred. No significant changes were found in the placebo group
- A significant difference in the level of difficulty between the different forms of the RBANS was found. Participants who started on form A and moved onto form B improved a lot more than participants who started on form B
- Non-specific changes in the resting state index at 6 week follow up in all three trial arms

Effect of Biofeedback Training on Immediate Memory

We found a first order effect on immediate memory with respect to time, but none with respect to randomisation, nor did we find a second order effect for a randomisation*time interaction. This means that the immediate memory scores changed over time, but this change was the same in each group. Post hoc testing of the change in immediate memory showed that this change was due to an increase between the pre training value and the immediate post training value, with very little change between the immediate post training value and the 6 week post training value. This difference was mostly due to the effect of switching between form A and form B of the RBANS. Because most people in the trial started on form A, and most people who started on form A scored

higher on form B at the immediate follow up session regardless of what treatment arm they were assigned to, this lead to the change in the immediate memory index seen over time. Therefore, it is unlikely that the biofeedback training had any real effect on participants' immediate memory recall ability.

Effect of Biofeedback Training on Delayed Memory

We found a first order effect in the delayed memory with respect to time, but no first order effect with respect to randomisation, nor a second order randomisation*time interaction. An approximately seven point increase in the delayed memory index was recorded in each group between the pre training score and the 6 week follow up score. In the broadband feedback group, the majority of this increase happened between the pre training and immediate follow up time points, in the narrowband feedback group and the placebo feedback training group, the majority of this change occurred between the immediate follow up score and the 6 week follow up score. Because the score increase was approximately the same in each group, it is more likely that the increase is attributable to form effects as discussed below, test retest bias and other unmeasured therapeutic factors, also discussed below.

Effect of Biofeedback training on other cognitive variables

Significant first order effects for time were found on linear modelling for the visuospatial and language indices. For the visuospatial index, a significant decrease was found in the broadband feedback group between the immediate follow up and the 6 week follow up period, whereas in the narrowband feedback group there was an increase in the visuospatial score between in the pre training test and the immediate follow up test. Both these changes were of a magnitude which we considered small, around 7-8 points on the RBANS scale. It is possible that significant time spent staring at a computer screen, as these participants had, might affect the participants' ability to process visual information, although this has been found not to affect visuospatial ability in children (238). Given that there was no change in visuospatial score in the placebo group, and the two training groups were affected differently, and the relatively poor localising ability of sLORETA in our

setup, it is possible that the changes in both the broadband feedback group and the narrowband feedback group represent real training effects of the different training protocols. It has been shown that training of alpha power in posterior electrodes can result in an increase in visuospatial ability (239). The effect seen in the narrowband feedback group could be a late or rebound effect of this phenomenon. Further careful study is required to evaluate whether this effect on visuospatial ability is a genuine effect of this kind of biofeedback training.

There was also a first order effect for time on the Language index score. The language index increased in the broadband feedback group and decreased in the narrowband feedback group between the pre training score and the 6 week follow up score. These are small absolute differences, and are unlikely to represent a clinically significant change in ability as a result of the training.

EEG Activity and Connectivity Outcomes

Comparison to matched 'normal brain'

No significant differences were found at baseline between participants who took part in the trial and the matched 'normal brain' controls. Our selection criteria into the study was very loosely based on MCI diagnostic criteria, which means we have a very heterogeneous cohort. This was done to increase the numbers of participants in the trial, given the sample was drawn from the Dunedin community; however it may have resulted in a cohort that was only very subtly different from the general population, and so the study was not powered to detect differences in the electrical activity between this cohort and the general population. This is also true for the group level analysis.

Change in Whole Brain Current Density Maps

No significant differences were found in the whole brain activity for the resting state recording between the pre-training recording and the immediate follow up recording. This is in line with what has been found with training of the PCC in the past. Activity remains unaffected by training of the PCC, whereas connectivity tends to change (134). Some significant changes were found between the 6 week follow up resting state recording and the pre training resting state recording in all of the

groups. However, the level at which these are significant has such a low spatial resolution means that the results are not very meaningful in reality.

Change in Default Mode Network Connectivity

No significant difference in the default mode connectivity between the cohort in the biofeedback training and the matched controls. Initially it was thought that people with decreased memory would have decreased connectivity of the default mode network, given the importance of the default mode network to memory as stated in the introduction. However, our study did not find any significant differences.

The biofeedback training was theorised to work by normalising abnormal connectivity, particularly in the default mode network. In order to assess whether this was happening at all, we looked at the general direction of changes rather than the specific changes which weren't statistically significant individually. If the training did normalise the connectivity, the changes seen between the pre training and immediate follow up would be in the opposite direction to the changes seen when comparing the participants in the trial to the 'normal brain' controls. In general, these results presented here do not support this trend. In the broadband feedback group, there was a reversal of the trend in the theta band but this was also true of the placebo feedback group. There was no reversal of trends seen in the narrowband feedback group. The mechanism of biofeedback using sLORETA feedback of the PCC does not appear to work through reversal of abnormal trends.

Other EEG Metrics

Significant trends were found in the in-training data of both the narrowband feedback group and the broadband feedback group. There was a significant trend in the beta connectivity of the PCC with the parahippocampal gyrus over time. In our hypothesis generation correlation matrix, a significant correlation was found between the beta connectivity in the resting state over time and the change in memory scores. This could mean that targeting beta 1 connectivity would lead more significant changes in memory in future studies.

A significant trend was found in the activity located in the PCC in the alpha 1 band in the narrowband feedback group. This is an interesting finding, because the activity in the alpha 1 band was a directly targeted by the biofeedback program. This was true for the in-training EEGs that were taken but not the resting state EEGs. This would seem to indicate that training of the PCC is possible with this sLORETA training technique; however two aspects of this training remain unproven. One is whether this training has any lasting impact on the EEG activity of the trainee. We found no evidence of this. The second aspect is whether training of the PCC can have an impact on the trainee's cognitive function. The evidence generated by this trial suggests that training of the alpha band has no impact on the cognitive functions we measured.

There is some evidence of a rebound effect of the biofeedback training. At the 6 week follow up recording, there was a substantial change in some variables from the other resting state recordings. In the placebo group, there was a change in the theta connectivity, in the broadband feedback group, there was a change in the alpha 1 connectivity, and in the narrowband feedback group there was a change in the beta 1 connectivity. The changes in the broadband and narrowband feedback groups were proportionately larger than that in the placebo group, which could suggest that this was a real effect of training. One theory on the mechanism of biofeedback is that training of a particular frequency in one direction can result in a shift in the opposite direction when the training stimulus is removed, as the brain corrects for the training stimulus. This has been described in previous studies (240). No evidence of immediate rebound effects was found in this study; however, the change in the broadband and narrowband feedback groups at the 6 week follow up session could represent a late effect of the biofeedback training. Closer follow up over the post training period could further elucidate this effect. An alternative hypothesis is that the effortful concentration of the participants on the biofeedback training screen resulted in long term changes in their EEG activity. Regardless of whether the participants were engaging in real feedback or placebo feedback, they all made an effort to concentrate on the bar on the screen. So all participants were engaged effortful activity which was regular and carried out intermittently over an extended period of time. This may have

had an effect on their EEG activity, which would explain why changes were seen in the placebo group as well as the active training groups.

The changes in the within session EEG metrics are likely to represent non-specific effects, given that significant changes were found within the placebo group as well as the active groups. The within session changes in the connectivity indices in the broadband feedback group could represent a real effect; however this is unlikely given that correlations with memory outcomes were found in all groups including the placebo feedback group.

Trial Aims

The randomised controlled phase of this study had four stated aims. These are addressed individually below.

Compare Source Localised EEG biofeedback to Placebo Feedback

The pilot study described in chapter 4 was an uncontrolled study in a small group of people. There were some interesting results from this study. In particular, although we did not find significant changes in the EEG metrics used in that study, we found an increase of 12.4 points on the RBANS, which assuming the standard deviation of 15 measured in the RBANS validation studies (178), gives an effect size of 0.82, a strongly positive result. This result was replicated by the broadband feedback arm of the randomised controlled trial, with an estimated effect size of 0.78. The randomised trial is therefore a good replication of the pilot study, despite the fact the cohort recruitment criteria was different.

However, the effect size in the placebo group was 0.63, meaning the effect found in the pilot study is unlikely to be a true effect of source localised EEG biofeedback. Most of this effect appears to be attributable to the differences in the forms of the RBANS, but test retest effects and non-specific placebo effects are also likely to play a part as well.

Compare the Narrowband Feedback to Broadband Feedback

Two slightly different forms of source localised EEG biofeedback were tested in this trial. The first group, the broadband feedback group, replicated the feedback in the pilot study, training both alpha and theta frequencies up (4-14Hz). The second active group, the narrowband feedback group, trained just the alpha frequencies up (8-14Hz). Both arms had protocols which trained beta and gamma frequencies down (20-40Hz). In the narrowband feedback group, there was a statistically significant trend toward increasing alpha frequencies during training, meaning the participants did manage to gain some control over the targeted frequency. In contrast, the trend found in the broadband feedback group was not a trained frequency. It would appear from this result, the participants are better able to change the narrower frequency band. It is unlikely that the effect is due to alpha frequencies being easier to train, because both groups were exposed to the 8-14Hz range. It is possible that if training were restricted to the 4-8Hz range, a similar effect would occur in the theta frequency range. However, there was no effect on cognitive outcomes in either group, and so changing these variables has no positive impact for the participants on the metrics we used.

Test Biofeedback in a Population with General Memory Deficits

There were two main reasons for testing the biofeedback training in a population of people with general memory deficit rather than a cohort with aMCI according to the NINCDS-ADRDA criteria (30). The first reason was so that we would be able to recruit enough people from the wider Dunedin area to be able to find a statistically significant change in the memory scores of approximately the same level found in the pilot study. The second reason is that this represents a population of people who might benefit from improved memory. Many of the participants in the study expressed concern about their perceived memory deficit, and wanted to help find potential solutions to the problem. In addition, subjective memory decline (SMD) is a clinical entity which describes cognitively normal adults who express greater than average concern over their memory, and represents a higher than average risk of developing Alzheimer's disease (241). Many of the participants who were in the trial

could be categorised as SMD, and therefore testing of interventions to restore function and prevent decline in this group is appropriate.

We were successfully able to recruit a moderate size cohort with our inclusion criteria from the Dunedin population. These participants had deficits in the immediate memory index as expected by our selection process, but also had delayed memory deficits and to a lesser extent lower scores in other domains as well. The deficits in domains other than the immediate memory index makes it likely that the cohort recruited is inherently different to the screened population, rather than an artefact produced by our selection criteria.

Because of the similar results found between the pilot study and the full randomised trial, it is likely the results of the randomised trial can be applied to a trial conducted under similar circumstances with the stricter inclusion criteria of the pilot study. Given the form effect and the placebo effect observed in the randomised trial, it is likely that a group of people with aMCI under the NINCDS-ADRDA criteria would have an improvement of around seven to nine points in the immediate memory index between pre training and immediate follow up score through repeat testing alone. An observed effect would need to exceed nine points significantly to be considered a genuine result of training.

In theory, people with aMCI should experience a greater improvement in memory in than people with SMD but not aMCI. This is because the people with aMCI should have patterns of EEG connectivity that are more unlike a healthy brain than people with SMD (242). And if the biofeedback works by reversing abnormal changes in the connectivity, it should be reversed more in people with more abnormalities. Conversely if there were no real training effect, we might expect the group with less cognitive decline to experience a greater improvement in memory score, because more they have more cognitive reserve, and non-specific therapeutic effects will have a greater impact on the result. The studies described here would seem to support the latter theory. Comparing the participants of the pilot study to those participants in the broadband feedback group

who were randomised to start on form A, which most closely replicates the circumstances of the pilot study, we find the people in the broadband feedback group improve by 16 points on the immediate memory index, whereas the people in the pilot study improve by 12.4 points.

Identify EEG Biomarkers for Mild Cognitive Impairment

This trial found no EEG biomarkers for Mild Cognitive Impairment. This study was not powered to find small effects, and given our inclusion criteria it is unlikely that large differences between the participants in the trial and the control participants would exist anyway. A much larger study of both participants with cognitive impairment and cognitively normal controls would be required to find significant differences in the baseline EEG parameters. No real change was observed in the memory scores between the pre training and immediate follow up scores, so it is unclear whether significant changes in the participants' EEG characteristics over time, such as the increase in the beta 1 connectivity between the PCC and the parahippocampal gyrus in the broadband feedback group or the increase in the alpha 1 current density in the PCC in the narrowband feedback group, are related to memory outcomes. The changes observed were not correlated with the memory scores using conservative assumptions such as Bonferroni correction.

A negative correlation was found between the theta connectivity of the PCC to the parahippocampal gyrus at baseline and the delayed memory score. This association was moderate. However, the correlation is the opposite of what we would expect given the model put forward in the introductory chapter. We postulated that phase lagged synchronisation in low frequency bands allows the transfer of information coded by high frequency activity between discrete brain regions. Under this theory, higher connectivity in the low frequency bands should result in more efficient information transfer. For example, greater synchronisation between the PCC and the parahippocampal gyrus should result in more efficient retrieval of memory information, and thus greater recall. However, we found that people with lower theta connectivity between the PCC and the medial temporal lobe at baseline tended to score worse on the delayed memory index. If this result is replicated in a larger

cohort, it could indicate that theta connectivity does not contribute to memory retrieval in the way predicted by this model.

Participants' view of Biofeedback Training

Most participants found the initial biofeedback sessions acceptable, because it was generally non-invasive and had very few side effects, other than general fatigue. However, the biofeedback program we designed for this trial was very arduous for the participants. At least 10 either refused to participate in the trial or dropped out of the trial when they realised the time commitment required to take part in the trial. This means in reality that most of the people who took part in the trial were retirees or did the training in the early morning or the late evening. Even so, many of them complained about the time commitment involved in the study.

The participants were asked about whether they thought they had experienced any memory benefit from the biofeedback training at the immediate follow up period. Fifteen of our participants stated that they had experienced some beneficial effect on their memory with the trial. Without taking into account the form effect, we checked to see whether these participants had improved by 10 or more points on the immediate memory index of the RBANS. Nine of these participants hadn't. Twenty three participants experienced an increase of 10 or more points on the RBANS but had denied experiencing any kind of benefit. In total 63% of our participants had a dissonance between the experienced benefit and the crude measured benefit. A major explanation for this is that the RBANS test has serious limitations in measuring real benefit. Another possible reason is that participants are attuned to noticing episodes of forgetfulness, because our recruiting method selects for a cohort that is particularly concerned about their memory. It has been documented that people's complaints about their memories are more related to anxiety about aging than actual memory performance (243). And so a substantial improvement, greater than one standard deviation, in memory scores is required to overcome the participant's inherent bias before they actually perceives a real benefit from the training.

When these two factors listed within this subsection are combined, it is possible to see that biofeedback is never likely to be a popular therapeutic strategy. The participants are engaging in a very time consuming and effortful activity that they may have difficulty perceiving a benefit from. Even if this biofeedback strategy had managed to generate moderate improvement in memory function for the participants it is unlikely that they would have had positive view about the treatment program.

RBANS Form Effect in the Immediate Memory Index

The two different forms of the RBANS were used to reduce repeat testing effects. In the validation cohort that validated the forms in the United States, the RBANS forms A and B are equivalent in all the RBANS index domains. The estimated effect of repeat testing in this validated cohort was 1.3 points in the immediate memory index, and 2.1 points in the delayed memory index. Difference between form B and form A, in a counterbalanced design of people switching from form A to form B and switching for form B to form A, with a testing interval of one to seven days, showed a difference of 0.2 points in the immediate memory index and -5.2 points in the delayed memory index (form A was higher) (178).This indicates a high degree of reliability between the forms in the United States. It is a reasonable assumption to believe the forms would act similarly in the New Zealand context, and this influenced the design of our study.

Amongst all the people who were screened into the biofeedback training there was a significant difference in the immediate memory index score of 7.8 points. However amongst the people who qualified to take part in the study, who scored below 90 in the immediate memory index, there was no significant difference between the forms, aside from the skewed number of people entering the trial on form A compared to form B. Additionally people who switched from form A to form B dramatically increased their immediate memory score. This was true both for people who were randomised initially to form A, who switched between form A and form B between the pre training and the immediate post training follow up, and for people who were randomised to form B, who

switched between form A and form B between the immediate follow up and the 6 week follow up score. It seems from this pattern that the form effect is particularly pronounced in the range between 90 and 110. A further study might be able to identify whether this pattern holds true for New Zealanders who initially score higher, such as 100 or 120.

There is some indication that there was a form effect in the likelihood of selection into the trial. More people were recruited when they were initially randomised to form A than when they were initially randomised to form B. This is probably because the memory section of form B is slightly easier, so somebody with a mild memory deficit has a greater chance of scoring a normal score on form B than on form A. However, there is little difference between the forms at the baseline test and the 6 week follow up test, and major differences are only found between the forms at the immediate follow up. The fact that the groups end up looking similar in this score at the 6 week follow up would seem to indicate that the group entered into the trial on form A, who wouldn't be entered into the trial in form B, do not exert a significant effect on the result of the mixed model analysis. In addition this is not likely to have affected the final result on the primary outcome of this study, because the proportion of people randomised to form A compared to the proportion randomised to form B is similar in each group.

There is a divergence in the immediate memory score between participants on form A and form B at the immediate follow up time point, and at the 6 week time point the difference between the forms seemed to disappear. Because participants were tested on the different forms on a 1-2-1 pattern, that is somebody starting on form A was tested on form B for the immediate follow up and then was tested on form A for the 6 week follow up, this meant that the form they were tested on at the beginning was the form they were tested on in at the end. Given that we have found evidence that no real group effect is occurring, we can therefore say that most of the difference between the pre-training score and the 6 week follow up score is due to a repeat testing bias. It is clear that while this is a substantial effect, it is fairly consistent between the groups. The RBANS test could therefore be

used in future studies, by consistently testing on one of the RBANS forms to remove the form effect, and measuring the difference in the rate of change of the immediate memory score, as a viable means of assessing the efficacy of a memory intervention.

The finding that the biofeedback training demonstrates no real effect is robust both to stratification analysis and to an adjusted analysis with some liberal assumptions. The form effect contributes around 16 point's difference between the groups at immediate follow up compared to the pretraining score. Because of the balance of form A and form B between the groups, this means that the change in score in the broadband feedback group as a whole for example is eight to nine points higher than it should be. If there is a further change in the immediate memory score additional to form effect, it cannot be a clinically significant difference, given that the magnitude of the change in score is so small.

There are a number of reasons a form effect could exist in this cohort. One of the main reasons for non-equivalence in a New Zealand setting, where equivalence was found in the validation studies in the United States, is the different frequency of words. It is well established that memory tests such as the list memory task in the RBANS are affected by the frequency of words in the background population (244). The words that make up the list memory in the RBANS form A may have equivalent frequency in the United States to the words in form B, but may not be in New Zealand. And so when testing in New Zealand, the forms may not be equivalent. In addition, the story memory in form A had an awkward phrase in the middle of it, about a 'three alarm fire'. It is not common practice in New Zealand to refer to the size of a fire by the number of alarms, and this feature of the story may have interrupted memory encoding for the rest of the story. These two features of the tasks that make up the immediate memory index score may mean that there is lower equivalence of form A and form B in the New Zealand population compared to a population from the United States

Discussion of Strengths and Limitations of the Trial

Heterogeneity of the Selected Cohort

The inclusion criteria of the randomised controlled trial was left deliberately wide, to maximise potential recruitment. Further, unless particular concerns were raised about a participant, their medical background was not checked independently, and therefore prompted disclosure was generally required to discover if a participant had a neurological or psychiatric condition that met our exclusion criteria. Furthermore, it is entirely possible that concurrent medical conditions that the participants may have had, including undiagnosed neurological conditions, may have impacted on the participants performance in both the cognitive assessment and the EEG parameters.

Therefore any real effect of the biofeedback training, if small, may have been masked by the underlying heterogeneity of the sample. If participants who did meet the stricter NINS-ARDA criteria for aMCI did genuinely benefit from biofeedback training, this effect would likely have been masked.

Effectiveness of Randomisation

The randomisation procedure used in this trial appears to work sufficiently. The broadband feedback group had an older average age, but the distribution was also more spread out. This could have had some influence over the results in this trial; however we did not find any effect of age on change in memory score, and the distribution was more spread out than in the other groups, so this would have cancelled out a linear effect with respect to age. The years of education and number of people who were initially randomised to form A was evenly distributed between the groups. The baseline memory index score were evenly distributed between the groups as well. The immediate memory score and the delayed memory score was only slightly lower than in the other two groups. So the trial result is unlikely to be affected by the characteristics at baseline.

2 Back testing

The 2 back testing was introduced in order to assess any effect of the biofeedback training on working memory, which is a functionally different system to the medial temporal lobe system that the biofeedback training was targeted to. However, the 2 back test was not sufficiently

discriminatory both within participants and between participants to make any conclusions. The test we used had both a ceiling, at 100% correctly identified, and a floor at 0% with no correctly identified matches. There was a large standard deviation in the percentage correct answers within each group, meaning that any change within the bounds of the test are unlikely to come up as statistically significant. In future studies in this area, a different set of parameters should be used to measure working memory, such as a digit span backward task. A more discriminatory kind of n-back testing could also be used, such as the percentage of omissions and commissions separately, and 3-back testing.

Placebo Effects

Both the pilot study and the randomised controlled trial required a significant amount of interaction between the biofeedback operator and the participant in the trial. The participant was required to complete a session about every second day for a month. Because the initial testing was undertaken by the same person as the final testing, and the same person who set up all the biofeedback training sessions, the participants were much more familiar and comfortable with the examiner during the final training session than during the first training session. A significant therapeutic relationship could develop between the biofeedback operator and the participant during this time. The participant also might become more comfortable with the examiner for the repeated memory testing, which could result in the participants scoring higher at follow up (245, 246). These two factors may have contributed to the increase in the RBANS immediate memory score over time. This effect is quite large. The difference between the average score at the 6 week follow up and the pre training was 12.2 points. At this time point the form effect did not have a large magnitude effect on the scores, so most of the increase in scores between the time points is due to these placebo effects. It was initially thought at the end of the pilot study that these placebo responses would have an even effect on each of the RBANS indices, and it was concluded that because the immediate memory index moved far out of line with the rest of the indices, it was unlikely placebo responses

had a large impact on the pilot study results. However it appears that the immediate memory index is particularly susceptible to these kinds of biases.

All study participants had the same biofeedback operator for every session. This controls for any potential bias that could develop from different therapeutic relationships between the operator and the participants. However, the biofeedback operator also carried out all the neuropsychological testing, meaning that over the course of the trial, the participant had a much greater familiarity with the operator than they did at the beginning, which would accentuate the change in memory score. This is true for all groups, which means that this familiarity effect is unlikely to have had a differential effect on the trial arms.

RBANS floor effect

The RBANS has a floor effect in each of the cognitive indices. The minimum score for each of the cognitive indices was 40 points, which would be scored if the participant scored poorly in the subtests that contributed to that cognitive index. aMCI participants of the pilot study typically scored very poorly in the delayed memory index. Several participants in the pilot study scored the minimum score of 40 points for the delayed memory index. This occurred more often in the pre training cognitive than the post training cognitive test. This introduces bias into this index, because the true extent of the delayed memory deficit beforehand is masked by the floor effect in the cognitive test.

Comparison to Other Trials

This is the first study to used source localised biofeedback, localised to the PCC in order to improve memory outcomes in people with mild memory problems. However, because of the low spatial resolution of the sLORETA method, it localises activity more generally than just the pre-specified voxels. Given the area and the frequency band that was targeted by the biofeedback program, this strategy is roughly equivalent to a posterior alpha strategy. There are a number of studies that use a posterior alpha strategy to improve memory outcomes, including studies which had either placebo or wait list controls such as Nan et al 2012 (147), Escalano et al 2014 (143), Escalano et al 2011 (142),

and Lecomte et al 2011 (195). In general, as was stated in chapter two, posterior alpha strategies tended to show an improvement in memory parameters regardless of whether there was an improvement in the alpha power. In contrast, the narrowband feedback group in our study found an increase in alpha in the PCC, with no apparent improvement in memory. This discordance was not found in any of the studies using an alpha strategy in mentioned in chapter two, although three of the eight studies which found an improvement in alpha power were uncontrolled studies. .

The method stated in chapter two to measure the difference in effect size between the intervention and control group was used to compare this trial to the other studies included in the meta-analysis in chapter 2. The broadband feedback group and the narrow band feedback group are analysed separately. Figure 7-1 compares the change in effect size to the size of study.

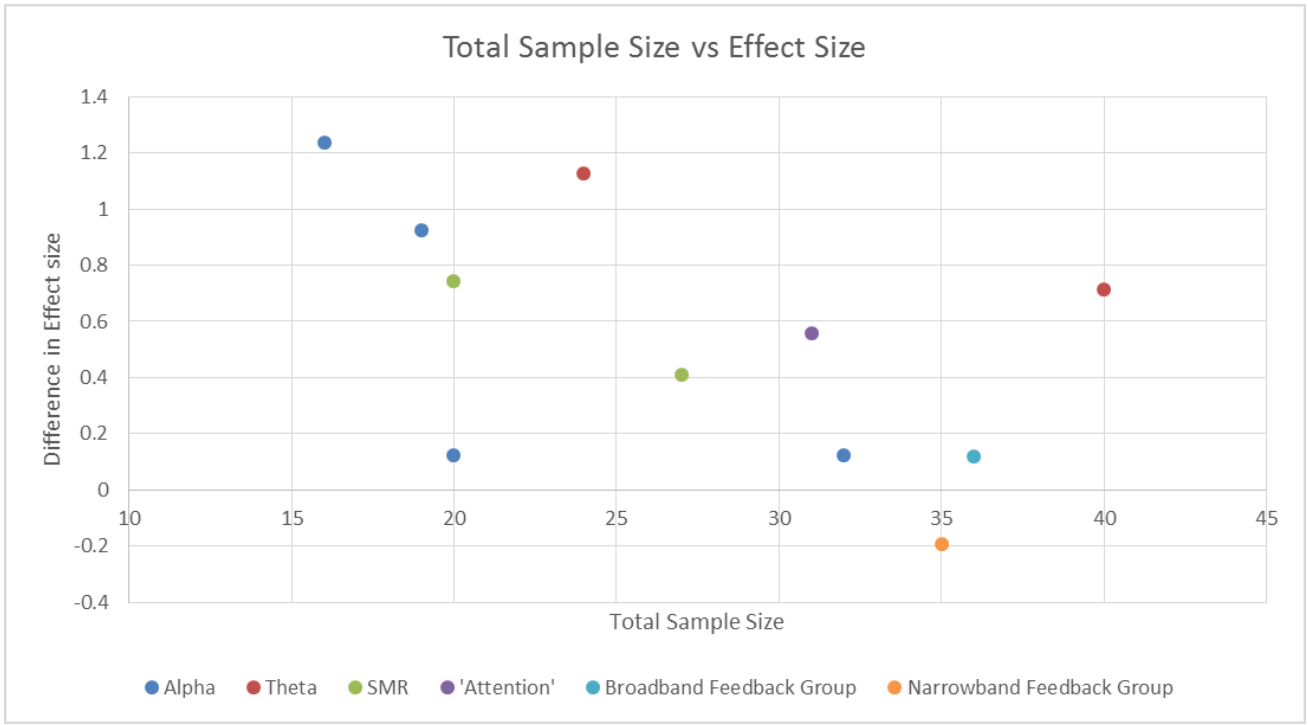


Figure 7-1: The effect size vs the total sample size of studies of biofeedback for memory

This trial showed a smaller effect size than previous studies, particularly smaller than previous alpha type strategies. Interestingly, though, it showed a similar effect size to a study of comparable size, Nan et al (147). Our study would seem to follow the trend that larger studies show smaller effect

sizes. This is particularly true of the narrowband feedback group, which is the only one with a negative effect size as per our calculations (that is the control group experienced a greater effect than the intervention group).

Validity

The criteria to demonstrate validity of biofeedback training, as set out by Gruzelier in his three part review of using biofeedback to improve performance (138-140), include specificity such as band specificity, cognitive specificity, or locality specificity, and either a unique cognitive change compared to a control group or a correlation between the neurological response and the cognitive change demonstrated by the experimental group. In this thesis, neither the broadband feedback group, nor the narrowband feedback group demonstrated band specificity. No group demonstrated an overall improvement in cognitive scores attributable to the training, so this training could not be defined as specific to any neuropsychological property assessed. There is also no evidence of topographical specificity. This might not be expected due to the fact that the memory networks involved such as the DMN are distributed over a wide topographic area.

Furthermore no unique cognitive change was observed in either of the active training groups in the validation analysis. Changes were observed in the immediate memory index in all groups, but also changes were observed in other cognitive domains. Therefore, even if a significant change was observed in a memory domain, it would not be a unique cognitive change as a result of training.

A correlation analysis did not reveal a unique correlation between the current density response to training and the cognitive outcomes. Significant correlations were found in all of the groups for both the between session measures and the within sessions measures. The fact that correlations were found in the placebo group means that the correlations found in the active groups cannot be interpreted as the unique effect of training.

A group analysis may hide a real effect if a significant number of non-responders are present within that group. Performing a correlation analysis should demonstrate that successful training can occur

in some people if this effect is hidden by the non-responders. The responders change their neurological profile and should therefore change in the cognitive measure as well. Therefore a strong correlation will occur in the active group. The placebo group should have no change in either parameter if the training is a real effect, and so no correlation should become apparent. This is why the presence of significant correlation in the placebo group means that the correlations found in the active group cannot be considered to be the result of the biofeedback training; they must be the result of non-specific influences on the EEG.

In order to confirm the validity, certain evidence is required. If the premise that training of the PCC does not affect the current density of theta but the phase lagged connectivity to the MTL (134) then the following would be shown:

1) Biofeedback training would result in a unique increase in the phase lagged synchronisation between the PCC and MTL
2) Biofeedback training would produce a unique increase in one cognitive domain, such as memory.
3) An increase in the phase lagged synchronisation would be uniquely correlated with the memory score.

These features were not present, hence additional validity analysis did not identify any subgroup of responders.

Conclusion of Randomised Controlled Trial

Source localised biofeedback of the PCC to increase in power of alpha and theta, or the power of alpha alone, does not appear to have any real effect on immediate or delayed memory outcomes. Most of the effect found in the pilot study can be attributable to the non-equivalency of the RBANS forms in the population tested and more general placebo effects. Training of the EEG parameters is possible; however this appears to be unrelated to memory outcomes.

Chapter 8 Implications for Future Research

From the data produced in this study, it is possible to conclude that there is no significant real effect of source localised biofeedback of the PCC in the bands we trained. If there was a real training effect, it is likely to be so small as to be not of any clinical value. As such, further trials of the feedback, using similar parameters tested in this study are unwarranted.

This trial highlights some issues with biofeedback trials in general and with interventions to improve memory in general. These are discussed in more detail below.

Future Trials to Improve Memory

One of the key failings of the pilot study was the assumption of the equivalency of the RBANS forms. The forms were regarded to be as equivalent, and would largely eliminate any repeated testing effect that would inflate the post test. This was a reasonable assumption at the time, given that the validity data behind the RBANS test seemed to support this assumption (178). However this did not turn out to be the case. There was both a significant form effect and a significant placebo response. This lead us to believe at the end of the pilot study that it was worth investing further resources into testing this intervention further, and hence the randomised controlled trial was designed. Several improvements to the design of pilot studies of biofeedback could be implemented to prevent this kind of false lead in the future.

Counterbalanced design

It was noted in chapter 4 that one of the weaknesses of the pilot study was the fact that all the participants started on form A and finished on form B. This was improved during the randomised controlled trial to have a counterbalanced randomisation of the forms, which meant that half of recruits were screened on form A or screened on form B. Using this counterbalanced design in the pilot study would likely have demonstrated a form effect, as people who started on form A would likely improve much more than those who started on form B. So where multiple forms are being used, a counterbalanced design should also be used

However, this kind of form effect is not the only way that cognitive testing might become biased. If a single form is used repeated testing effects, which are discussed in chapter 3, might have an influence, or repeated testing with the same examiner might have a very significant effect on participant's performance. In this study we found that at the 6 week follow up participant performance had improved, and this was not due to the difference between the two RBANS forms. This repeated testing effect would not have been controlled for by a counter balanced design.

Inclusion of a Placebo Control in the Pilot Phase

If a placebo control had been included in the pilot phase of the trial, this would have highlighted the issue with using the RBANS as it was being used. This potentially would have led to the earlier conclusion that there doesn't seem to be therapeutic value to this intervention. A placebo group was not included at the time due to recruiting constraints and because the limitations of the RBANS test were unknown at the time. Repeated testing effects are well known within neuropsychological testing, and may be controlled with alternate forms (247), but this turned out to be too unpredictable in our population. In a setting where neuropsychological tests are used these can be very significant, and placebo treatments have a tendency to exaggerate the repeated testing bias (247). Therefore, particularly in a population which the neuropsychological test hasn't been validated, a placebo group should always be included. This removes the effect of the treatment and therefore this repeated testing effect can be quantified, and therefore controlled for. If this occurs during the pilot phase of the trial, it would indicate earlier whether there was a potential therapeutic value earlier.

Validation of a New Zealand Specific Repeated Memory Assessment

It seems clear from the data we gathered that the RBANS test in the New Zealand context does not operate in the way it did in the validation studies in the United States. Potential reasons for this have been discussed previously. A short, but repeatable test that has alternative versions which are validated in a population of New Zealanders is required. Other tests such as the Weschler Memory Scale do seem to work in New Zealand populations (248), but require a neuropsychologist to

administer. Requiring a neuropsychologist to administer a repeatable memory battery would greatly increase the complexity of a trial like the one described here, and greatly increase the resources needed to carry out such a trial. It would therefore seem prudent to investigate whether any of the existing tools available generally to health care professionals is valid for this kind of repeat testing. If such a test does not exist, one should be developed and validated.

Further, the test should be validated against real world outcomes. A 10 point difference was selected somewhat arbitrarily as a clinically significant change in immediate memory scores. The RBANS does differentiate between different kinds of dementias and cognitive functioning in different mental health conditions (212); however this is not the same as correlating through to functional outcomes in patients. An important outcome to many patients is the loss of function in their everyday lives, such as an inability to read or carry out hobbies (249). This leads to the question, how much more memory do participants need to be able to maintain the activities that are important to them? Is 10 points on the RBANS immediate memory score the difference between having a drivers licence in two years' time or not? Given the intensive commitment required to undergo the biofeedback training, or take part in any trial of novel therapeutics, it would be important to create an outcome that was clinically relevant to the patient, and if an extra 10 points on the immediate memory index of the RBANS was not going to have an impact on the participants abilities to do the things they wanted to, then it would not be worth doing despite being a massive improvement on the cognitive score. The clinical effect might also be related to the baseline capacity of the individual, for example a participant who has a 10 point improvement from 60 to 70 points might experience a greater improvement in functional capacity than a participant who improves 10 points from 90 to 100. If a new New Zealand specific memory test was developed for use in clinical trials, it would be worth benchmarking functional capacity to the score on the test, and even assessing whether the current score had any predictive value for the functional capacity of the participant in the future.

Use of biomarkers

The biofeedback tool we developed was ostensibly developed to target Alzheimer's type pathology in a Mild Cognitive Impairment population. The pilot study used a strict clinical definition of mild cognitive impairment to closely target this population. The randomised controlled phase of the study targeted a much more loosely defined group, who have a subjective memory complaint and have a demonstrated memory deficit. However, clinical research in preclinical Alzheimer's disease tends to use biomarkers, such as PiB enhanced PET imaging, CSF Aβ, APOE genotype, or neurofilament light, in order to more clearly define a population at risk of dementia due to Alzheimer's pathology (31, 32, 250, 251). Use of these biomarkers can be used to define a population which has probable Alzheimer's pathology, rather than bluntly target memory loss which may or may not be due to Alzheimer's pathology.

The kind of intervention we tested targeted memory centres in general, by targeting the posterior cingulate cortex which links the medial temporal lobe memory system to the default mode network. In theory, strengthening the functional connectivity of these two networks should result in better memory encoding and retrieval, both for people with AD pathology and those without. Further in people who have altered connectivity, restoring the connectivity should mean there is a greater effect than in people with normal connectivity, as was discussed in chapter 1. However, we failed to find any evidence of an effect in the mild memory deficit cohort that we recruited. In addition, the size of the effect, when taking the form effect into account, was similar between the mild memory deficit cohort and the clinically diagnosed aMCI cohort in the pilot study. Therefore it is unlikely that any significant effect would be found even if the cohort was restricted to just people with aMCI with evidence of AD pathology.

It is also possible that people with evidence of AD pathology might have a reduced responsiveness to this kind of technology. It is known that a relative inability to learn compared to age matched controls is a feature of Alzheimer's disease (252), which may translate into an inability to respond to biofeedback..It is possible that disruption to white matter networks causes the participant to be

unable to restore functional connectivity relationships despite the assistance of visual feedback. However, there is also no evidence in the pilot study that participants with clinically diagnose aMCI with worse baseline (potentially reflecting a greater burden of pathological changes) did not improve as much as others, to the contrary they appeared to improve more.

Therefore, it is still unknown if imaging or biochemical biomarker confirmed Alzheimer's pathology has an impact on the effectiveness of a biofeedback training regime. It could potentially be more effective, but could also be potentially be less effective. Thus it will be an important aspect of trials of interventions to improve memory in older people.

Future trials of Biofeedback

Posterior Alpha and Theta strategies

When presented with the instruction to find methods to raise the vertical bar in the biofeedback program, the first participants found very quickly that the easiest way of doing so was to close their eyes. This was true for both the broadband feedback and narrowband feedback conditions. With eyes closed, the biofeedback parameter would rise substantially, often more than doubling. We hypothesised that this effect occurred because the program was detecting posterior alpha rhythms from the occipital cortex when the eyes were closed. The participants after the first participant in the pilot study were instructed to keep their eyes open for the duration of the training, because participants needed to see the biofeedback parameter in order for the biofeedback to work. In addition, several participants made comments suggesting that 'not concentrating' directly on the vertical bar actually helped raise it higher, suggesting that attention to the visual stimulus may hinder training. However, it may be possible to use this effect to enhance a training procedure using a posterior alpha strategy. Rather than using a visual stimulus for biofeedback, an audio stimulus could be used, such as a tone that sounds when the biofeedback parameter is below the threshold value.

There is no evidence to suggest that using an audio stimulus is better or worse than the visual stimulus that this study design used. Therefore, it is worth investigating whether it makes a difference to the clinical or electrophysiological effect of biofeedback training using a posterior alpha or theta strategy, for any indication of biofeedback training.

Other Strategies

There are a huge number of potential strategies for biofeedback. The review in chapter 2 highlights the variety of strategies that have already been tried in order to improve memory outcomes, including EEG, fMRI and infrared modalities. Narrowing the scope of possibilities down to just sLORETA feedback still leaves thousands of opportunities for feedback. There are 6239 different voxels that could theoretically be targeted in this way, although due to the spatial resolution of sLORETA the number of appreciably different targets would be in the hundreds rather than the thousands. Different frequency bands can be targeted for up training and down training. In the near future it may be possible to directly train functional connectivity in the form of phase lagged synchronisation (253), rather than target indirectly through training activity as was attempted during this trial. Therefore there are thousands of potential methods of biofeedback possible, and it would be incredibly time consuming to test them all in randomised controlled trials of the kind presented here. A different strategy for generating potentially fruitful biofeedback parameters for testing is therefore required. Therefore there is still a place for small pilot open label studies.

In this thesis, a theory of altered connectivity between the default mode and memory networks was presented to justify an intervention in that pathway. In general, the literature describing studies looking at connectivity in aMCI and AD would tend to support the idea that altered connectivity is an important factor in AD. However, none of the studies found actually sought to find out whether the connectivity between the default mode network and the medial temporal lobe system was altered always in a specific direction in a specific frequency bands. Different studies appeared to come to different conclusions over the state of default mode connectivity, often finding that different connections were affected in different ways. In future, it may improve the likelihood of finding a

therapeutic biofeedback intervention by finding a consistent parameter that is altered in people with AD, or whatever condition is being considered. For example, for the purposes of this study, a large cohort of people with aMCI could be recruited and compared to a cohort of age and sex matched normal controls. We should specifically look for whether the connectivity in question, between the PCC and medial temporal lobe, is consistently reduced in aMCI in the theta and alpha bands. If it is found that it is, then it can be specifically targeted in order to normalise the parameter. If it is not consistently different to the control group, than it is unlikely to be a target that is amenable to intervention on a population basis. Redefining the group more narrowly could improve the likelihood of finding potential targets, for example using biomarkers to enrich a cohort of aMCI might improve the likelihood of finding an EEG marker amenable to intervention. However, doing this could pose a challenge for recruitment of participants into trials.

Having the requirement to find a consistent parameter to target reduces the possibilities for intervention. A large database of EEGs from aMCI participants and cognitively normal participants could be queried repeatedly for different parameters, both using sLORETA and using other analytical techniques. When and intervention is hypothesised, the parameter can be searched for in the database and if it moves in a consistent direction, then this can be considered stronger grounds for designing a trial.

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Appendix A

Appendix A1: List of MNI Coordinates for Default Mode Network Analysis

Table A-1: MNI Coordinate of the default mode network

X co-ordinate	**Y co-ordinate**	**Z co-ordinate**	**Anatomical Name**
-5	-50	10	Posterior Cingulate Cortex
-4	-58	44	Precuneus
2	32	-8	Ventral Anterior Cingulate Cortex
52	-28	24	Right Inferior Parietal Lobule
-2	50	18	Medial Prefrontal Cortex
46	-66	16	Right Middle Temporal Gyrus
-26	16	44	Left Middle Frontal gyrus
-56	-36	28	Left Inferior Parietal Lobule
-42	-6	16	Left Middle Temporal Gyrus
-22	-27	-21	Left parahippocampal
25	-26	-18	Right parahippocampal

Appendix A2: List of MNI Coordinates for Whole Brain Connectivity Analysis

Table A-2: MNI coordinates from 88 Brodmann areas for whole brain connectivity analysis

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
-53	-25	50	Left Postcentral Gyrus
-47	-30	47	Left Postcentral Gyrus
-37	-27	53	Left Precentral Gyrus
-37	-22	51	Left Precentral Gyrus
-17	-44	60	Left Paracentral lobule
-27	-3	53	Left Middle Frontal Gyrus
-17	-63	50	Left Precuneus
-22	28	49	Left Superior Frontal Gyrus
-29	30	33	Left Middle Frontal Gyrus
-22	54	9	Left Superior Frontal Gyrus
-18	43	-17	Left Superior Frontal Gyrus
-39	-8	9	Left Insula

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
-12	-90	-1	Left Lingual Gyrus
-17	-85	1	Left Lingual Gyrus
-28	-76	9	Left Cuneus
-47	-22	-29	Left Fusiform Gyrus
-57	-18	-15	Left Middle Temporal Gyrus
-56	-25	5	Left Superior Temporal Gyrus
-6	-40	24	Left Posterior Cingulate Gyrus
-8	2	36	Left Cingulate Gyrus
-8	18	-17	Left Medial Frontal Gyrus
-19	-33	-4	Left Parahippocampal Gyrus
-20	-9	-24	Left Parahippocampal Gyrus
-7	-50	7	Left Posterior Cingulate Gyrus
-13	-58	5	Left Posterior Cingulate Gyrus

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
-11	-50	32	Left Precuneus
-9	29	21	Left Anterior Cingulate
-5	15	23	Left Anterior Cingulate
-18	1	-19	Left Parahippocampal Gyrus
-22	-25	-20	Left Parahippocampal Gyrus
-31	-28	-24	Left Parahippocampal Gyrus
-46	-54	-14	Left Fusiform Gyrus
-39	13	-27	Left Superior Temporal Gyrus
-46	-66	24	Left Middle Temporal Gyrus
-49	-43	40	Left Inferior Parietal Lobule
-46	-29	10	Left Transverse Temporal Gyrus

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
-62	-23	12	Left Superior Temporal Gyrus
-58	-12	16	Left Transverse Temporal Gyrus
-52	9	14	Left Precentral Gyrus
-51	21	13	Left Inferior Frontal Gyrus
-45	36	18	Left Middle Frontal Gyrus
-34	25	-13	Left Inferior Frontal Gyrus
55	-24	50	Right Post Central Gyrus
48	-30	47	Right Inferior Parietal Lobule
40	-27	52	Right Postcentral Gyrus
37	-23	52	Right Postcentral Gyrus
13	-43	59	Right Paracentral Lobule
27	-3	54	Right Middle Frontal Gyrus

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
15	-63	49	Right Precuneus
20	29	49	Right Superior Frontal Gyrus
28	32	33	Right Middle Frontal Gyrus
22	54	9	Right Superior Frontal Gyrus
19	43	-17	Right Superior Frontal Gyrus
40	-7	9	Right Insula
12	-90	0	Right Lingual Gyrus
14	-85	2	Right Lingual Gyrus
29	-76	9	Right Cuneus
47	-22	-29	Right Fusiform Gyrus
58	-17	-15	Right Middle Temporal Gyrus
56	-22	3	Right Superior Temporal Gyrus
4	-43	24	Right Posterior Cingulate Gyrus
7	1	36	Right Cingulate Gyrus

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
5	14	-14	Right Subcallosal Gyrus
18	-33	-4	Right Parahippocampal Gyrus
21	-9	-24	Right Parahippocampal Gyrus
6	-50	8	Right Posterior Cingulate Gyrus
12	-58	7	Right Cuneus
9	-48	33	Right Precuneus
8	30	20	Right Anterior Cingulate
3	18	23	Right Anterior Cingulate
18	1	-19	Right Parahippocampal Gyrus
23	-25	-21	Right Parahippocampal Gyrus

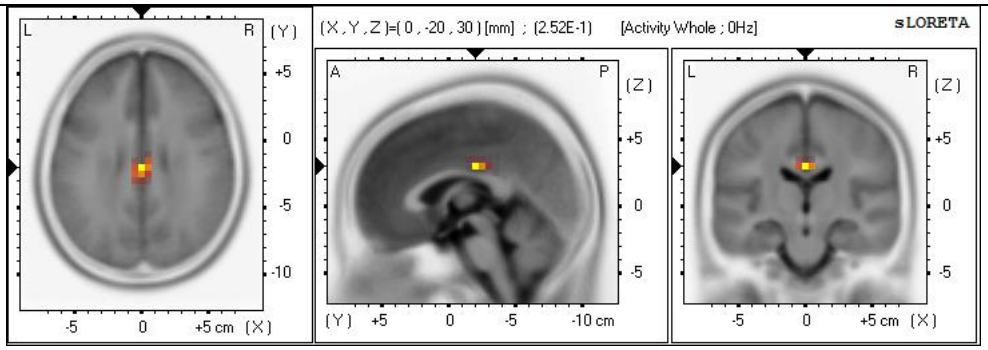
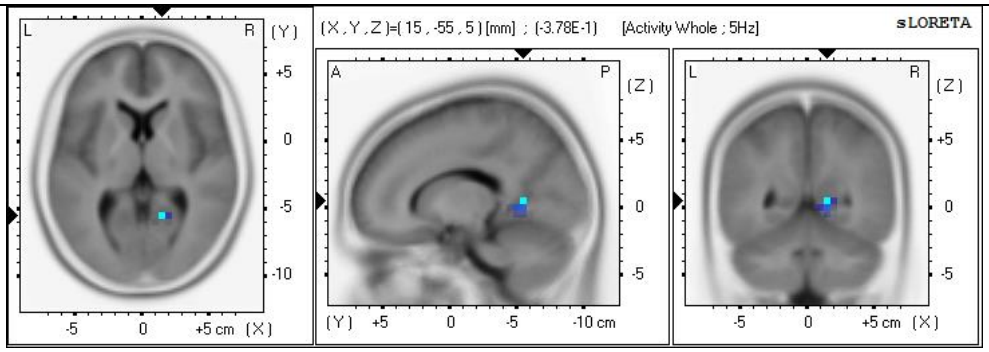
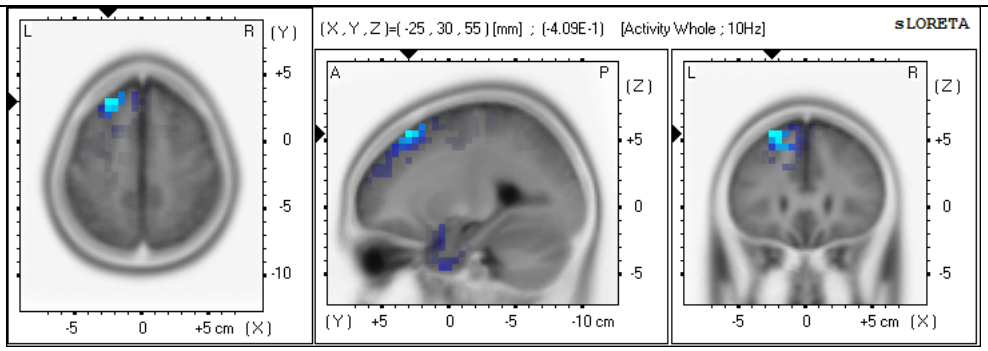
X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
30	-26	-24	Right Parahippocampal Gyrus
46	-54	-14	Right Fusiform Gyrus
39	13	-28	Right Superior Temporal Gyrus
46	-65	24	Right Middle Temporal Gyrus
50	-43	41	Right Precentral Gyrus
47	-29	10	Right Transverse Temporal Gyrus
63	-24	12	Right Superior Temporal Gyrus
58	-10	15	Right Transverse Temporal Gyrus
53	9	14	Right Precentral Gyrus
52	21	13	Right Inferior Frontal Gyrus
47	36	18	Right Middle Frontal Gyrus

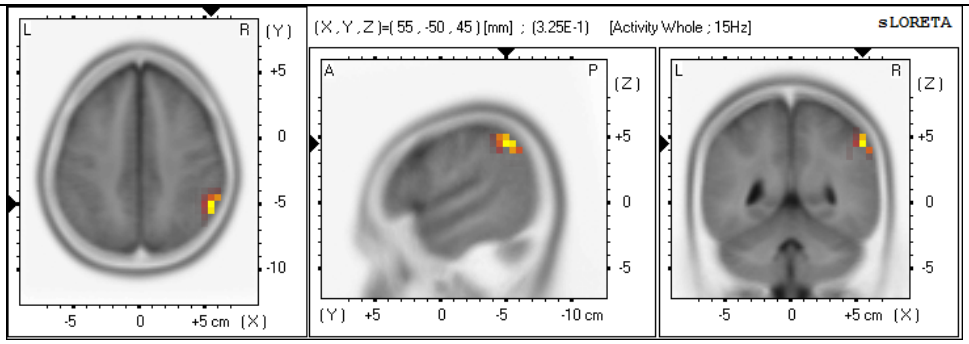
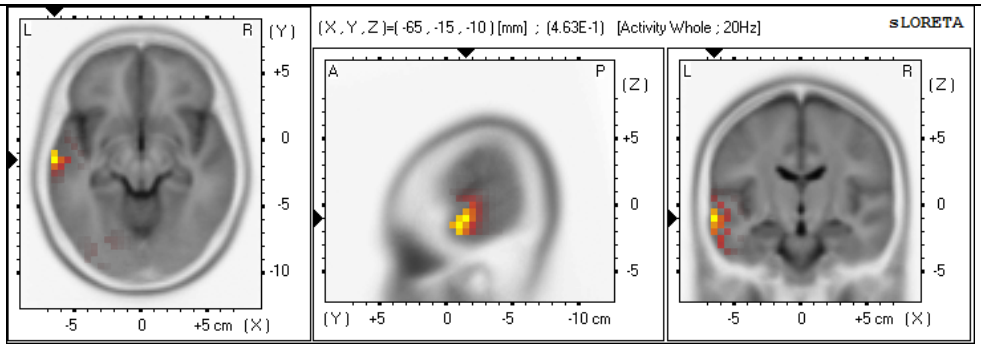
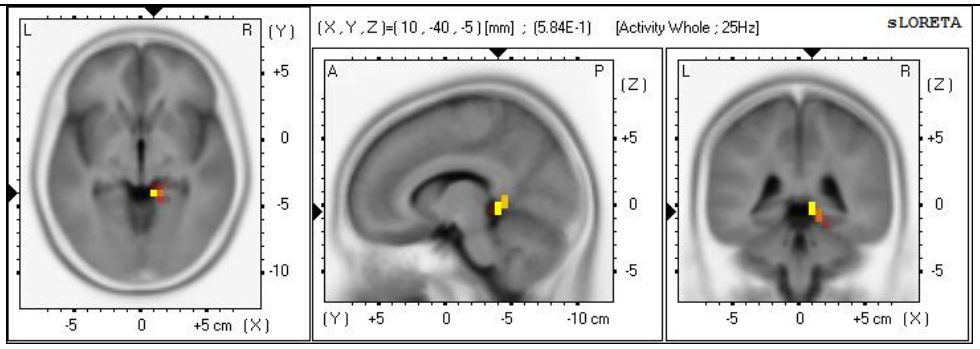
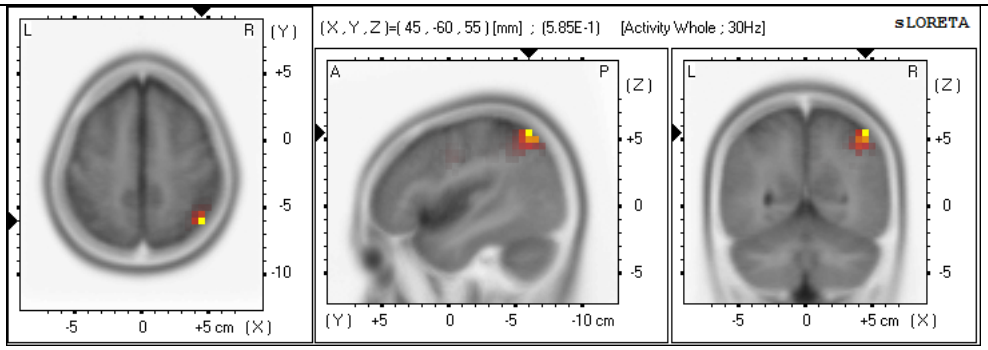
X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical Name
34	25	-13	Right Inferior Frontal Gyrus

Appendix B

Appendix B1: sLORETA activity changes

Figure B-1 below show the voxel with the maximal change in activity in each frequency band. Red voxels represent areas where activity was higher in the post training EEG, and blue voxels show where activity was lower in the post training EEG.

Activity band	
Delta	
Theta	
Alpha 1	

Alpha 2	
Beta 1	
Beta 2	
Beta 3	

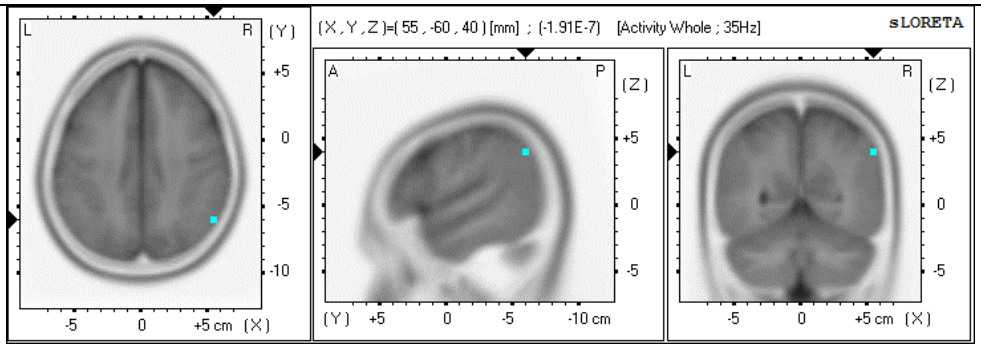
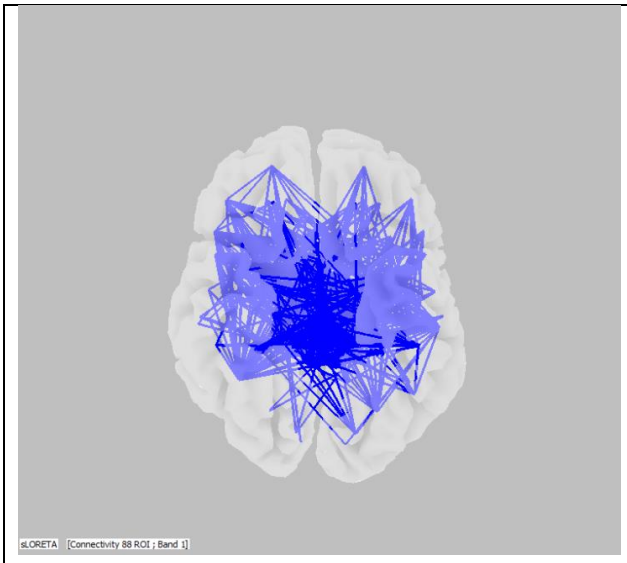
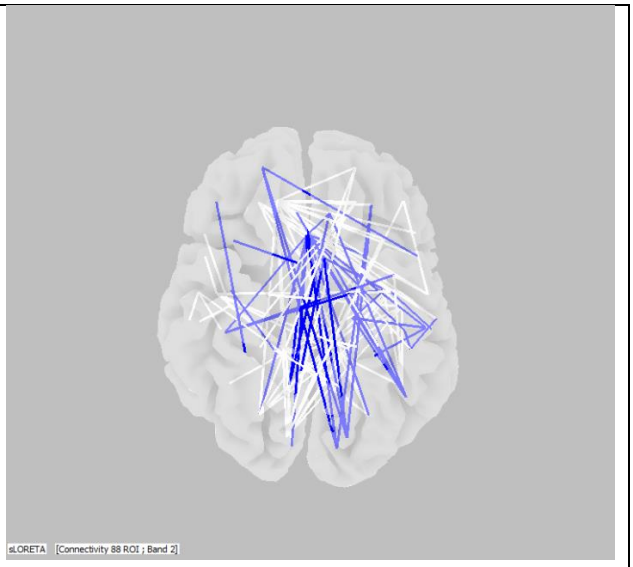
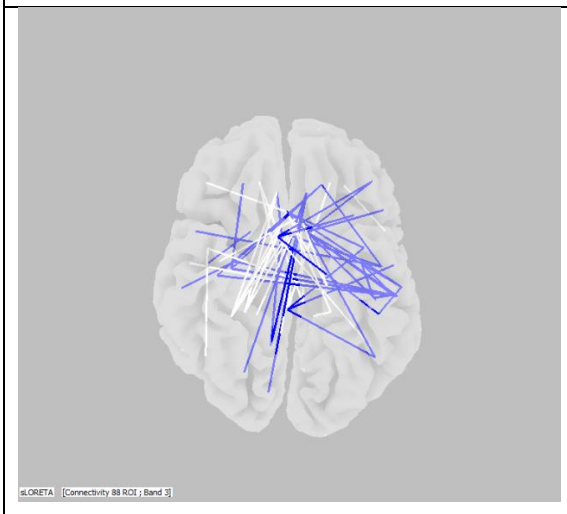
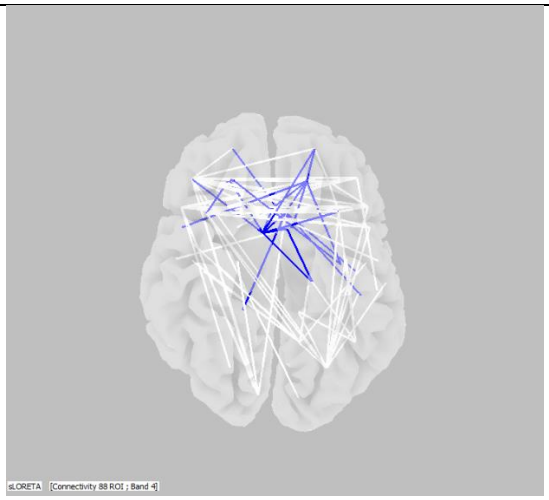
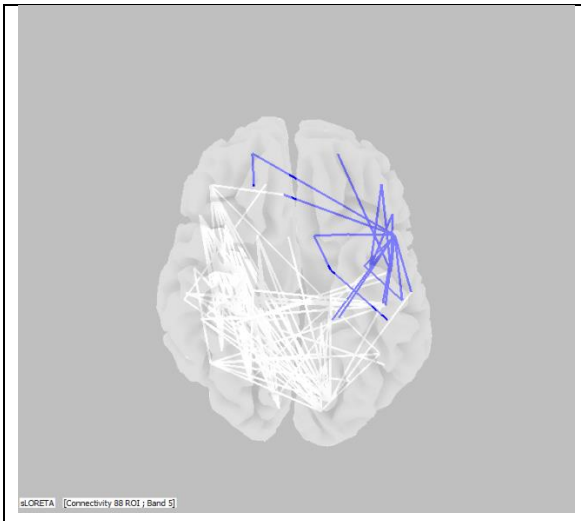
Omega	

Figure B-1: Maps of change in current density between pre training and post training resting state recordings

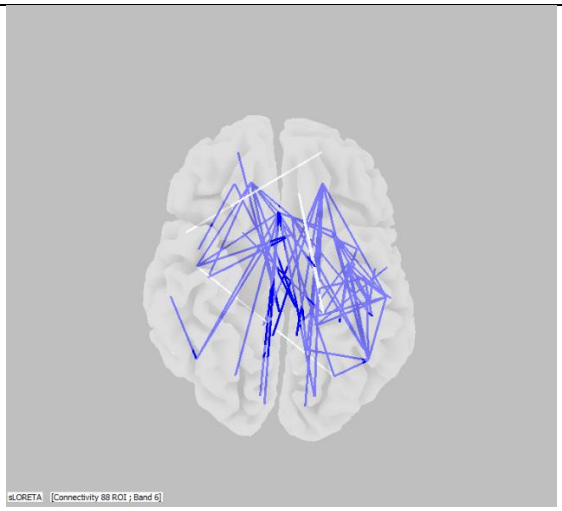
Appendix B2: Whole Brain Connectivity with 84 Regions of Interest

Figure B-2 below shows the changes in lagged phase synchronisation between 84 regions of interest in each frequency band. Only statistically significant decreases were detected, no statistically significant increases were detected. Blue lines represent decreased connectivity between regions of interest. White lines represent non-significant increases in function connectivity between regions of interest.

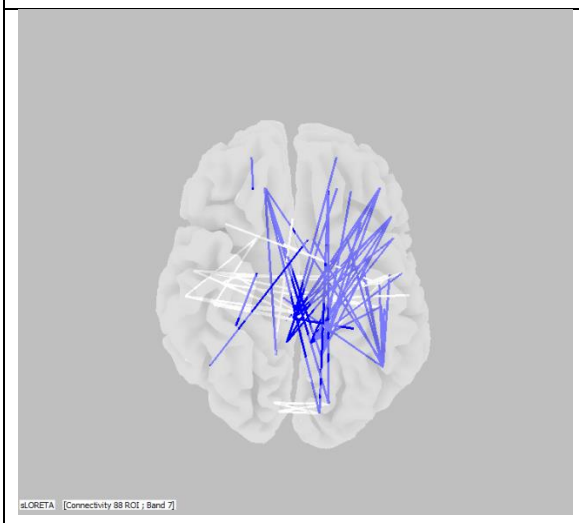
<table>
<tr><td>  </td><td>  </td></tr>
<tr><td>Delta band</td><td>Theta band</td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Alpha 1 band</td><td>Alpha 2 band</td></tr>
</table>



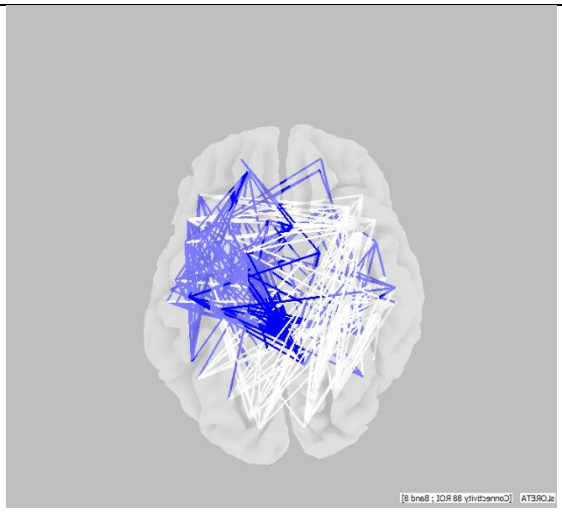
Beta 1 band



Beta 2 band



Beta 3 band

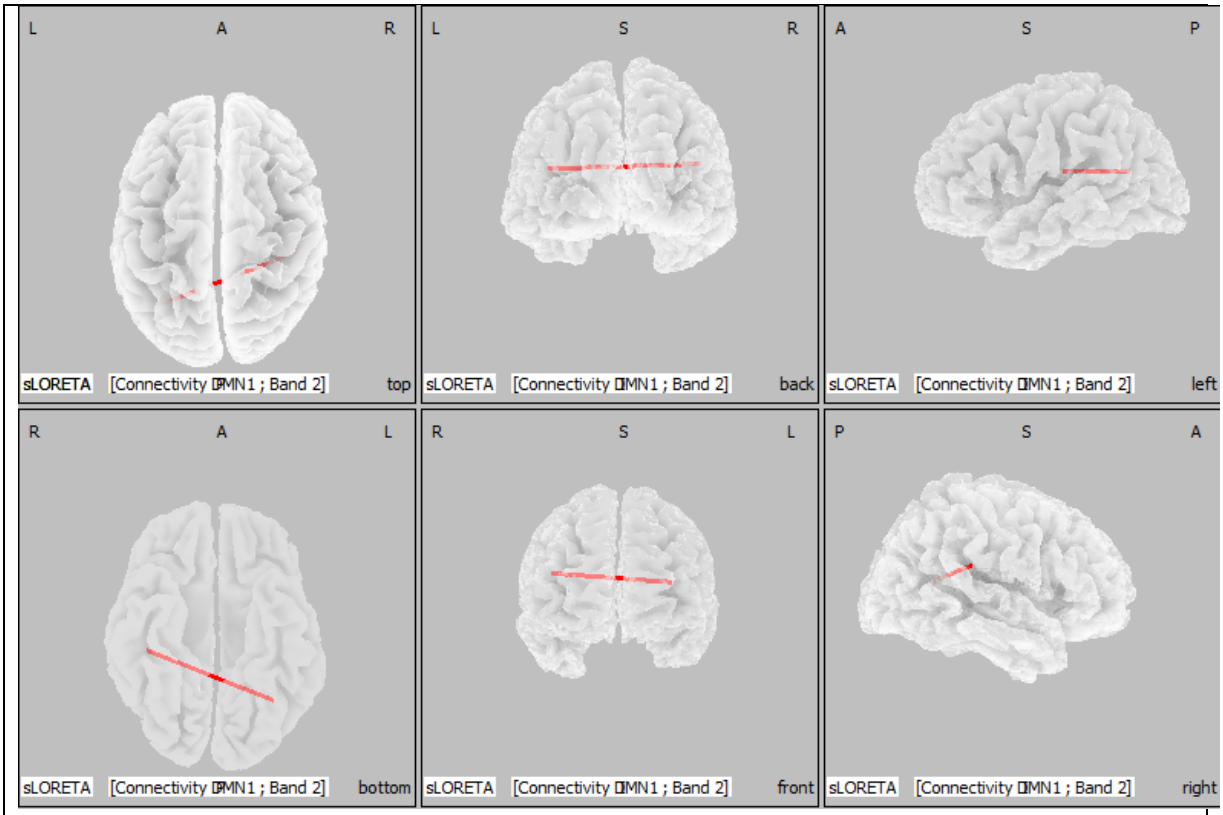


Omega band

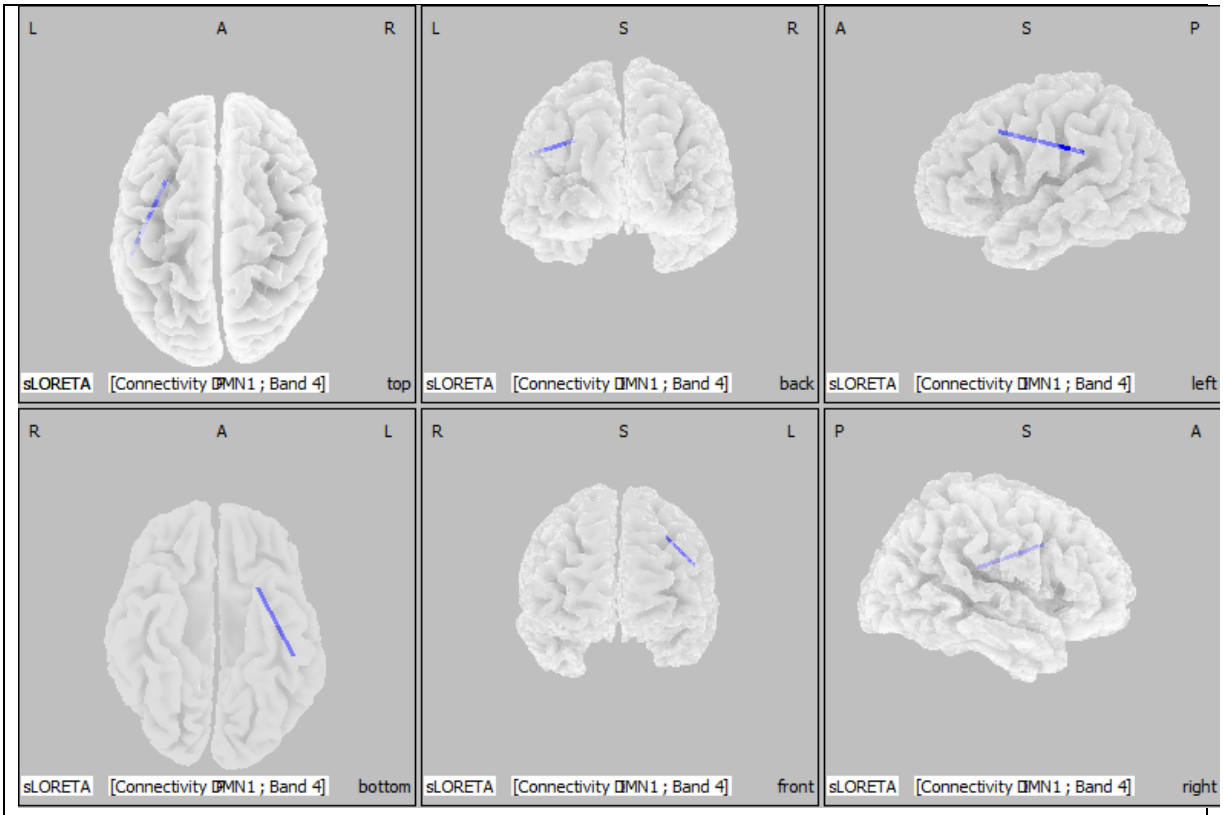
Figure B-2 Change in whole brain connectivity between the pre training and post training resting state EEG

Appendix B3: Default Mode Network Connectivity with 11 Regions of Interest

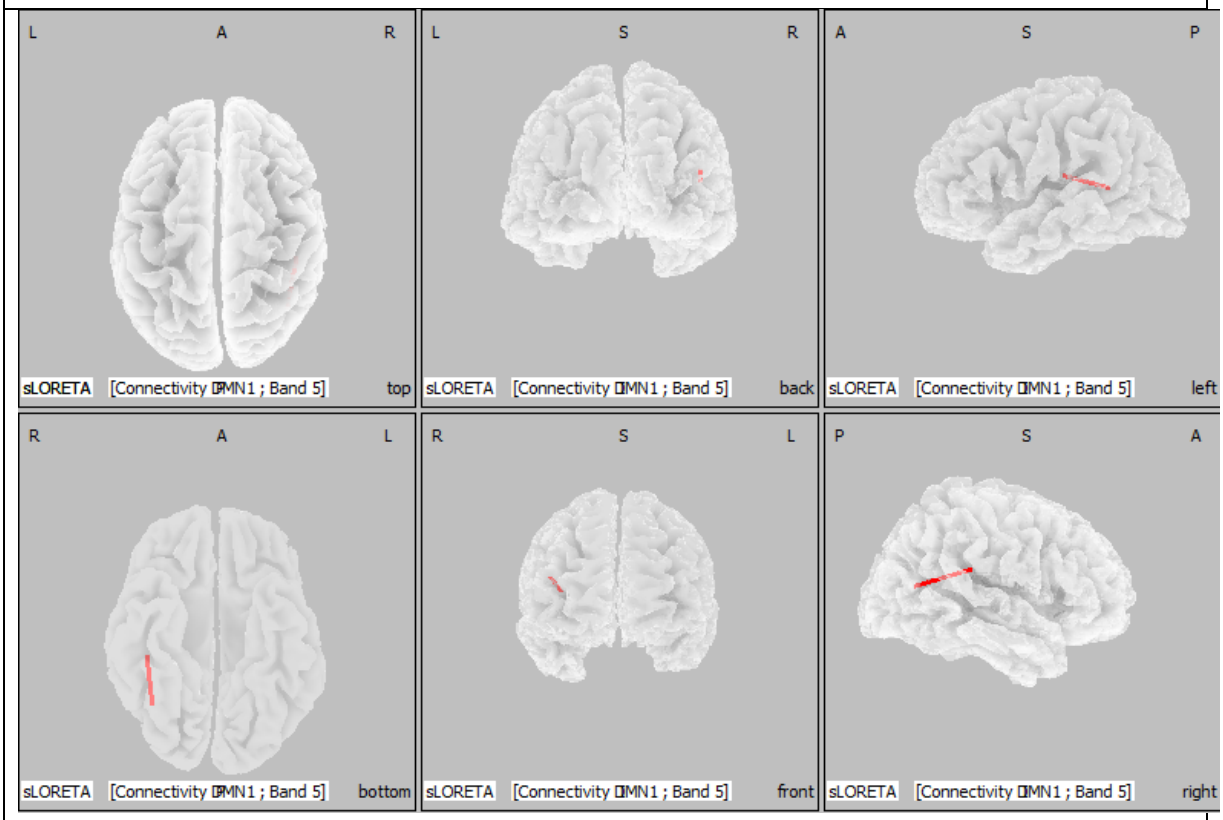
The figure B-3 below shows the lagged phase synchronisation of 11 regions of interest in the default mode network. Blue lines represent significant decreases in functional connectivity between pairs of regions of interest. White lines represent non-significant increases in functional connectivity. Red lines represent statistically significant increases in the functional connectivity between regions of interest. The two diagrams that show increases in functional connectivity used a higher threshold of change than the other diagram, because at that threshold, those changes became significant.



Theta band



Alpha 2 band



Beta 1 band

Figure B-3: Change in the DMN connectivity between the pre training and post training resting state EEG

Appendix B4: In training Activity in the PCC over Time

Figures B-4 to B-7 below show the in training activity in the PCC over time. The first and every second point from thereon represents the activity during the first five minutes of that training session. The second, and every second from thereon represents the last five minutes of that training session. Participants are randomly assigned the same number throughout.

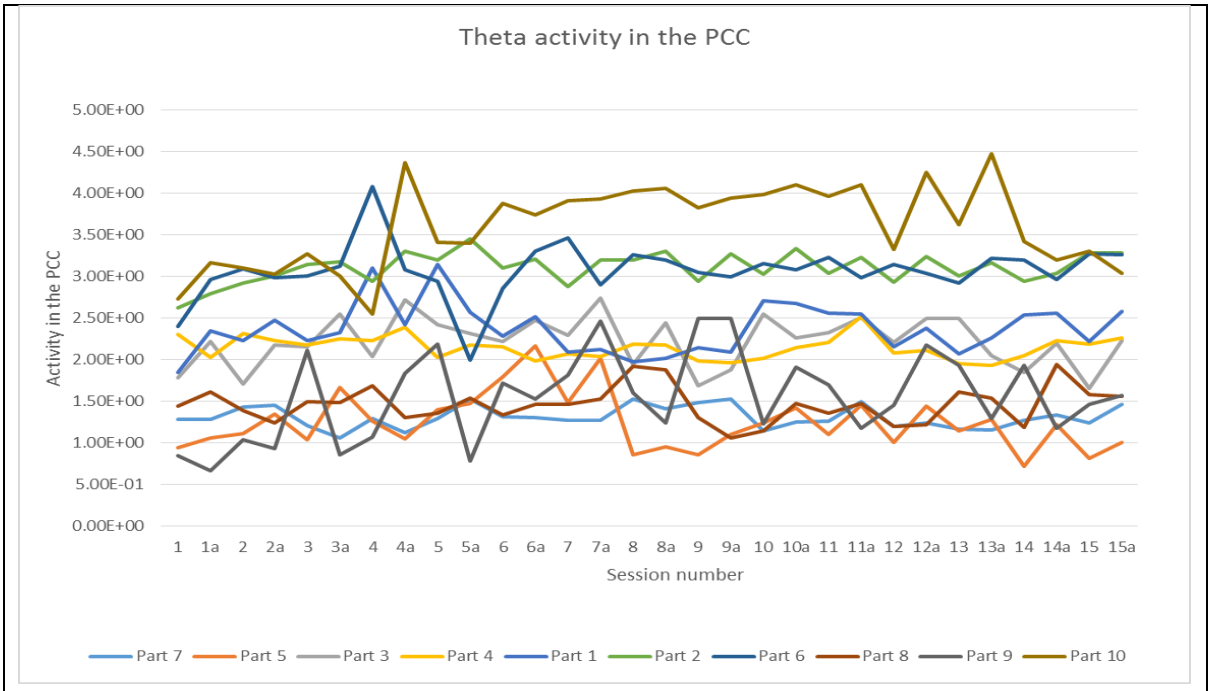


Figure B-4: Change in the theta current density in the PCC in the in-training data

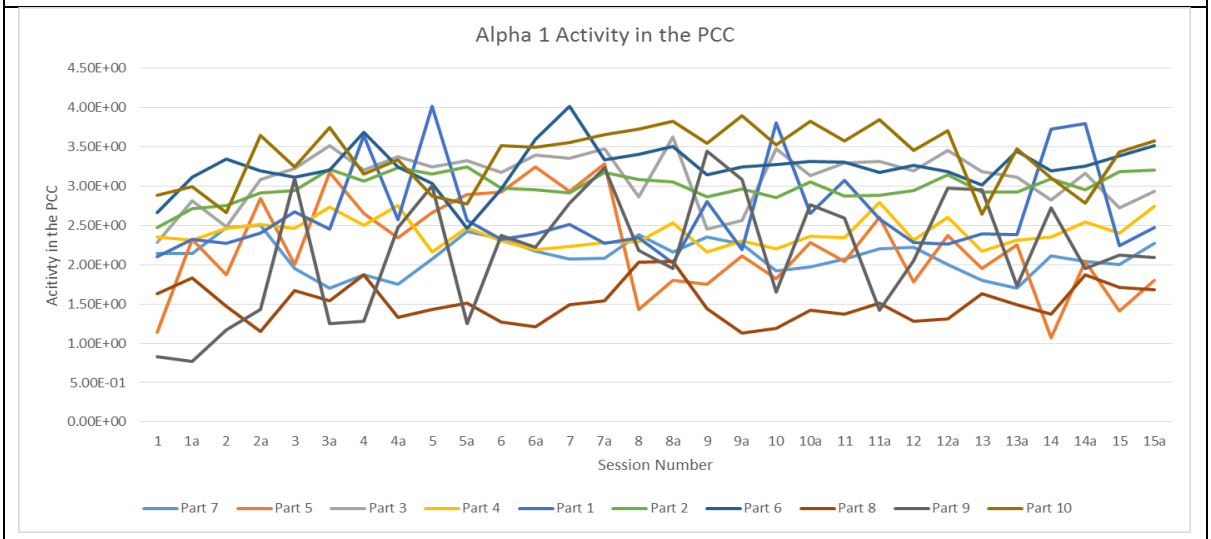


Figure B-5 Change in the alpha 1 current density in the PCC in the in-training data

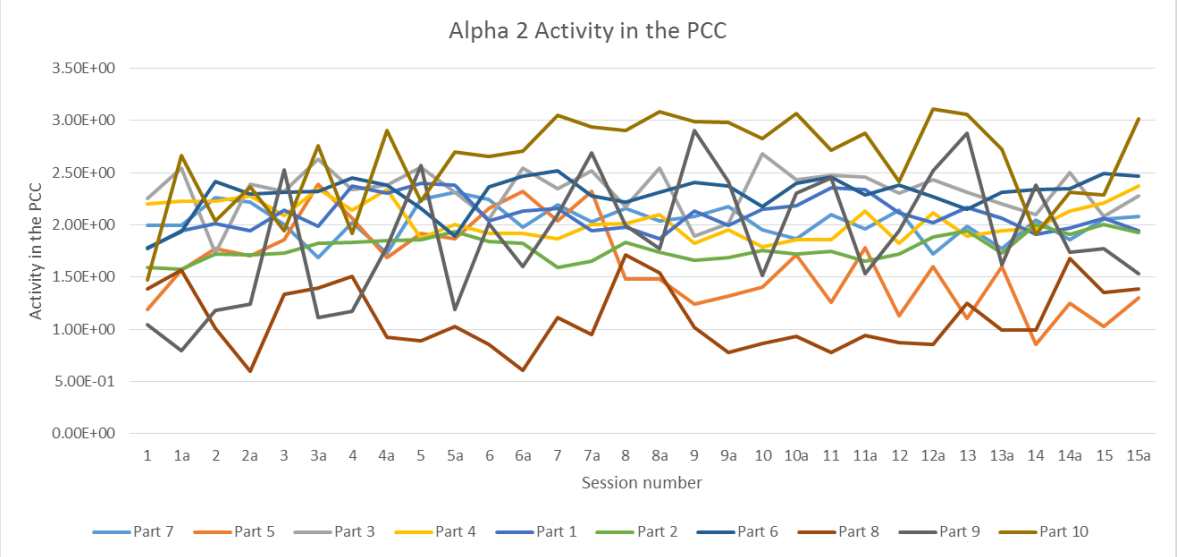


Figure B-6 Change in the alpha 2 current density in the PCC in the in-training data

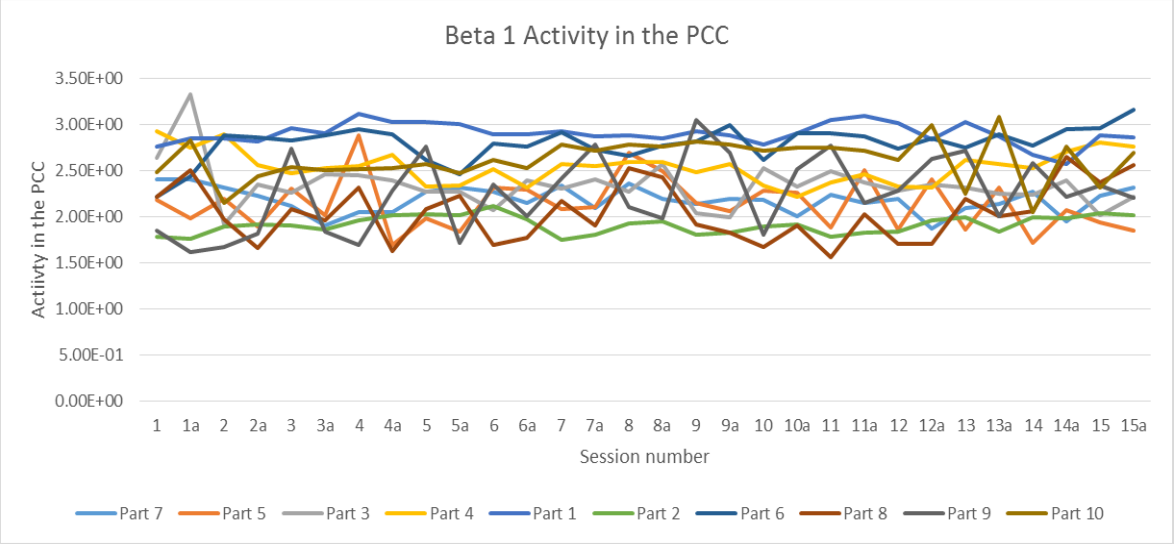


Figure B-7 Change in the beta 1 current density in the PCC in the in-training data

Appendix B5: Resting State activity in the PCC over time

Figures B-8 to B-11 below show the resting state activity in the PCC over time. This was measured at session 1, 8, 12 and 15.

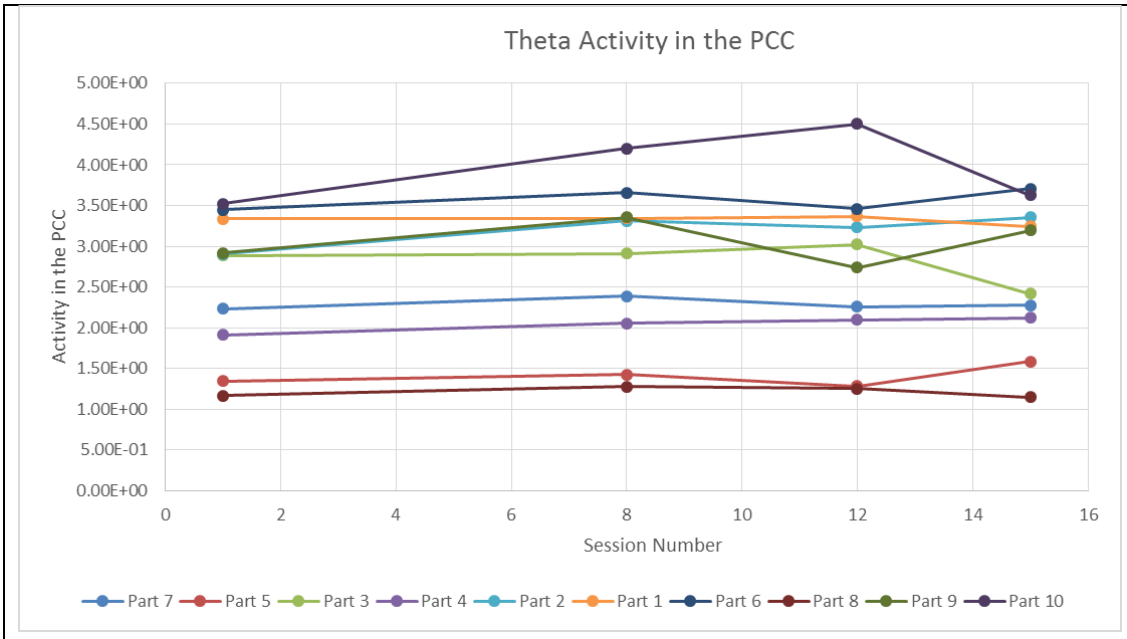


Figure B-8 Change in the theta current density in the PCC in the resting state data

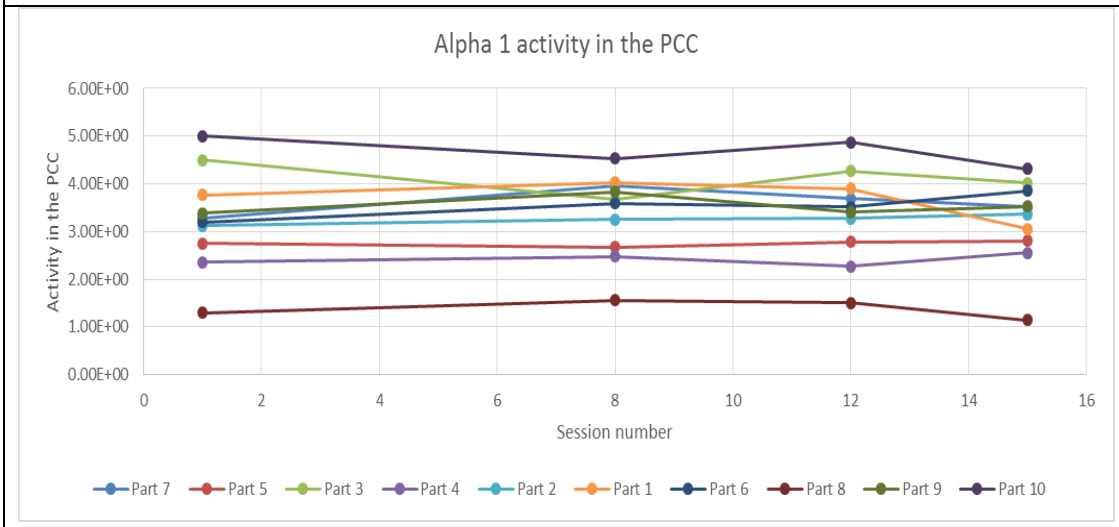


Figure B-9 Change in the alpha 1 current density in the PCC in the resting state data

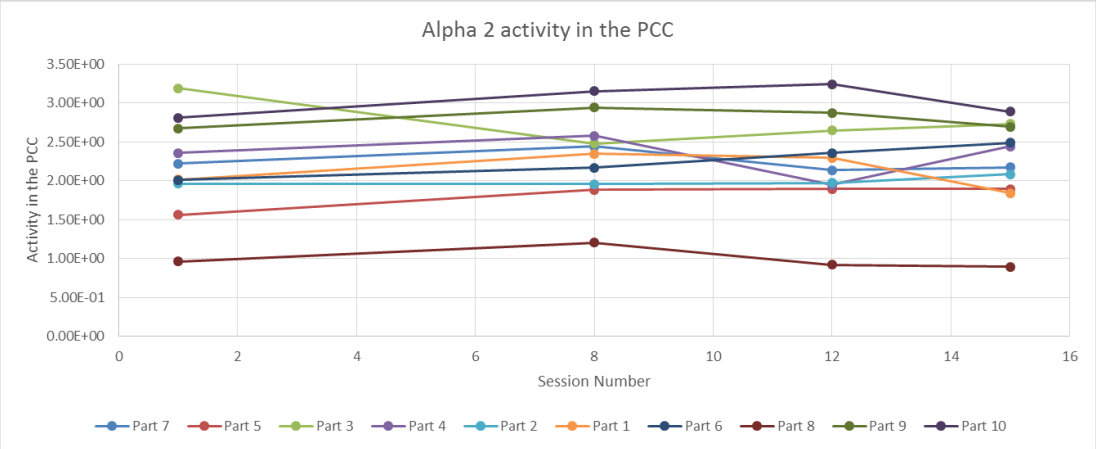


Figure B-10 Change in the alpha 2 current density in the PCC in the resting state data

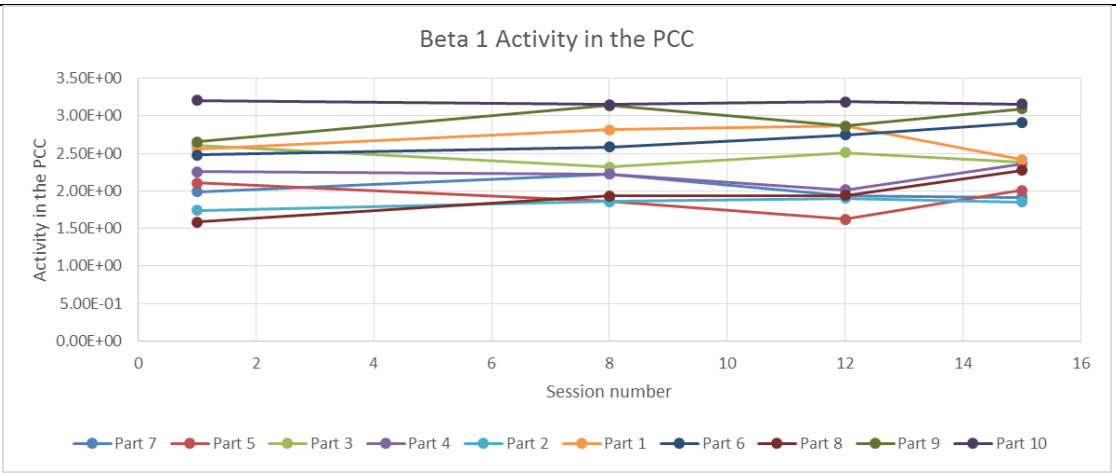


Figure B-11 Change in the beta 1 current density in the PCC in the resting state data

Appendix B5: In Training Connectivity between the PCC and the Left Parahippocampal Gyrus over Time

Figures B-12 to B-15 show the change in phase lagged synchronisation between the PCC and the parahippocampal gyrus over time. The first and every second point thereon represents the connectivity during the first 5 minutes of each session. The second, and every second point thereon represents the connectivity during the final 5 minutes of each session.

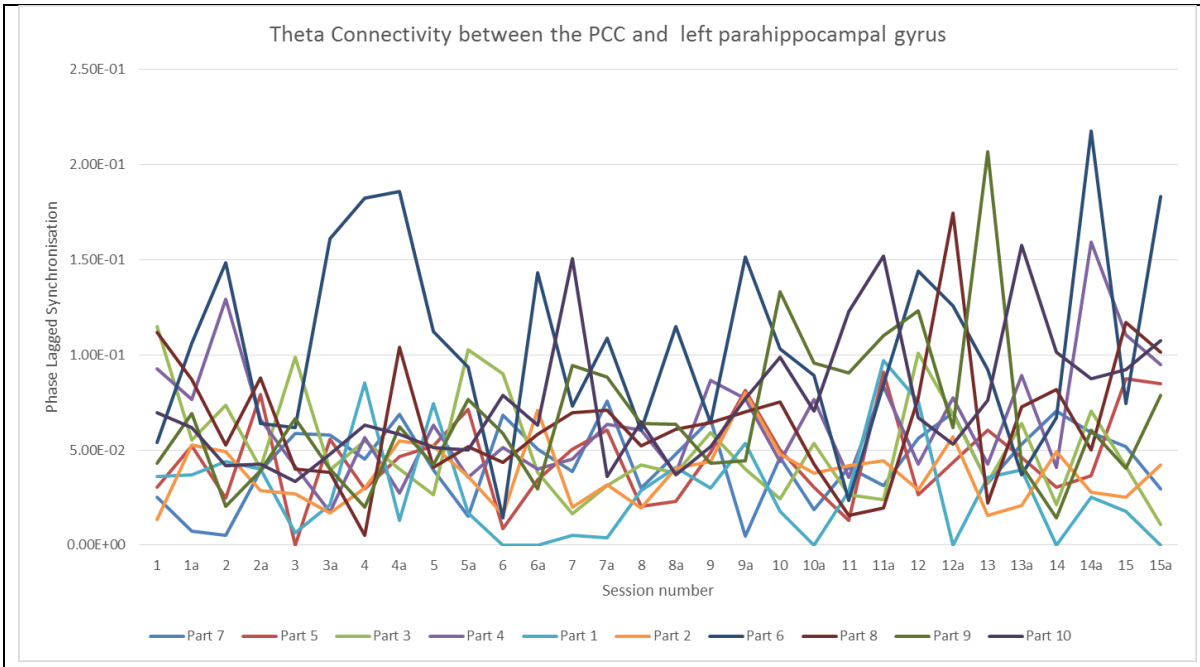


Figure B-12: Change in the theta phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

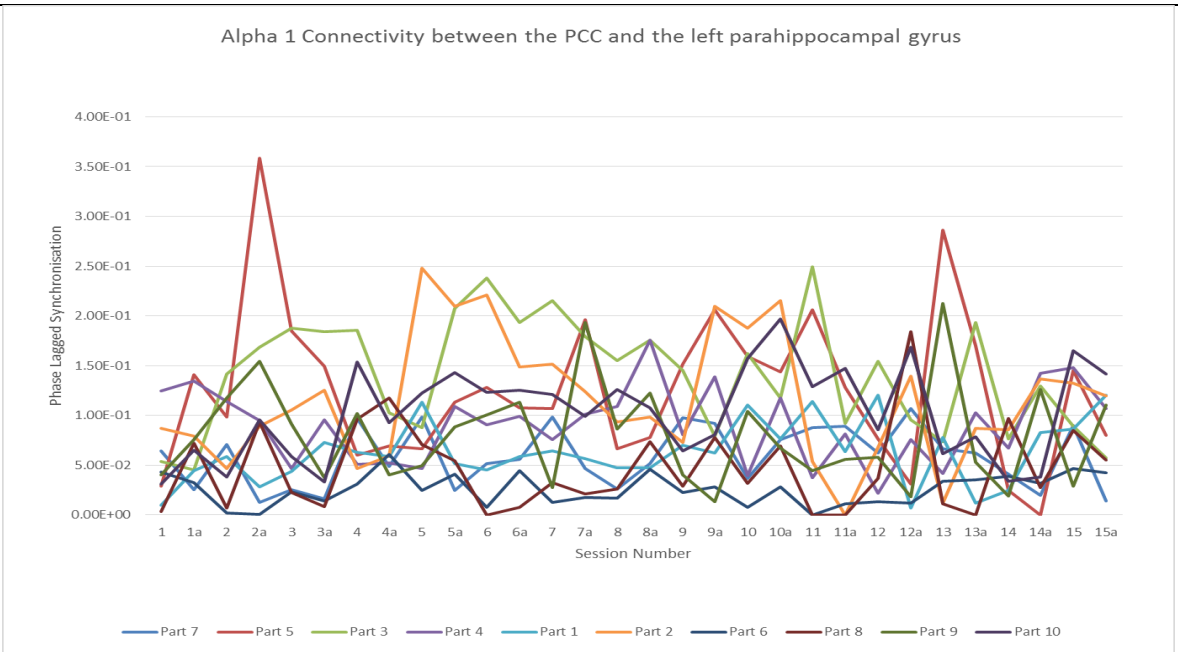


Figure B-13 Change in the alpha 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

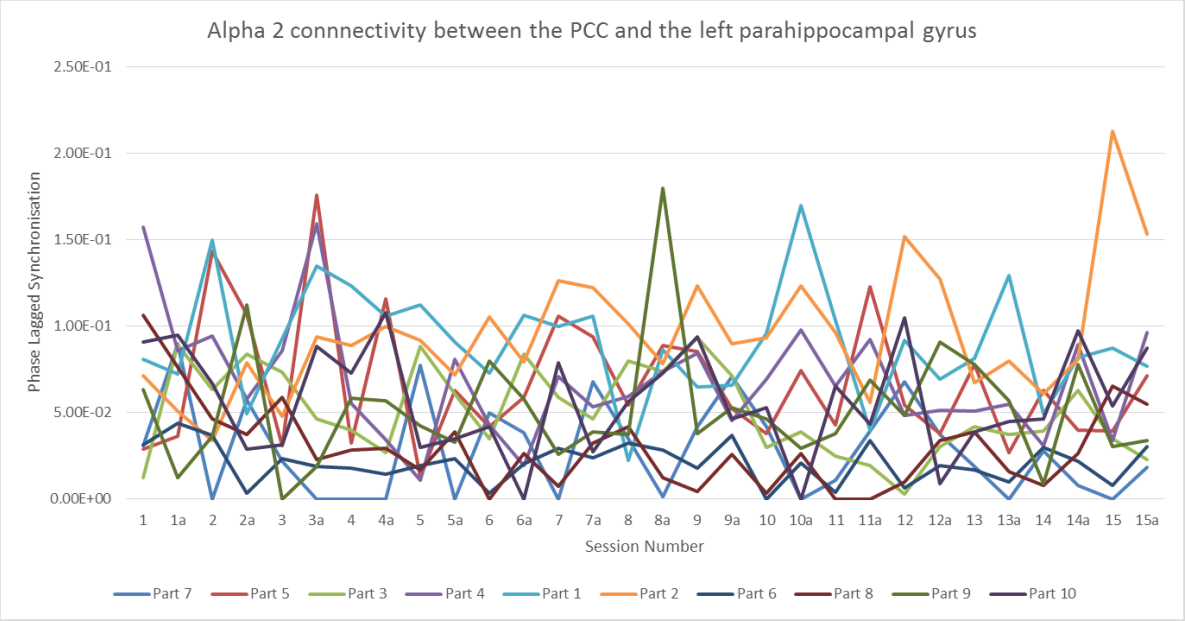


Figure B-14 Change in the alpha 2 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

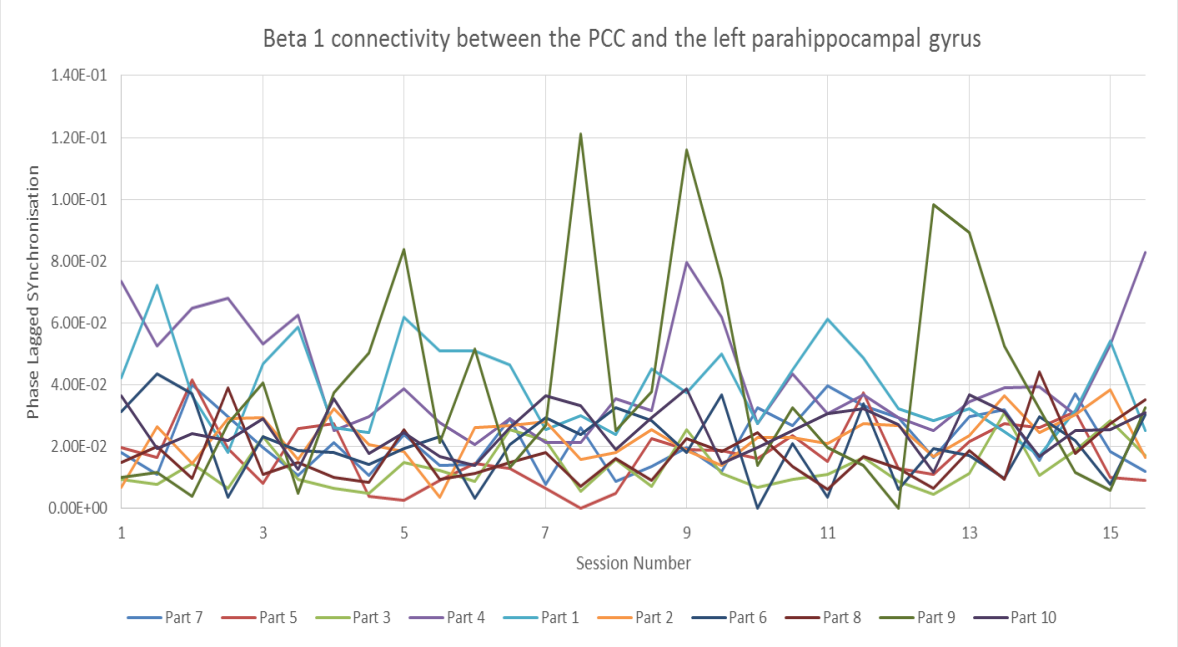


Figure B-15: Change in the beta 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

Appendix B7: Resting State Connectivity between the PCC and the Left Parahippcampal Gyrus

The resting state phase lagged synchronisation between the PCC and the left parahippocampal gyrus was calculated for the resting state EEGs taken at sessions 1, 8, 12 and 15. These are shown in Figures B-16 to B-19 below

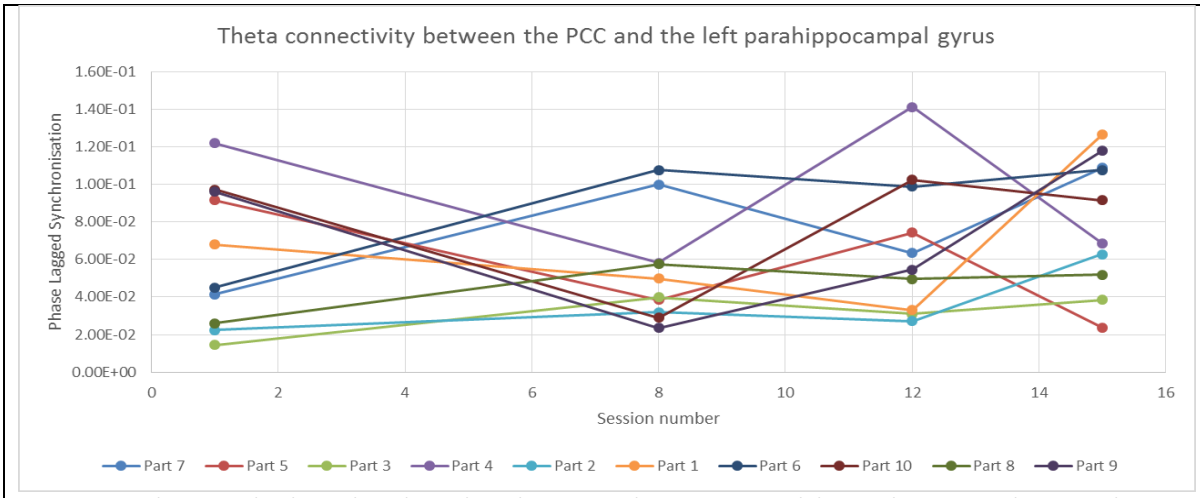


Figure B-16: Change in the theta phase lagged synchronisation between PCC and the parahippocampal gyrus in the resting state data

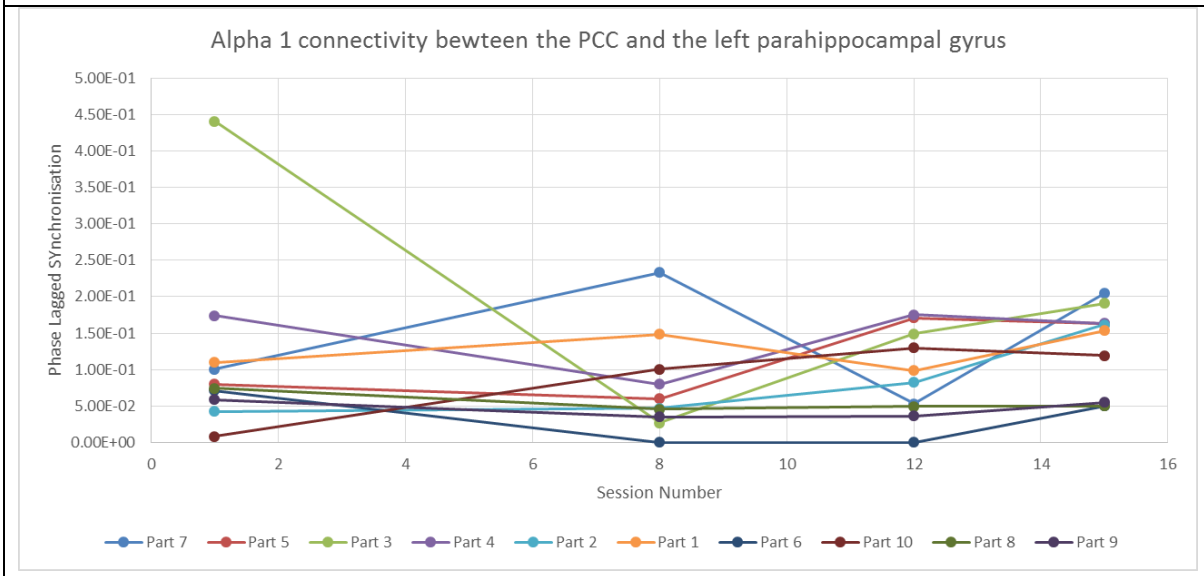


Figure B-17: Change in the alpha 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

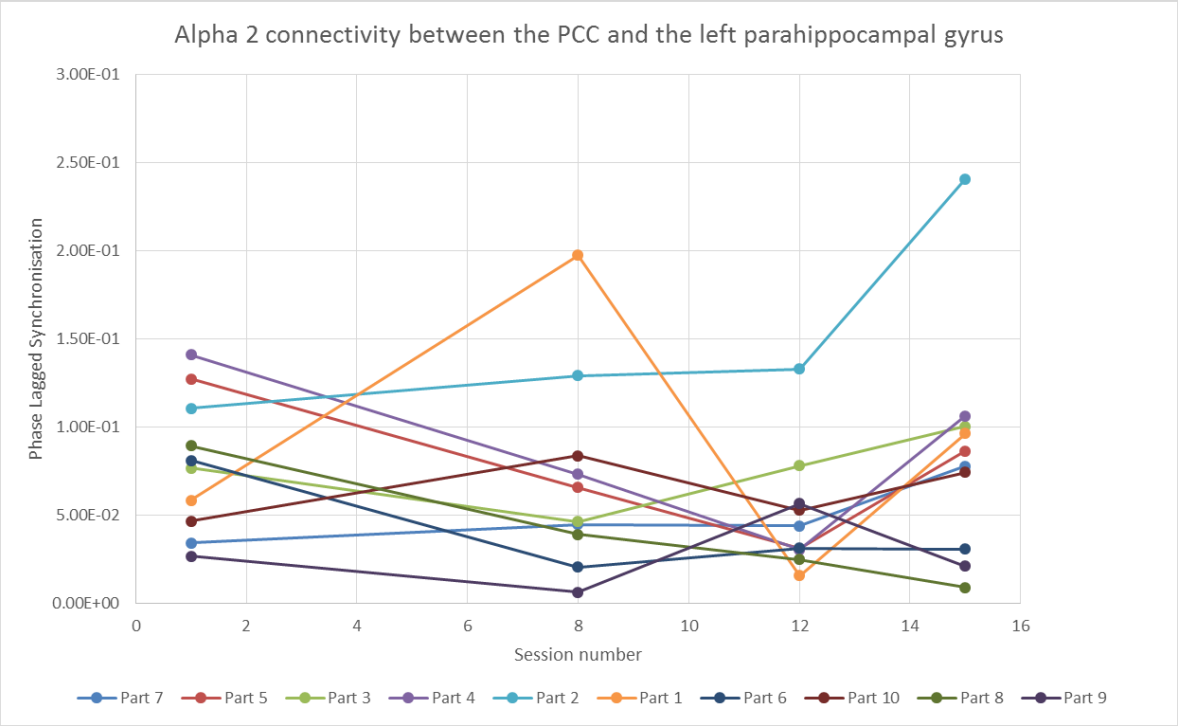


Figure B-18: Change in the alpha 2 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

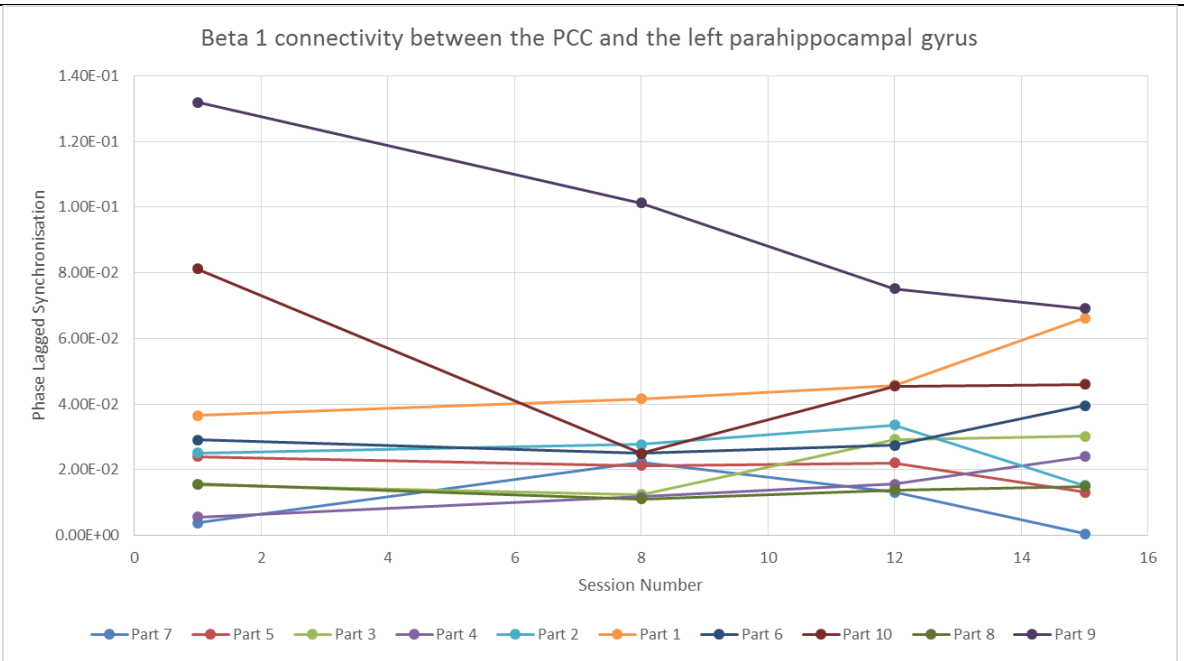


Figure B-19: Change in the beta 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the in-training data

Appendix B8: Table of Mean Correlation Coefficient

Table B-2 shows the averaged correlation coefficient for each frequency band in each condition, for the sLORETA indices shown in the graphs in Appendices B4 to B7.

Table B-1: Mean correlation coefficient for activity and resting state indices

Condition/Band	**Mean (SD)**	**Median**	**Significance**
In Training Activity			
Theta Correlation Coefficient	0.0774 (0.21)	0.0776	p=0.241[b]
Alpha 1 Correlation Coefficient	**0.153 (0.17)**	**0.183**	**p=0.028[b]**
Alpha 2 Correlation Coefficient	0.0248 (0.32)	-0.0127	p=0.814[a]
Beta 1 Correlation Coefficient	0.03769 (0.28)	-0.0121	p=0.686[a]
Resting State Activity			
Theta Correlation Coefficient	0.240 (0.51)	0.240	p=0.646[b]
Alpha 1 Correlation Coefficient	0.105 (0.17)	0.173	p=0.592[a]
Alpha 2 Correlation Coefficient	0.125 (0.58)	-0.0674	p=0.516[a]
Beta 1 Correlation Coefficient	0.0824 (0.68)	-0.182	p=0.575[b]
In Training Connectivity			
Theta Correlation Coefficient	0.137 (0.24)	0.194	p=0.110[a]
Alpha 1 Correlation Coefficient	0.0635 (0.18)	0.0384	p=0.285[a]
Alpha 2 Correlation Coefficient	-0.123 (0.25)	-0.194	p=0.114[b]
Beta 1 Correlation Coefficient	0.0859 (0.182)	0.107	p=0.170[a]
Resting State Connectivity			
Theta Correlation Coefficient	0.343 (0.51)	0.500	p=0.063[a]
Alpha 1 Correlation Coefficient	0.154 (0.58)	0.135	p=0.422[a]

Condition/Band	Mean (SD)	Median	Significance
Resting State Connectivity			
Alpha 2 Correlation Coefficient	-0.0150 (0.65)	0.0880	p=0.878[b]
Beta 1 Correlation Coefficient	0.221 (0.69)	0.366	p=0.333[b]

[a] *significance was calculated using a one sample t test. H_0 = mean of correlation coefficients is 0*

[b] *significance is calculated using a Wilcoxon signed rank test. H_0 =median of correlation coefficients is 0*

Appendix C

Appendix C1: Baseline Characteristics of Volunteers

Table C-1 below shows the baseline characteristics of people who qualified to take part in the biofeedback training, who scored below 90 on the immediate memory index.

Table C-1: Baseline characteristics of participants all volunteers who scores below 90 on the immediate memory index

	Group total Mean (SD)	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Age	67.6 (9.65)	67.5 (9.44)	67.8 (9.99)
Number of Women (%)	31 (45.6%)	20 (46.5%)	11 (44.0%)
Years of Education	14.1 (2.50)	14.2 (2.49)	13.9 (2.51)
List Learning	22.4 (4.82)	22.5 (5.03)	22.4 (4.44)
Story Learning	12.5 (2.93)	12.0 (2.83)	13.3 (2.91)
Figure Copy	18.4 (1.78)	18.5 (1.83)	18.0 (1.64)
Line Orientation	17.0 (2.41)	17.1 (2.48)	16.9 (2.28)
Picture Naming	9.4 (0.85)	9.3 (0.96)	9.6 (0.56)
Semantic Fluency	19.2 (4.27)	20.1 (4.21)	17.6 (3.90)
Digit Span	10.3 (2.21)	10.0 (2.09)	10.7 (2.34)
Coding	39.5 (8.85)	39.6 (7.55)	39.4 (10.73)
List Recall	4.0 (2.20)	4.2 (2.26)	3.8 (2.08)
List Recognition	18.4 (1.81)	18.5 (1.73)	18.2 (1.92)
Story Recall	6.2 (2.60)	5.9 (2.51)	6.8 (2.66)
Figure Recall	12.1 (4.62)	12.2 (4.77)	11.8 (4.34)

	Group total Mean (SD)	RBANS A group Mean (SD)	RBANS B group Mean(SD)
Immediate Memory Index	80.6 (9.24)	79.5 (9.57)	82.6 (8.30)
Visuospatial Index	105.0 (15.56)	106.3 (15.80)	102.7 (14.86)
Language Index	96.6 (10.41)	97.4 (10.97)	95.2 (9.19)
Attention index	96.3 (12.66)	95.2 (12.12)	98.1 (13.34)
Delayed Memory index	88.8 (15.13)	89.0 (15.43)	88.4 (14.60)
Sum of Indices	467.2 (40.52)	467.3 (40.90)	467.0 (39.85)
Total Scale Index	90.8 (10.32)	90.8 (10.38)	90.7 (10.21)
Average last two 2-back	42.5 (23.62)	45.0 (24.24)	38.1 (21.81)

Table C-2 shows the baseline characteristics of the volunteers who scored above 90 on the immediate memory index, had and EEG taken and were matched to participants in the biofeedback training. They form the 'normal brain' control group.

Table C-2 Baseline Characteristics of volunteers who scored above 90 and were matched to participants

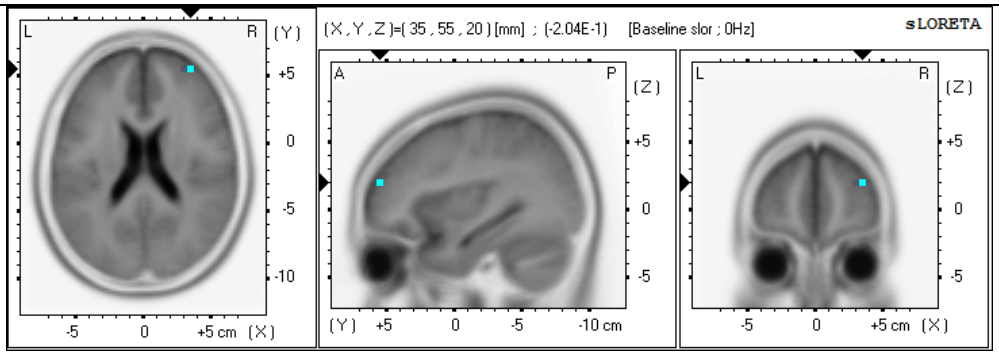
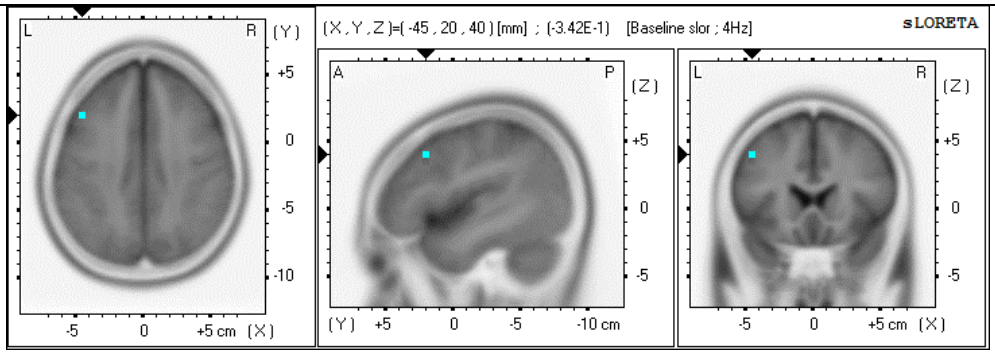
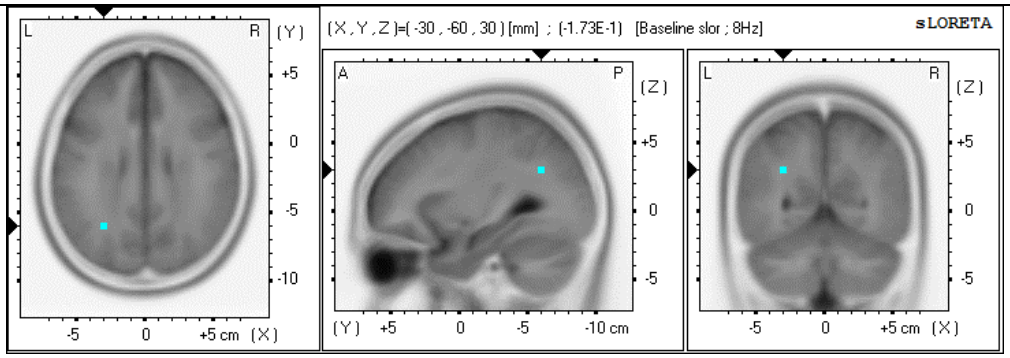
	Group Total	RBANS A	RBANS B
Age	66.1 (10.77)	62.9 (11.25)	67.7 (10.19)
Number of Women (%)	22 (46.8%)	11 (73.3%)	11 (34.3%)
Years of Education	16.0 (2.70)	16.3 (3.09)	15.9 (2.48)
List Learning	28.7 (3.40)	28.3 (3.45)	28.9 (3.35)
Story Learning	18.7 (2.42)	17.7 (2.74)	19.2 (2.09)

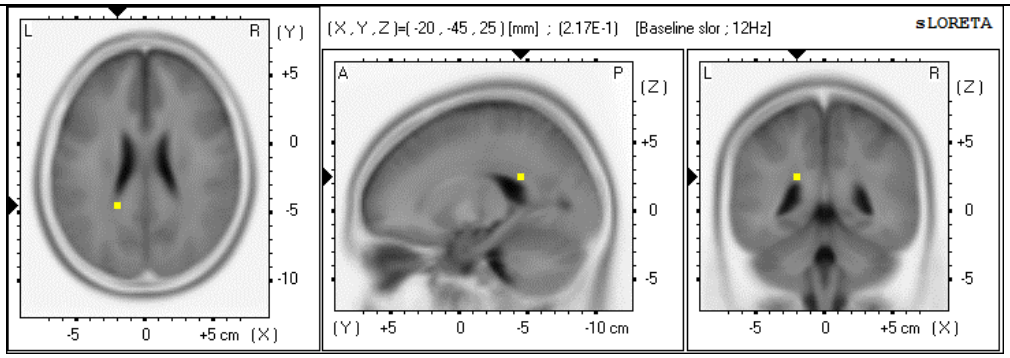
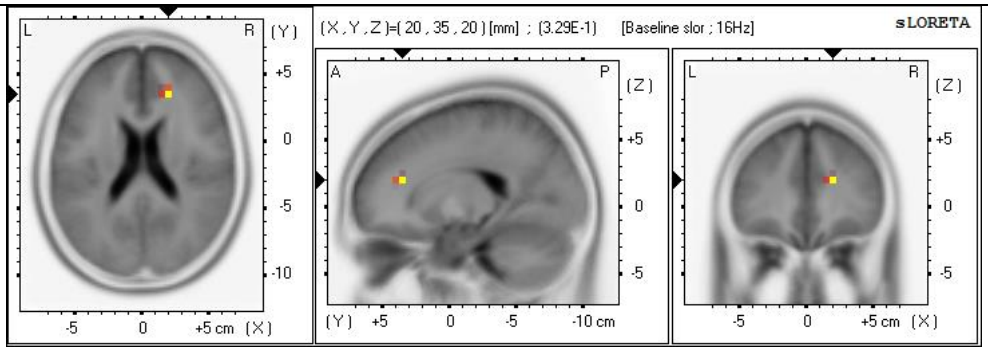
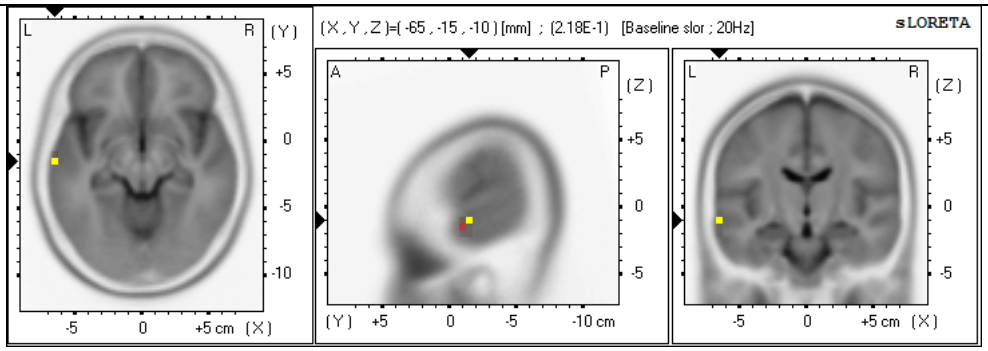
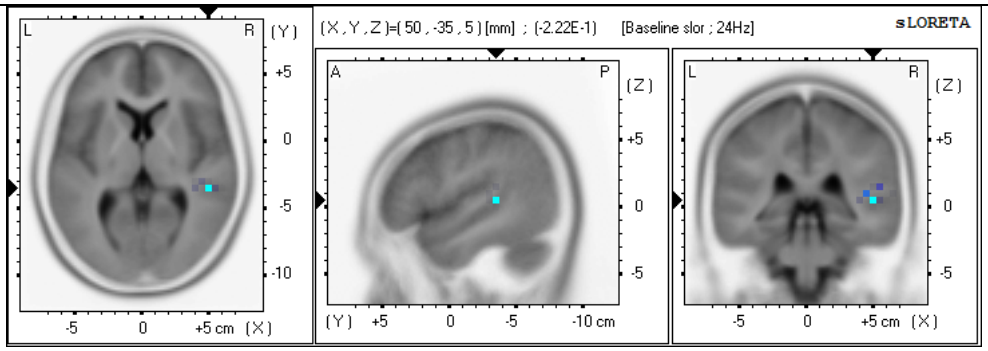
	Group Total	RBANS A	RBANS B
Figure Copy	18.7 (1.51)	19.2 (0.83)	18.5 (1.70)
Line Orientation	17.7 (3.13)	17.9 (2.21)	17.6 (3.48)
Picture Naming	9.9 (0.31)	9.8 (0.40)	9.9 (0.24)
Semantic Fluency	21.8 (5.20)	25.0 (5.07)	20.3 (4.55)
Digit Span	10.6 (2.46)	10.9 (1.88)	10.4 (2.67)
Coding	46.3 (8.71)	48.5 (8.21)	45.3 (8.76)
List Recall	6.5 (2.00)	6.0 (1.79)	6.7 (2.05)
List Recognition	19.5 (0.82)	19.3 (1.07)	19.6 (0.66)
Story Recall	9.9 (1.76)	9.2 (1.76)	10.2 (1.68)
Figure Recall	15.0 (2.82)	14.1 (3.19)	15.4 (2.52)
Immediate Memory Index	107.9 (8.94)	105.6 (9.11)	109.0 (8.65)
Visuospatial Index	110.5 (13.35)	112.6 (12.86)	109.5 (13.47)
Language Index	104.5 (11.81)	111.2 (12.01)	101.4 (10.32)
Attention index	104.4 (13.85)	108.3 (10.95)	102.6 (14.67)
Delayed Memory index	107.1 (10.25)	101.9 (10.74)	109.6 (9.01)
Sum of Indices	534.5 (37.20)	539.6 (38.25)	532.1 (36.45)
Total Scale Index	109.6 (11.57)	111.5 (12.16)	108.8 (11.18)
Average last two 2-back	34.4 (17.22)	55.6 (18.02)	57.2 (28.3)

Appendix C2: Whole Group Baseline Comparisons to 'Normal Brain' Controls

Activity

Figure C-1 below show the comparison of the baseline EEG recordings of the participants and the 'normal brain' control group. Blue voxels indicate the activity was lower in the participants and orange voxels indicate the activity was higher in the participants. In the omega band, no significant voxels could be found.

Delta band	
Theta band	
Alpha 1 band	

Alpha 2 band	
Beta 1 band	
Beta 2 band	
Beta 3 band	

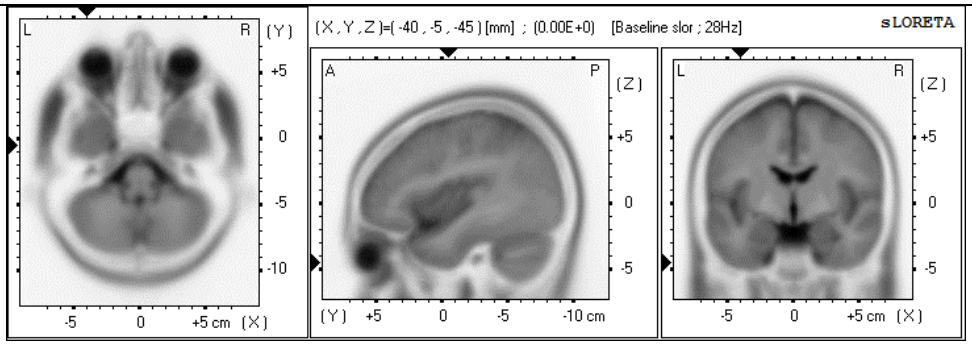
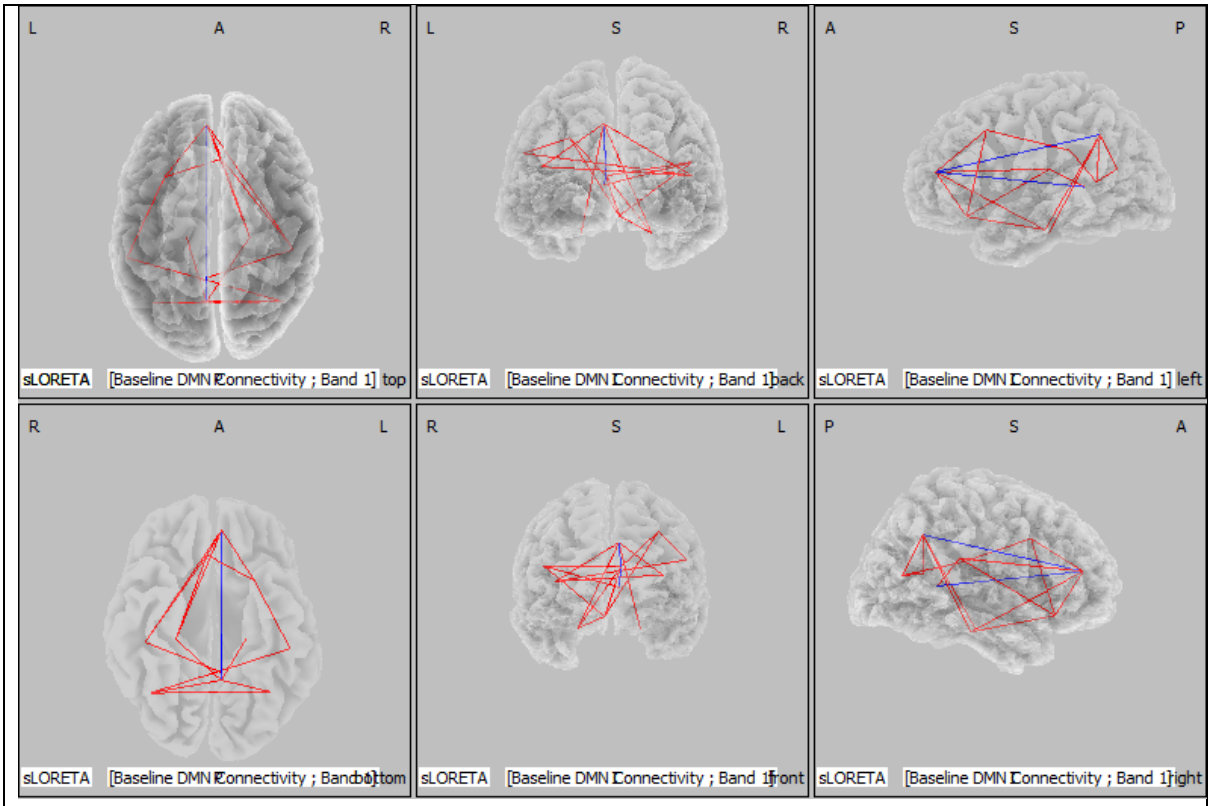
Omega band	

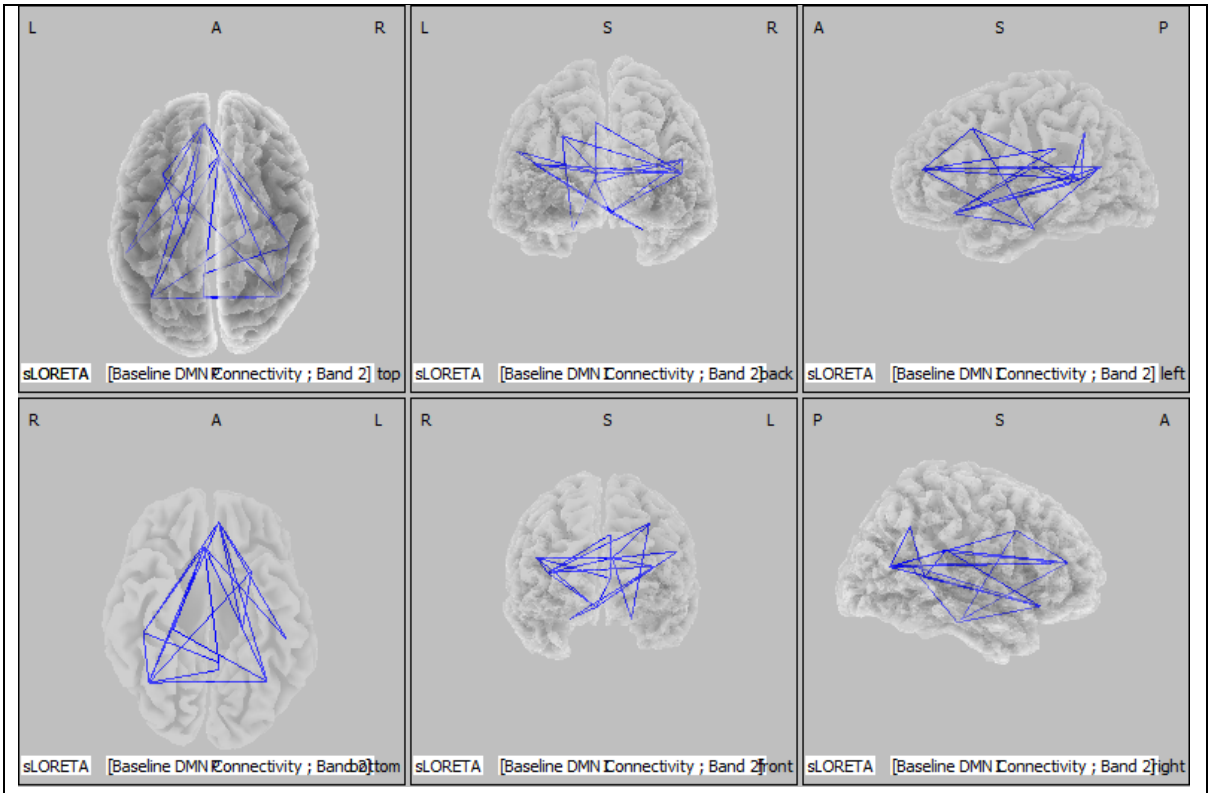
Figure C-1: Maps of current density comparing the matched participants at baseline and 'normal brain' controls

Connectivity

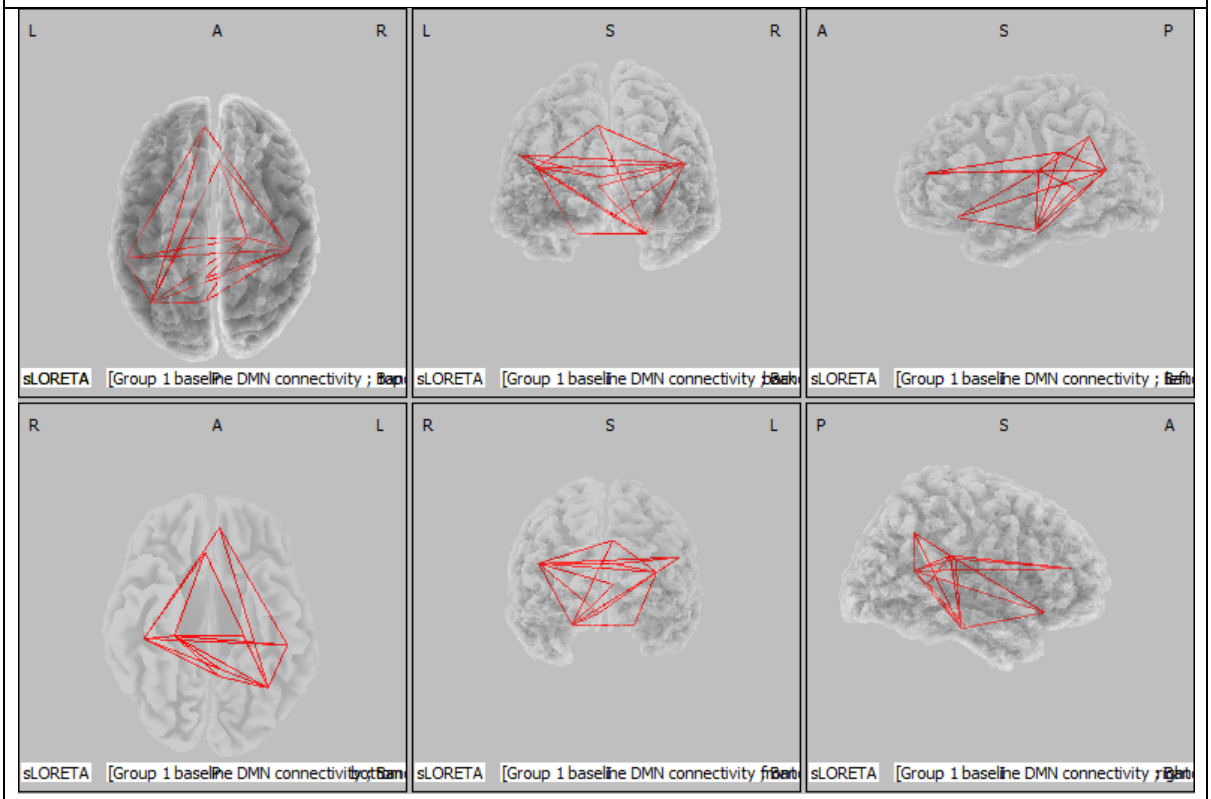
Figure C-2 below shows the difference in the connectivity between the participants and the 'normal brain controls. These represent changes significant at the p=0.12 level. Blue lines indicate there is decreased connectivity between the nodes in the participants and red lines indicate that there is decreased connectivity between the nodes in the participants.



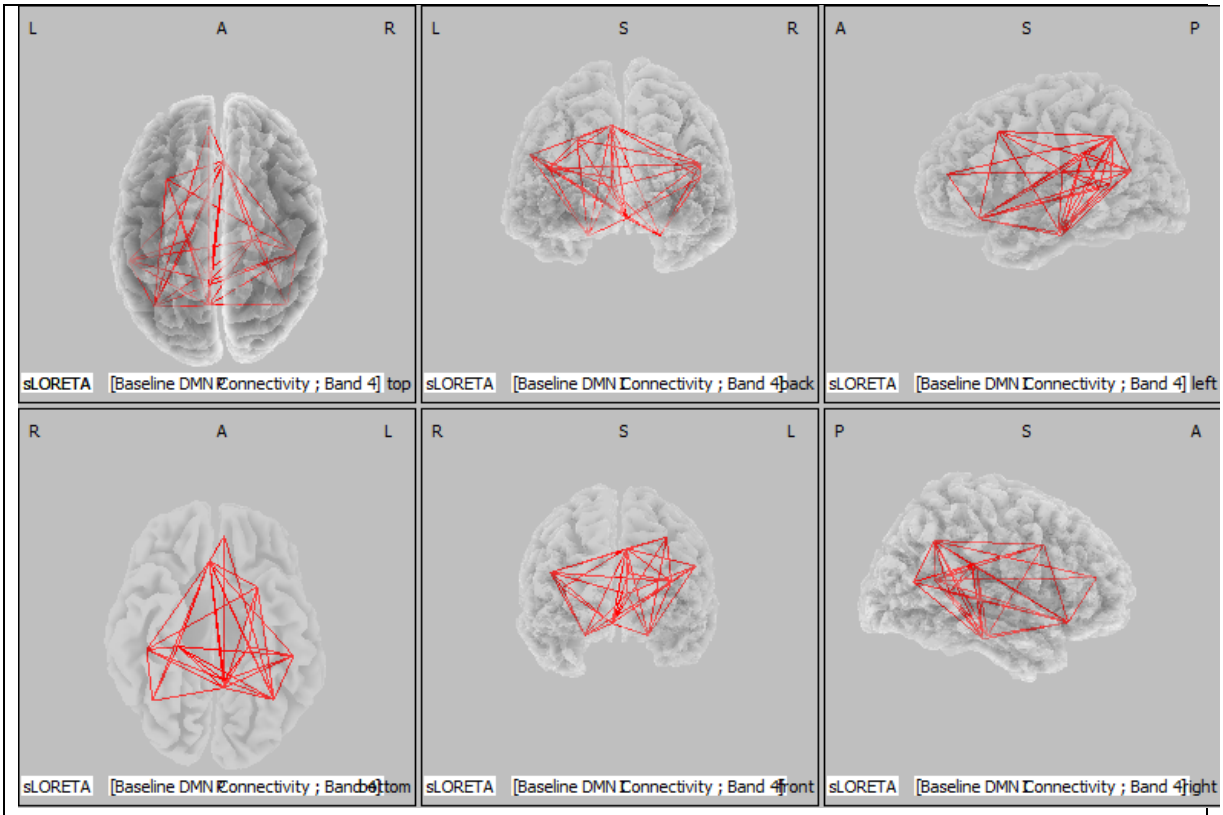
Delta band



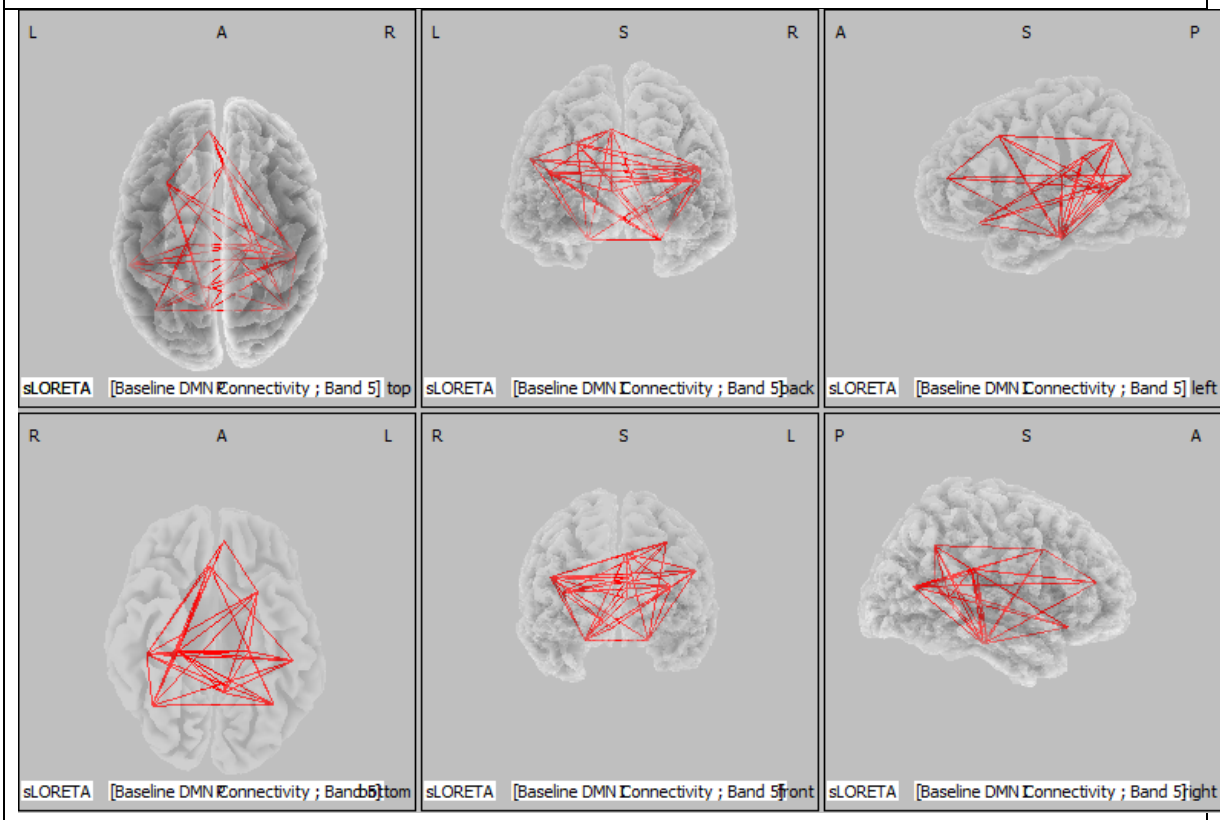
Theta band



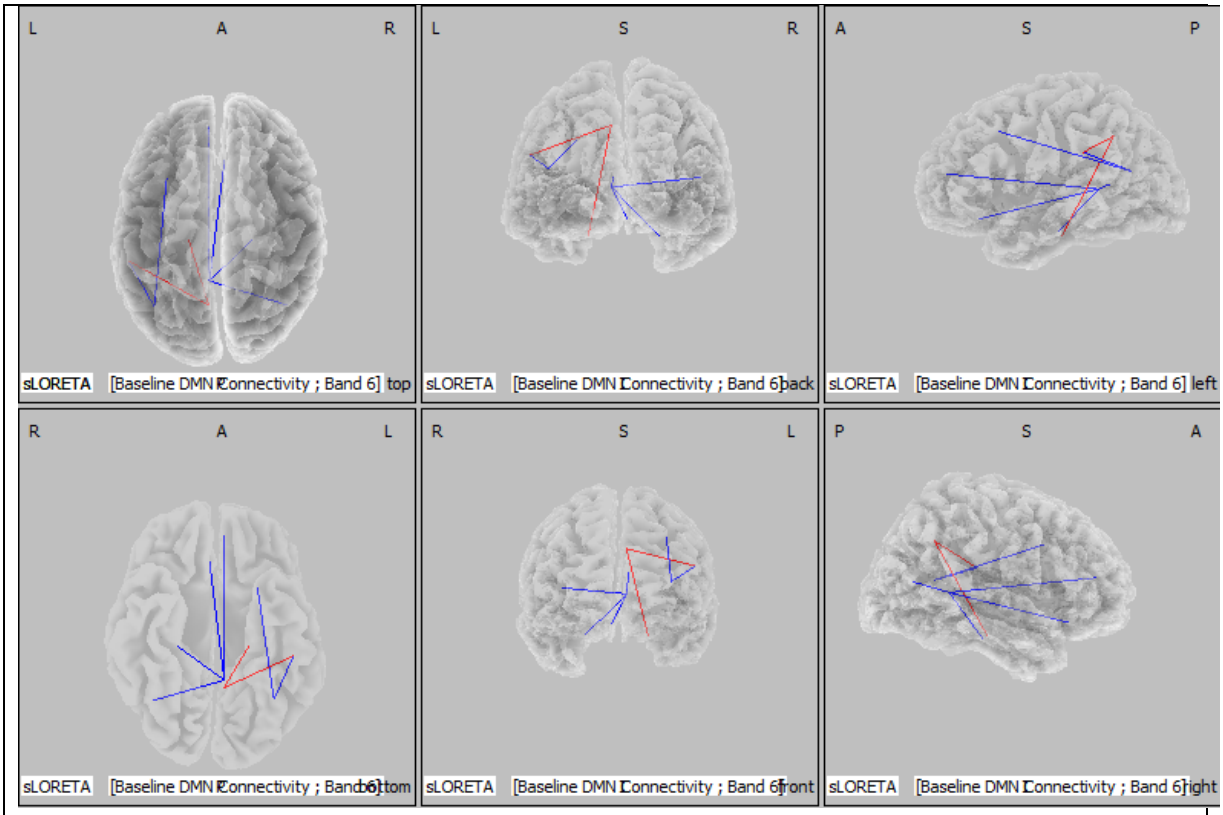
Alpha 1 band



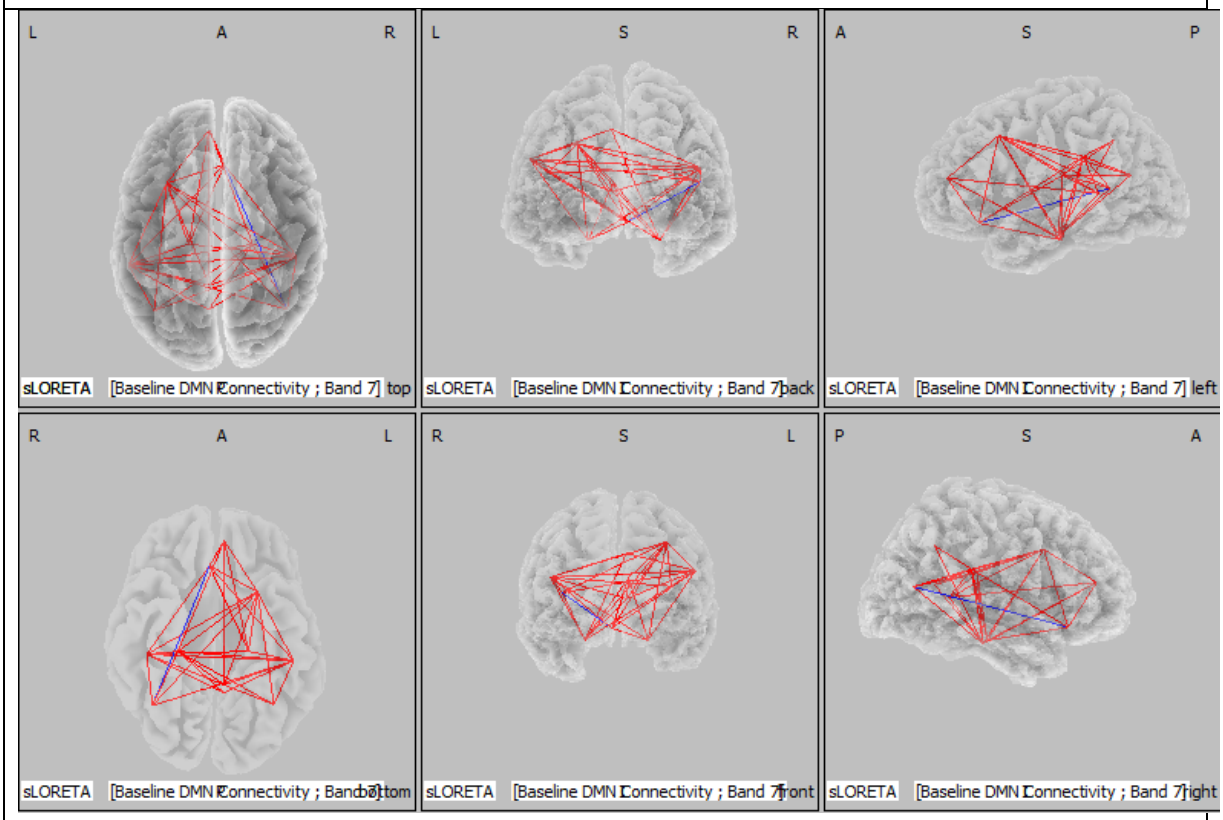
Alpha 2 band



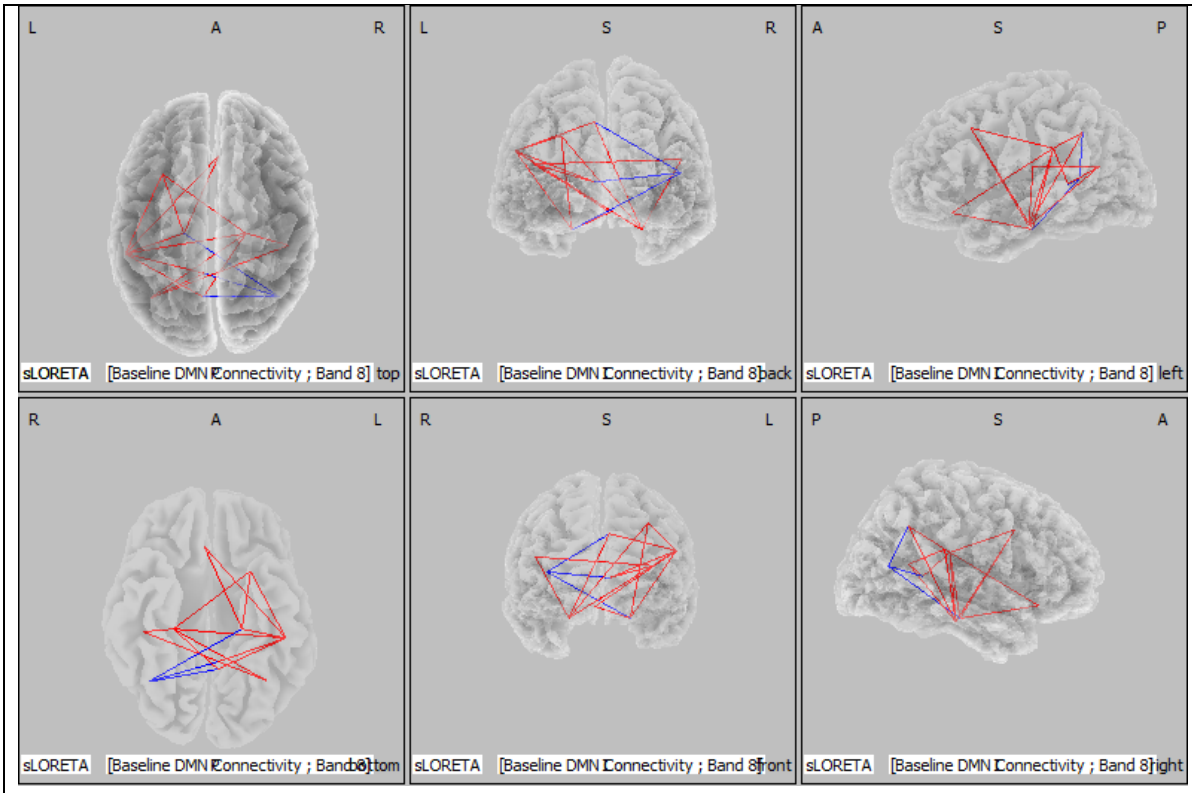
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure C-2: Maps comparing the phase lagged synchronisation of the DMN of matched participants at baseline and 'normal brain' controls

Appendix C3: Baseline RBANS Score Separated by Initial Form

Table C-3 to C-5 below show the baseline RBANS scores in each group individually, separated by RBANS form.

Broadband Feedback Group

Table C-3: Baseline RBANS score of the broadband feedback group

	Total	RBANS A Mean (SD)	RBANS B Mean SD
Age	70.8 (12.1)	70.3 (11.77)	71.4 (12.50)
Number of Women (%)	8 (44.4%)	5 (50.0%)	3 (38.9%)
Years of Education	14.2 (2.29)	14.2 (2.09)	14.1 (2.52)

	Total	RBANS A Mean (SD)	RBANS B Mean SD
List Learning	21.3 (5.8)	22.7 (6.15)	19.6 (4.90)
Story Learning	12.2 (2.90)	12.3 (2.87)	12.1 (2.93)
Figure Copy	17.8 (1.93)	17.8 (2.48)	17.8 (0.83)
Line Orientation	17.2 (2.09)	17.7 (1.90)	16.5 (2.12)
Picture Naming	9.3 (0.80)	9.3 (0.90)	9.3 (0.66)
Semantic Fluency	18.1 (4.71)	19.6 (4.15)	16.1 (4.65)
Digit Span	9.8 (1.50)	9.8 (1.17)	9.9 (1.83)
Coding	34.4 (9.85)	36.2 (8.33)	32.1 (11.06)
List Recall	3.4 (2.52)	4.1 (9.95)	2.6 (1.49)
List Recognition	17.8 (2.48)	17.9 (2.30)	17.6 (2.69)
Story Recall	5.4 (2.41)	5.5 (2.20)	5.3 (2.63)
Figure Recall	11.4 (5.37)	11.9 (5.32)	10.8 (5.36)
Immediate Memory Index	79.8 (9.91)	81.6 (10.34)	77.5 (8.85)
Visuospatial Index	102.7 (14.11)	105.3 (15.89)	99.5 (1.64)
Language Index	94.8 (13.09)	97.5 (13.54)	91.5 (11.68)
Attention index	91.3 (7.93)	92.8 (7.12)	89.5 (8.49)
Delayed Memory index	84.4 (18.68)	86.4 (18.85)	82.0 (18.16)
Sum of Indices	453.1 (49.12)	463.6 (52.37)	440.0 (41.14)
Total Scale Index	87.1 (12.34)	89.7 (13.24)	83.9 (10.24)
Average last two 2-back	35.2 (22.4)	35.6 (24.26)	34.7 (19.87)

Narrowband Feedback Group

Table C-4: Baseline RBANS score of the narrowband feedback group

	Group Total	RBANS A Mean (SD)	RBANS B Mean (SD)
Age	66.7 (9.77)	69.0 (9.09)	62.5 (9.57)
Number of Women (%)	7 (41.1%)	4 (36.3%)	3 (50%)
Years of Education	13.1 (2.49)	13.3 (2.49)	12.8 (2.48)
List Learning	22.6 (4.22)	22.2 (4.93)	23.3 (2.21)
Story Learning	12.9 (2.53)	12 (2.45)	14.7 (1.60)
Figure Copy	18.9 (1.26)	18.7 (1.42)	19.3 (0.75)
Line Orientation	17.1 (2.69)	17.1 (2.91)	17 (2.24)
Picture Naming	9.5 (1.04)	9.2 (1.19)	10 (0.00)
Semantic Fluency	18.6 (3.98)	19.5 (4.38)	17.2 (2.54)
Digit Span	10.2 (2.34)	9.5 (1.92)	11.7 (2.36)
Coding	43.9 (7.89)	41.3 (6.94)	48.8 (7.15)
List Recall	4.2 (1.98)	4.1 (1.83)	4.5 (2.22)
List Recognition	18.8 (1.11)	18.9 (1.08)	18.5 (1.12)
Story Recall	6.6 (2.63)	5.8 (2.59)	8.2 (1.95)
Figure Recall	12.6 (3.34)	12.5 (3.58)	12.7 (2.87)
Immediate Memory Index	81.5 (8.38)	79.8 (8.70)	84.7 (6.72)
Visuospatial Index	108.1 (14.17)	107.5 (13.8)	109 (14.79)
Language Index	95.2 (9.90)	96.1 (11.35)	93.7 (6.16)
Attention index	100.5 (12.67)	95.7 (11.67)	109.2 (9.39)

	Group Total	RBANS A Mean (SD)	RBANS B Mean (SD)
Delayed Memory index	91.4 (11.91)	90.5 (12.6)	93.2 (10.32)
Sum of Indices	476.7 (26.80)	469.6 (26.03)	489.7 (23.10)
Total Scale Index	93.0 (6.99)	91.2 (6.58)	96.5 (6.40)
Average last two 2-back	47.8 (26.03)	37.6 (18.75)	54.8 (23.36)

Placebo Feedback Group

Table C-5: Baseline RBANS score in the placebo feedback group

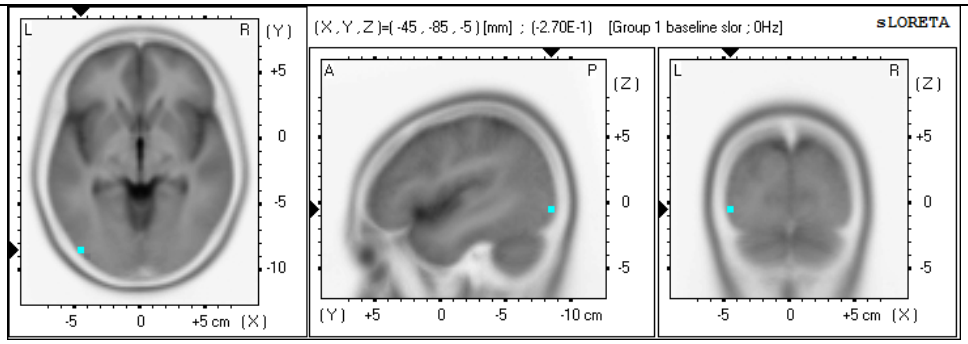
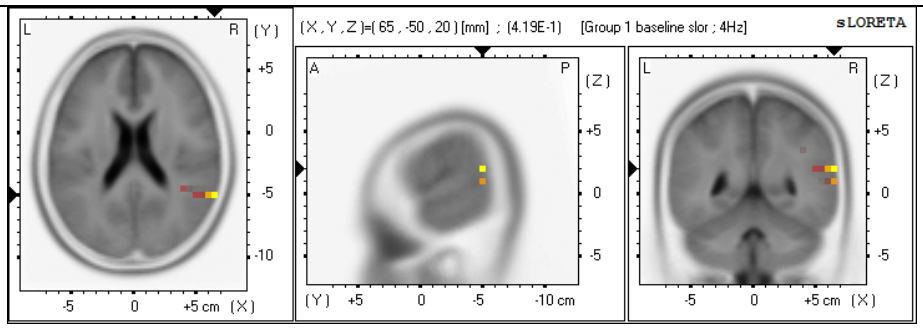
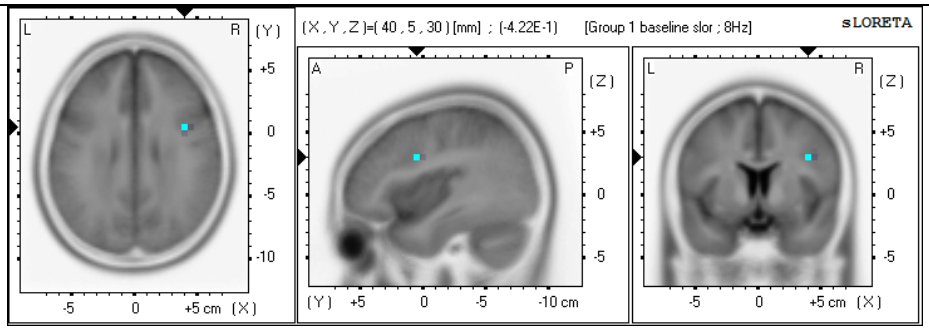
	Group Total	RBANS A	RBANS B
Age	66.0 (7.43)	64.8 (8.23)	68.3 (18.14)
Number of Women (%)	7 (38.9%)	0.3 (0.47)	0.5 (0.43)
Years of Education	14.9 (2.18)	15.3 (1.89)	14 (4.13)
List Learning	23.6 (3.89)	23.3 (3.59)	24.2 (6.94)
Story Learning	12.5 (3.17)	11.8 (3.13)	13.8 (4.14)
Figure Copy	18.3 (1.67)	18.6 (1.50)	17.8 (5.09)
Line Orientation	16.5 (2.41)	16.9 (2.33)	15.8 (4.54)
Picture Naming	9.3 (0.67)	9.2 (0.69)	9.7 (2.58)
Semantic Fluency	19.2 (3.88)	19.9 (4.13)	17.7 (4.52)
Digit Span	10.3 (2.11)	10.3 (2.09)	10.3 (2.86)
Coding	40.5 (7.56)	41.4 (7.55)	38.7 (10.55)
List Recall	4.4 (1.92)	4.5 (1.66)	4.2 (2.10)

	Group Total	RBANS A	RBANS B
List Recognition	18.6 (1.50)	18.7 (1.37)	18.3 (5.07)
Story Recall	6.5 (2.69)	6.3 (2.62)	7.0 (2.68)
Figure Recall	12.1 (4.42)	13.4 (4.21)	9.5 (4.67)
Immediate Memory Index	81.5 (9.59)	79.5 (9.90)	85.5 (22.67)
Visuospatial Index	101.8 (16.31)	104.0 (15.42)	97.3 (28.62)
Language Index	96.3 (6.31)	96.6 (7.05)	95.7 (25.56)
Attention index	95.9 (13.88)	96.9 (14.20)	93.8 (24.73)
Delayed Memory index	90.4 (9.96)	92.8 (8.82)	85.7 (25.32)
Sum of Indices	465.8 (35.05)	469.8 (36.67)	458 (124.07)
Total Scale Index	90.6 (8.78)	91.7 (9.18)	88.3 (23.7)
Average last two 2-back	52.0 (26.15)	63.9 (21.4)	28.2 (23.96)

Appendix C4: Difference in Current Density to 'Normal Brain' Controls

Figure C-3 to C-5 below shows the difference in the current density between each group and their matched 'normal brain' controls. Each image shows the voxel with the greatest change from baseline. Blue voxels indicate the activity was lower in the participants and orange voxels indicate the activity was higher in the participants. In the omega band, no significant voxels could be found.

Broadband Feedback group

Delta band	
Theta band	
Alpha 1 band	

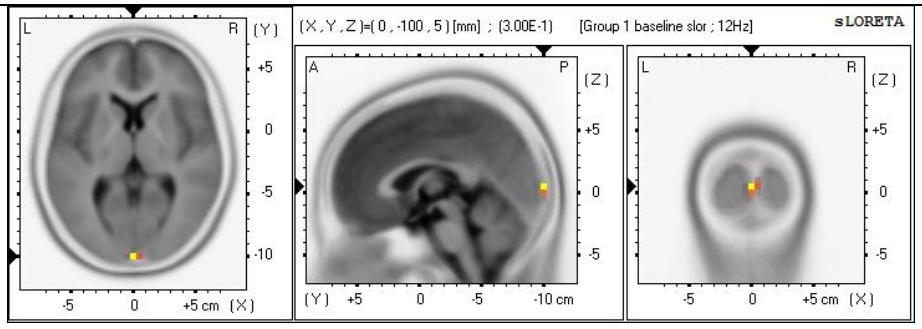
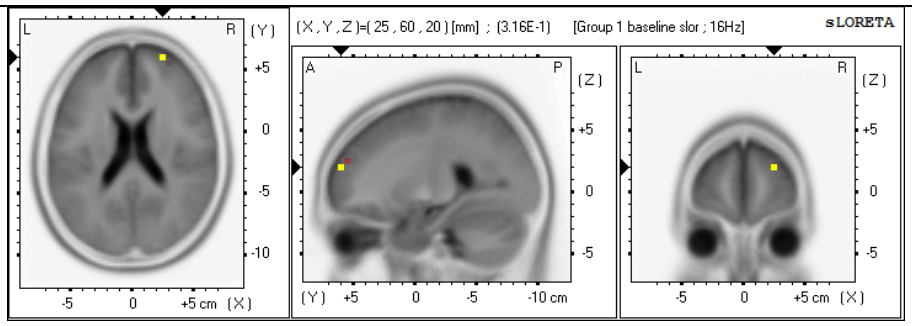
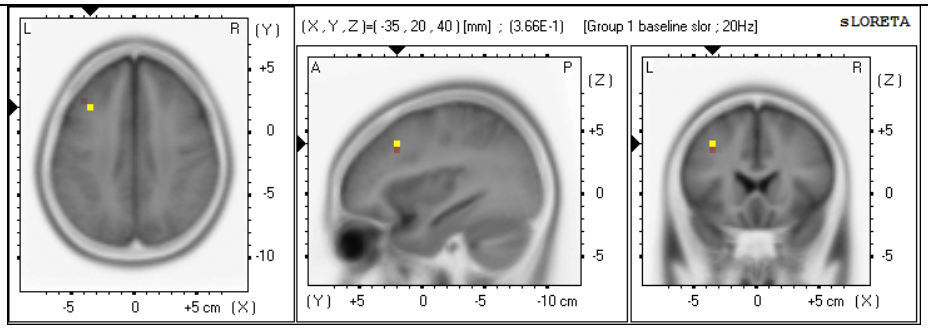
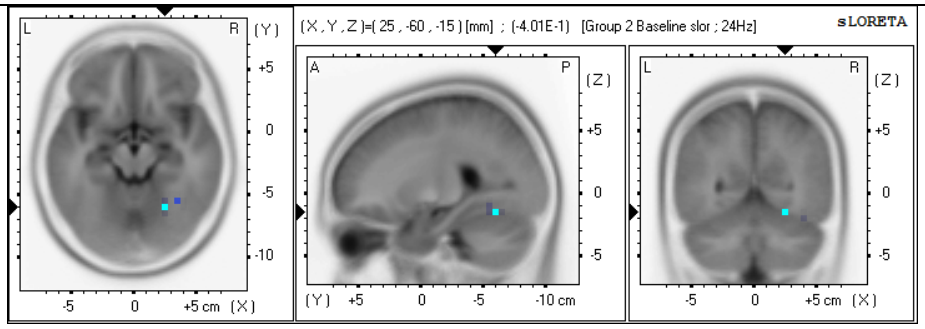
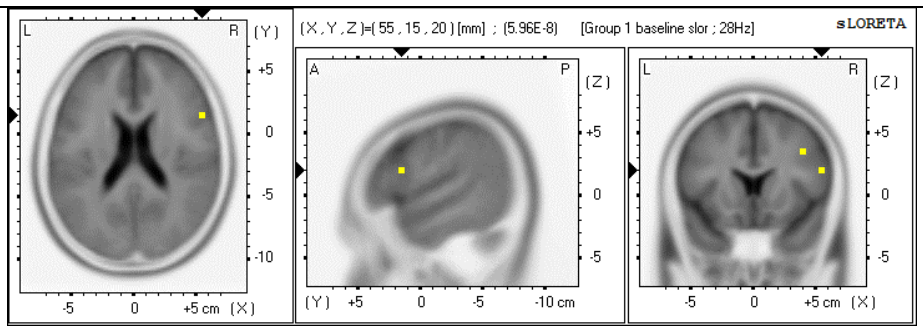
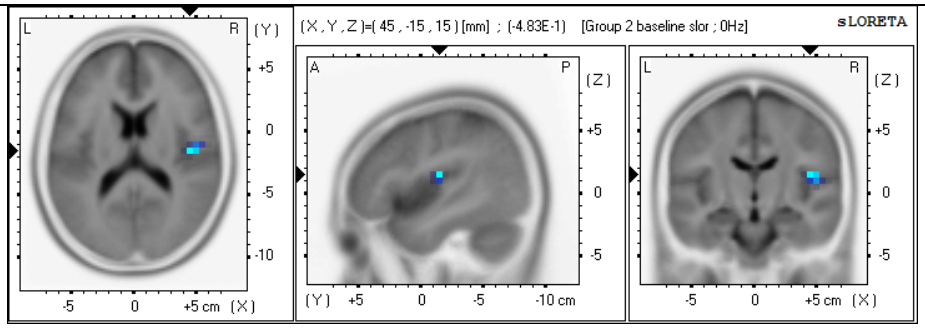
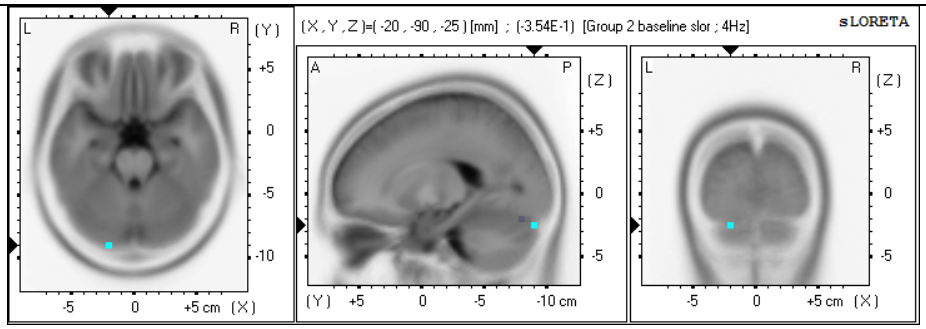
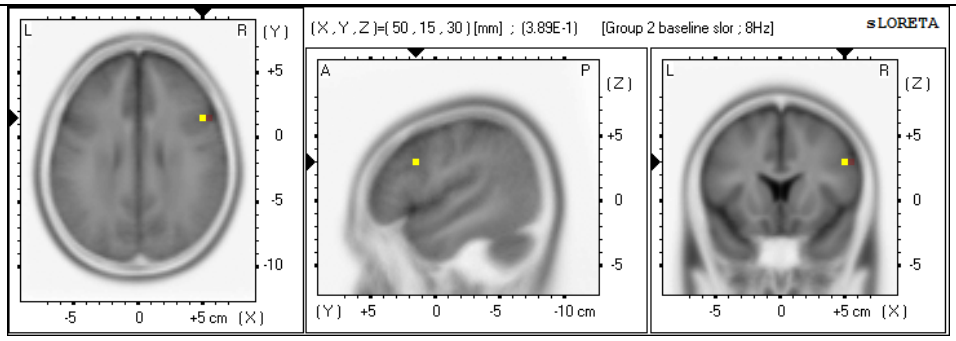
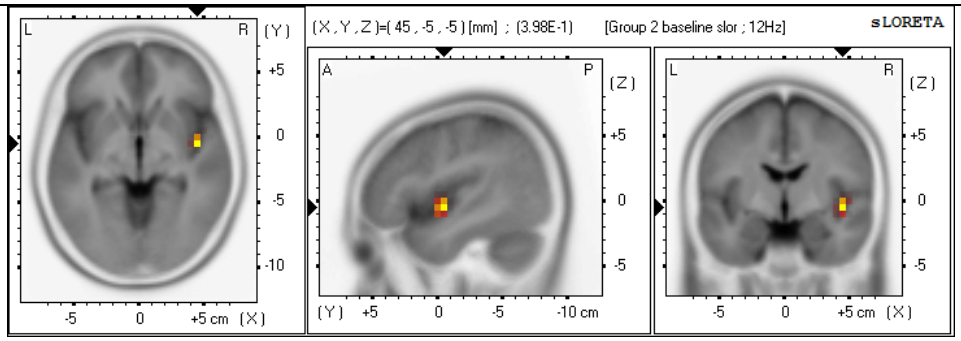
Alpha 2 band	
Beta 1 band	
Beta 2 band	
Beta 3 band	
Omega band	

Figure C-3: Maps of current density comparing matched participants in the broadband feedback group at baseline and 'normal brain' controls

Narrowband Feedback group

Delta band	
Theta band	
Alpha 1 band	
Alpha 2 band	

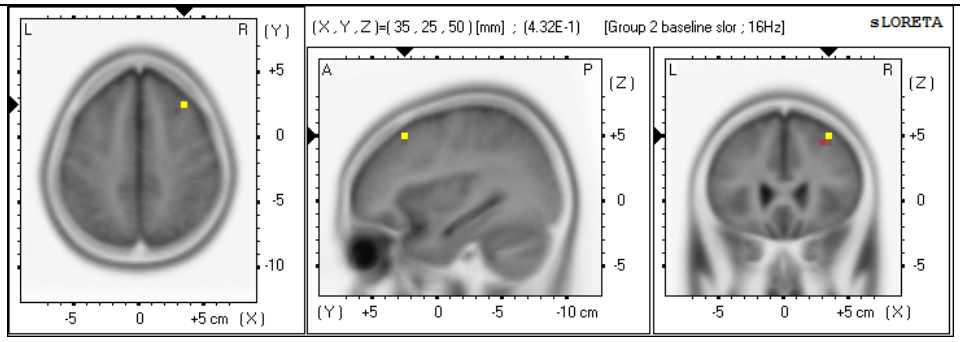
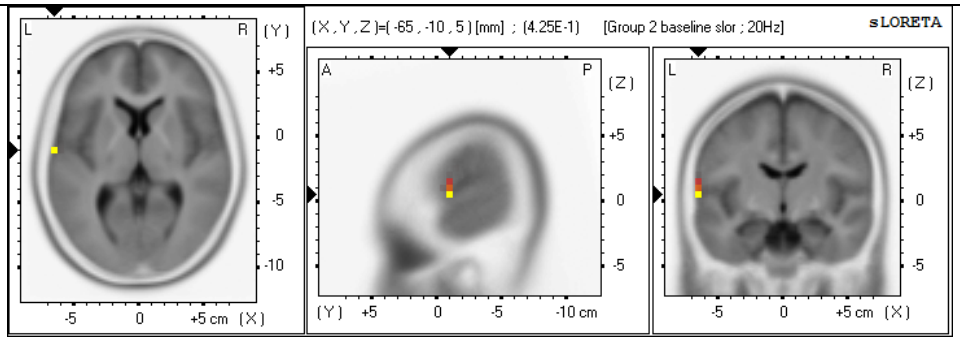
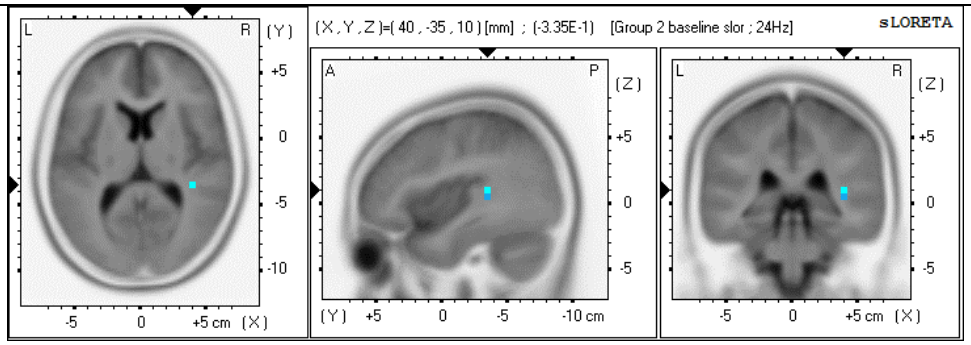
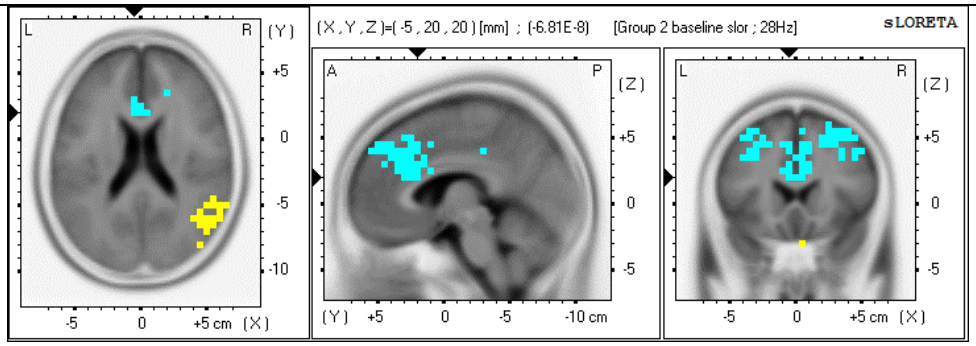
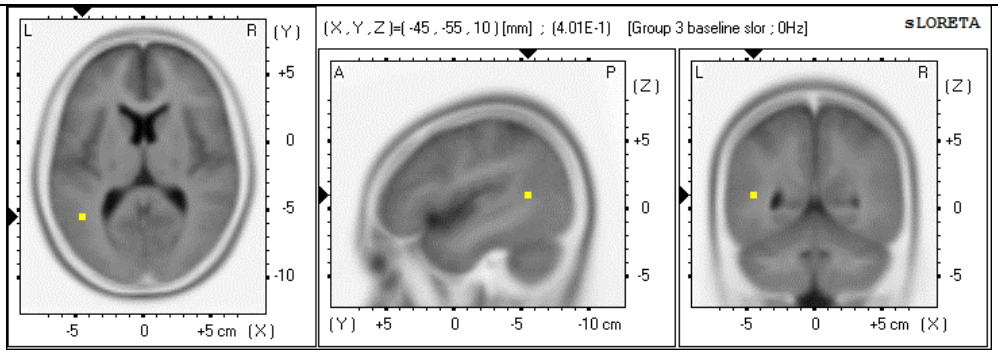
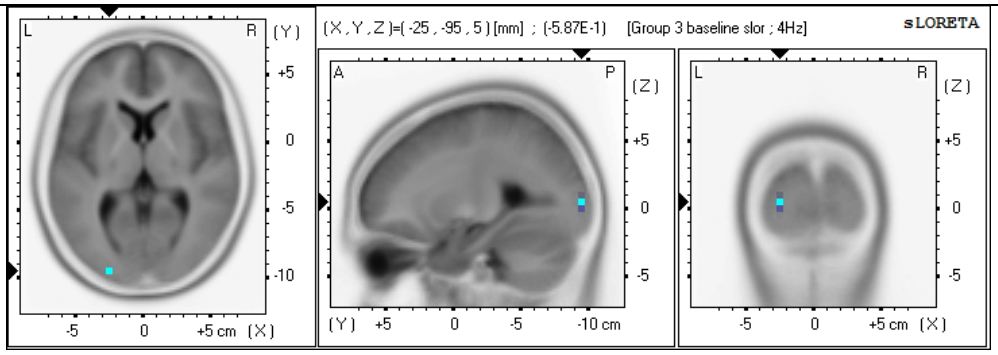
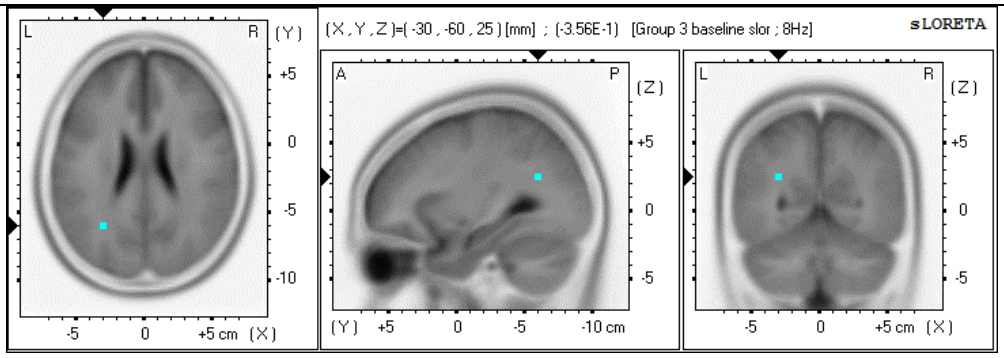
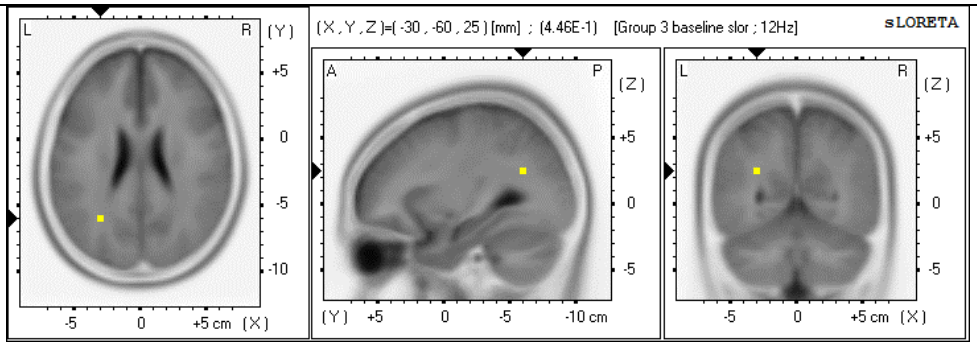
Beta 1 band	
Beta 2 band	
Beta 3 band	
Omega band	

Figure C-4: Maps of current density comparing matched participants in the narrowband feedback group at baseline and 'normal brain' controls

Placebo Feedback group

Delta band	
Theta band	
Alpha 1 band	
Alpha 2 band	

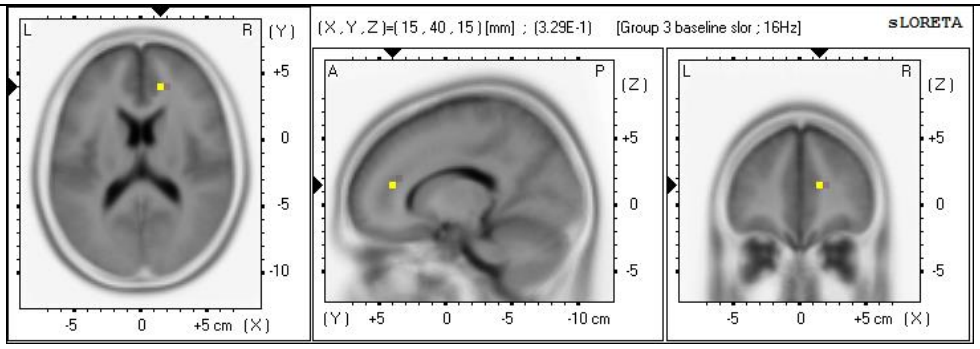
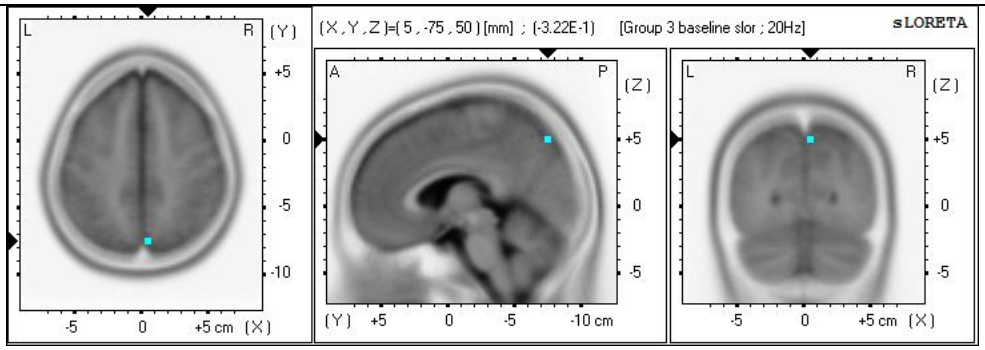
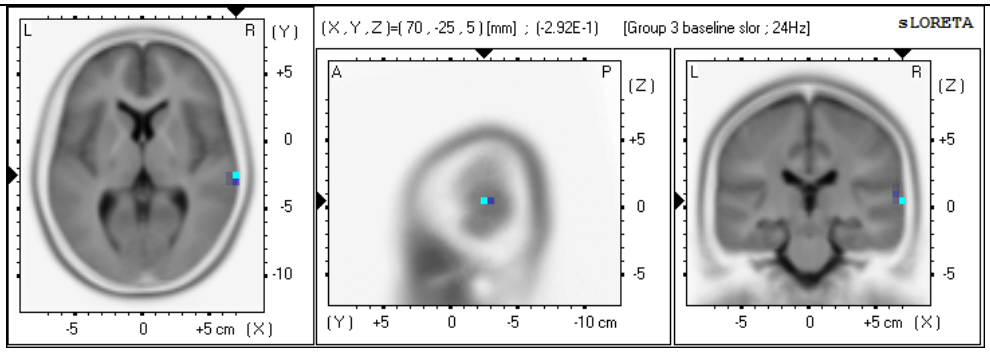
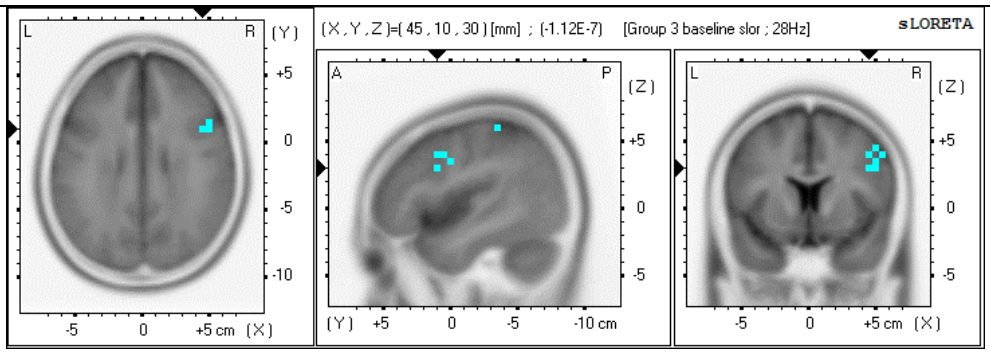
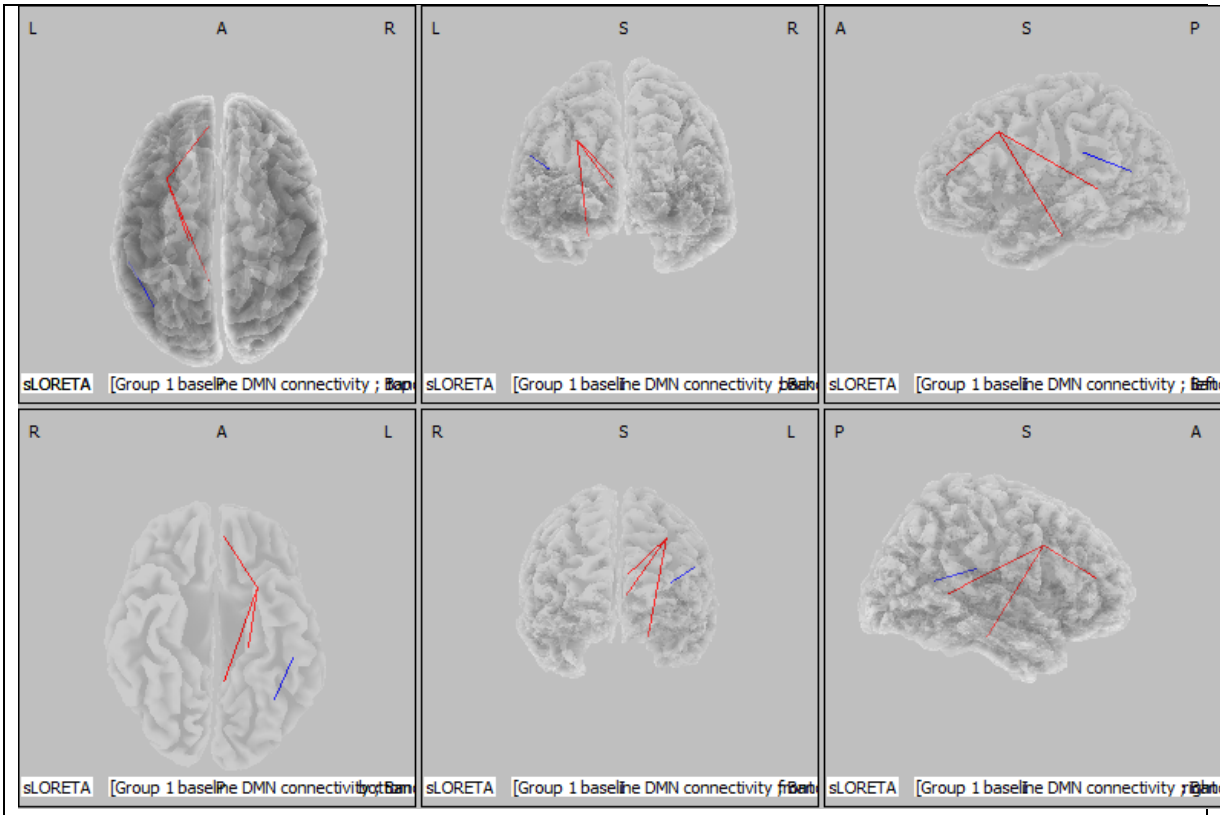
Beta 1 band	
Beta 2 band	
Beta 3 band	
Omega band	

Figure C-5: Maps of current density comparing matched participants in the placebo feedback group at baseline and 'normal brain' controls

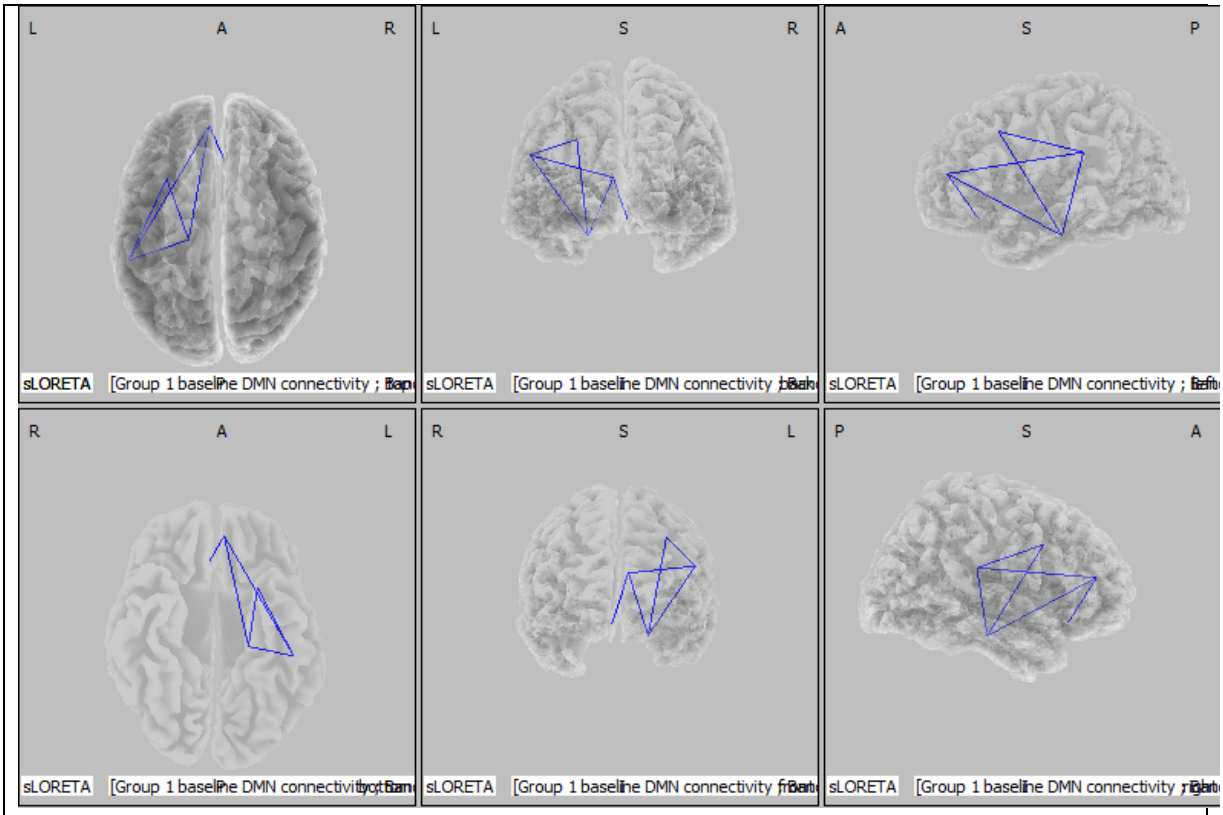
Appendix C5: Difference is Phase Lagged Synchronisation of the DMN to 'Normal Brain' Controls

Figures C-6 to C-8 below show the differences in the default mode connectivity between the participants in each group and the matched 'normal brain' controls. Red lines indicate higher connectivity in the participants than in the 'normal brain' controls, and blue lines indicate lower connectivity in the participants than the 'normal brain' controls.

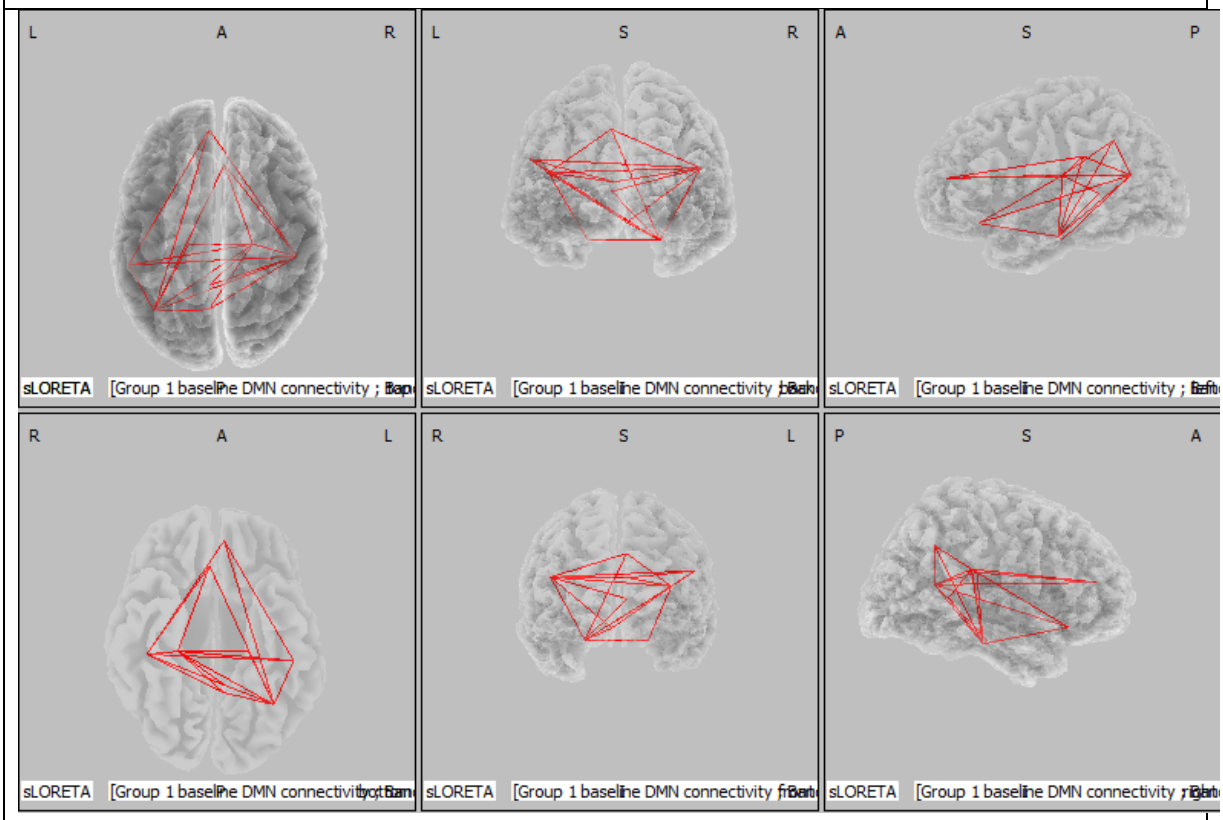
Broadband feedback group



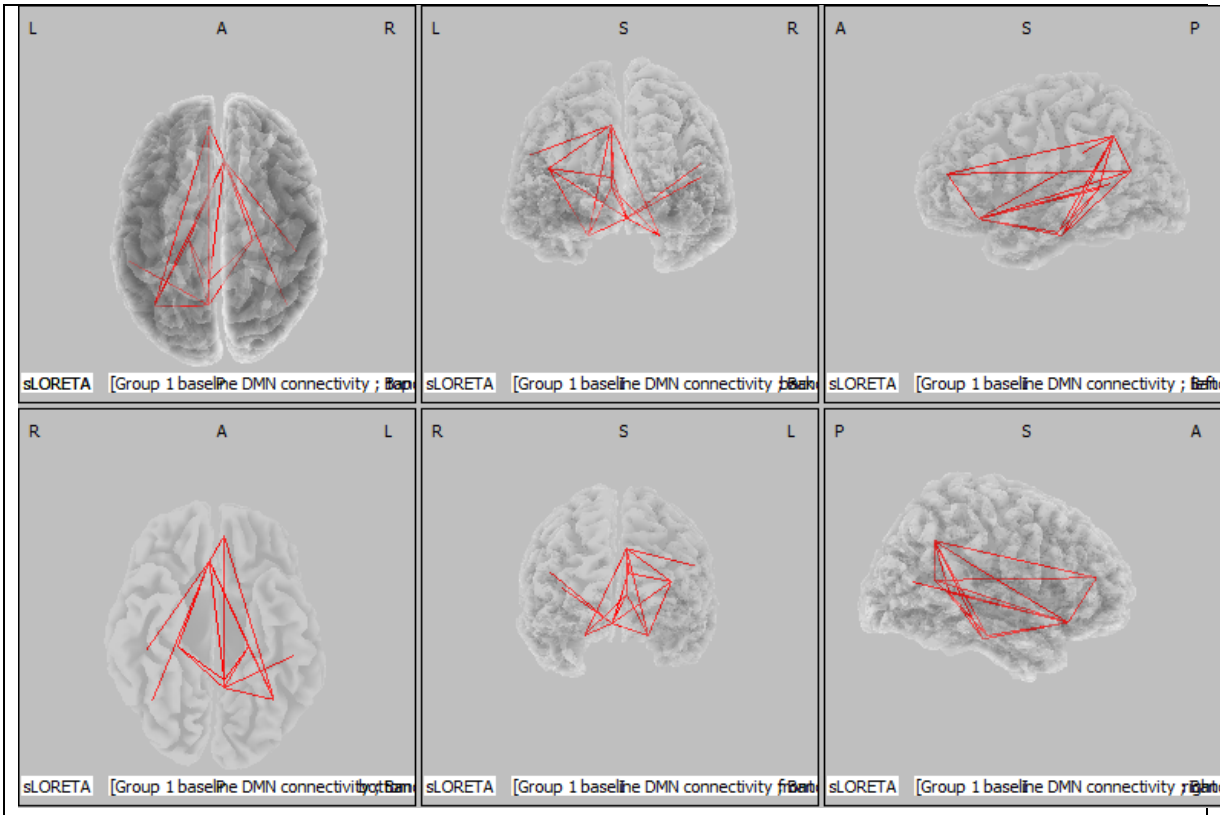
Delta band



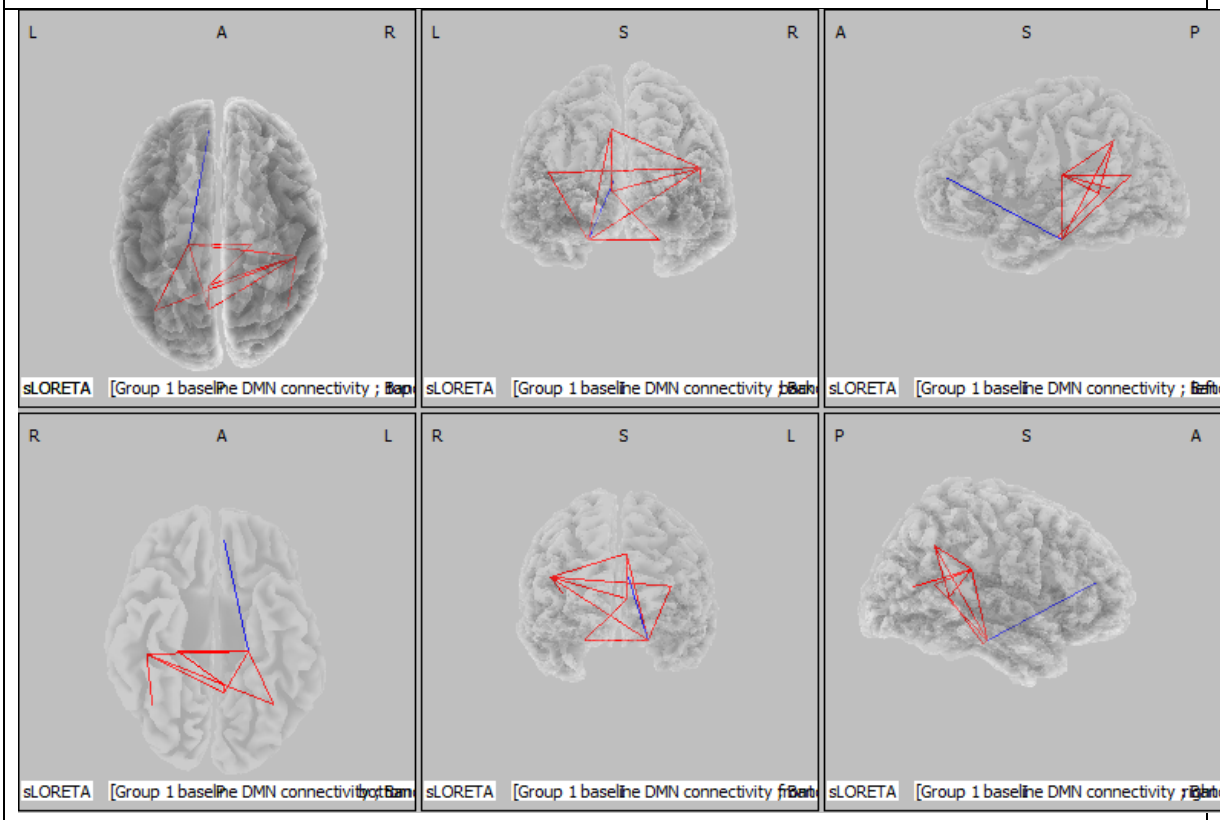
Theta band



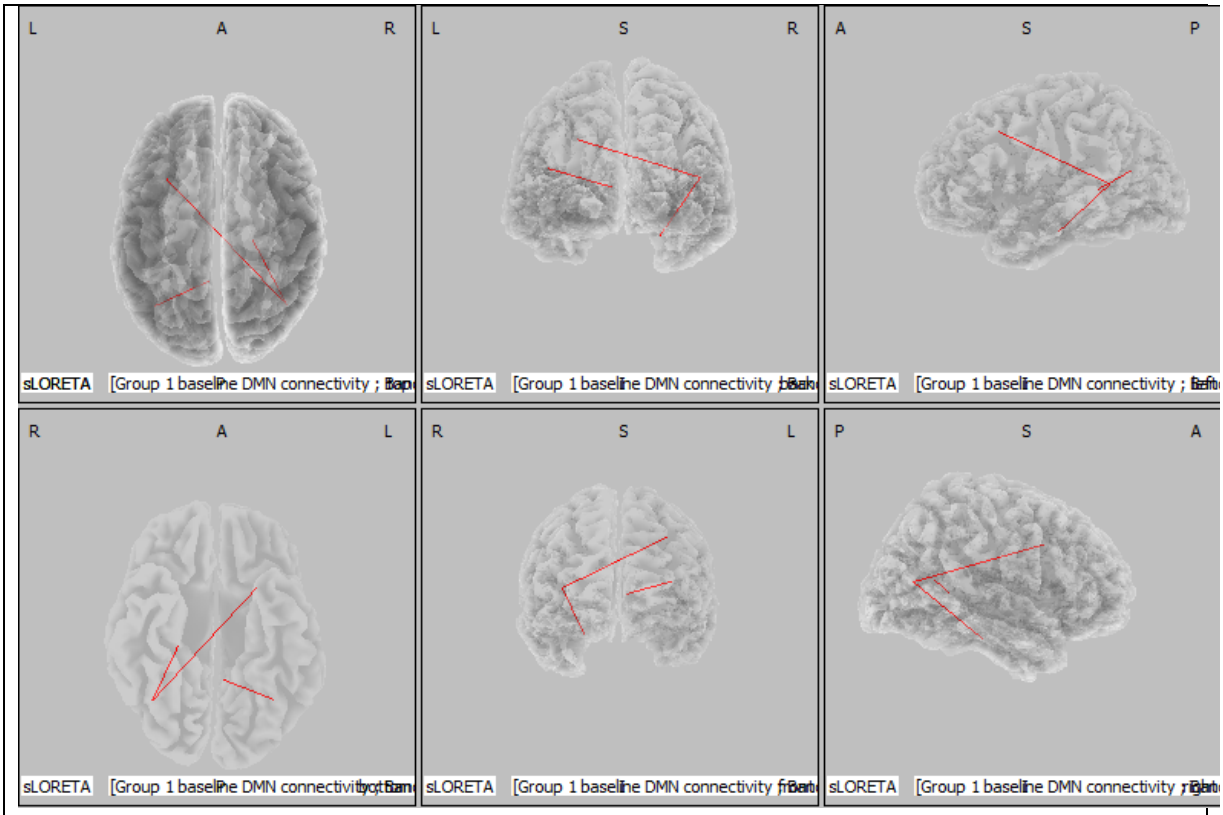
Alpha 1 band



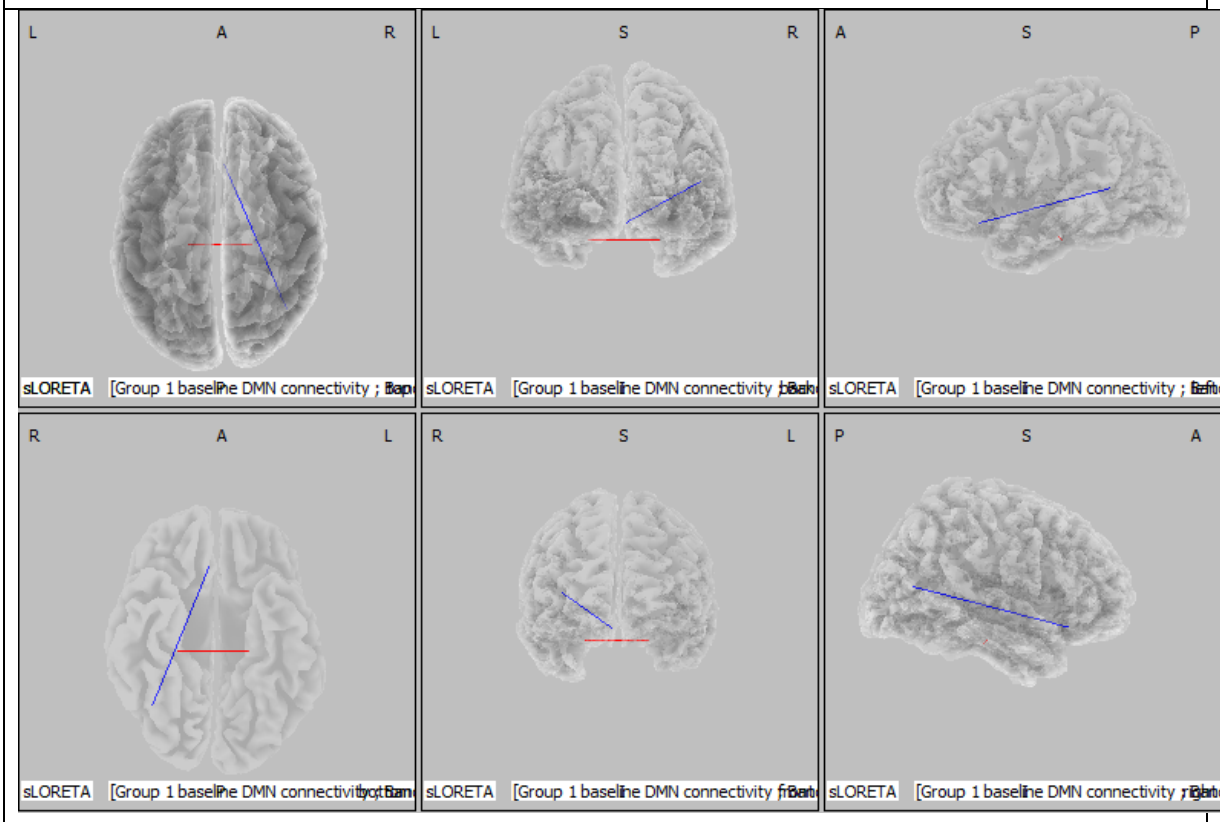
Alpha 2 band



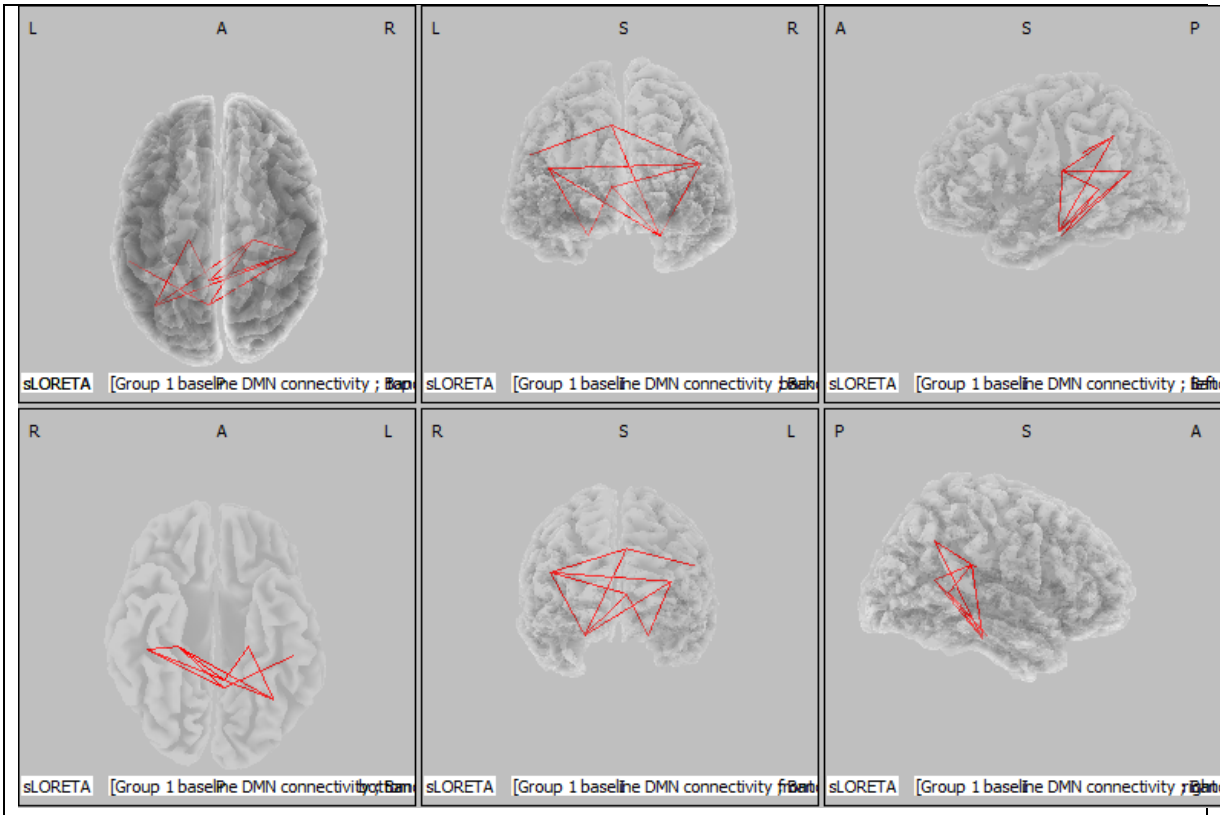
Beta 1 band



Beta 2 band



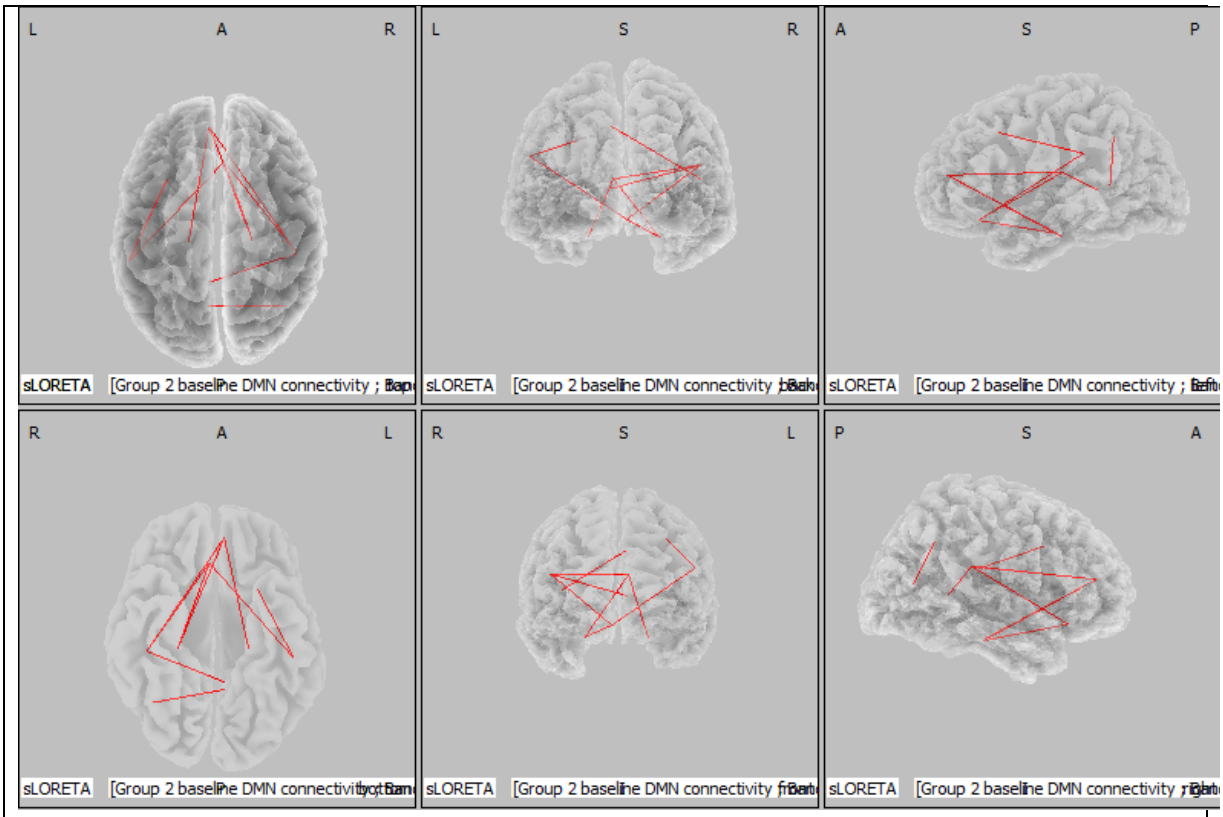
Beta 3 band



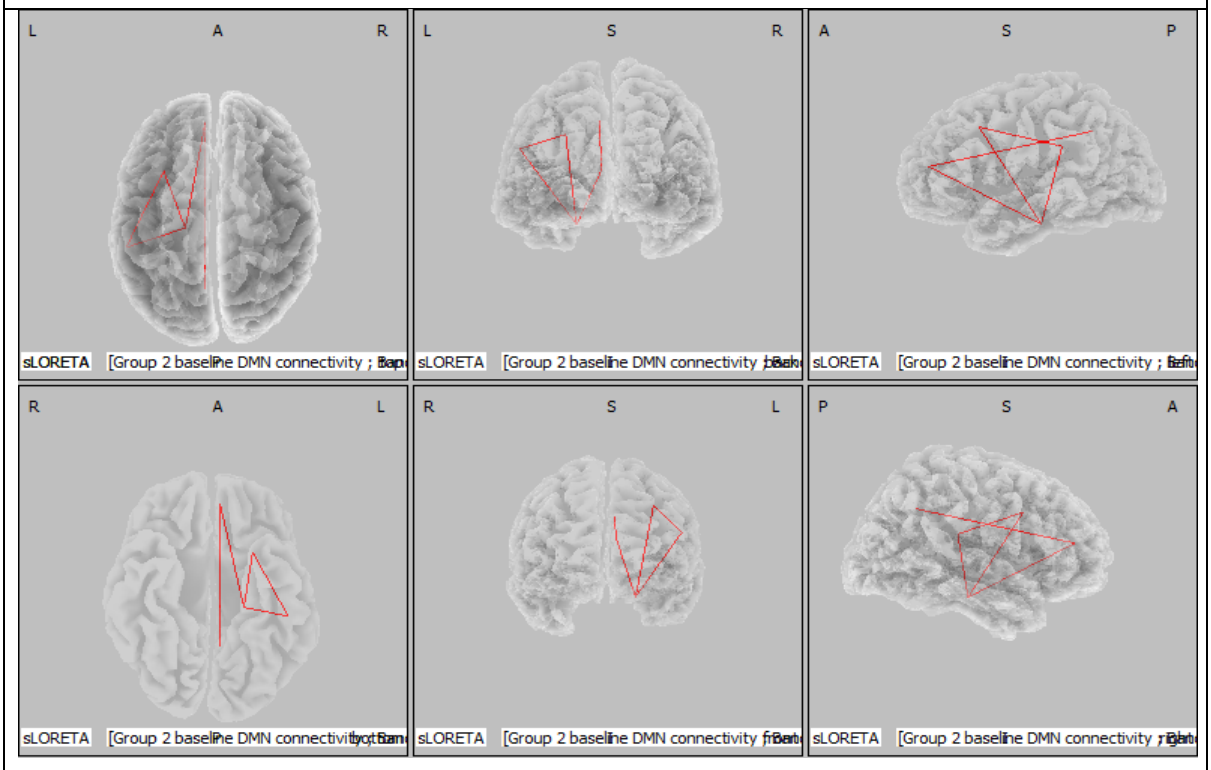
Omega band

Figure C-6: Maps of phase lagged synchronisation of the DMN comparing match participants in the broadband feedback group at baseline with 'normal brain' controls

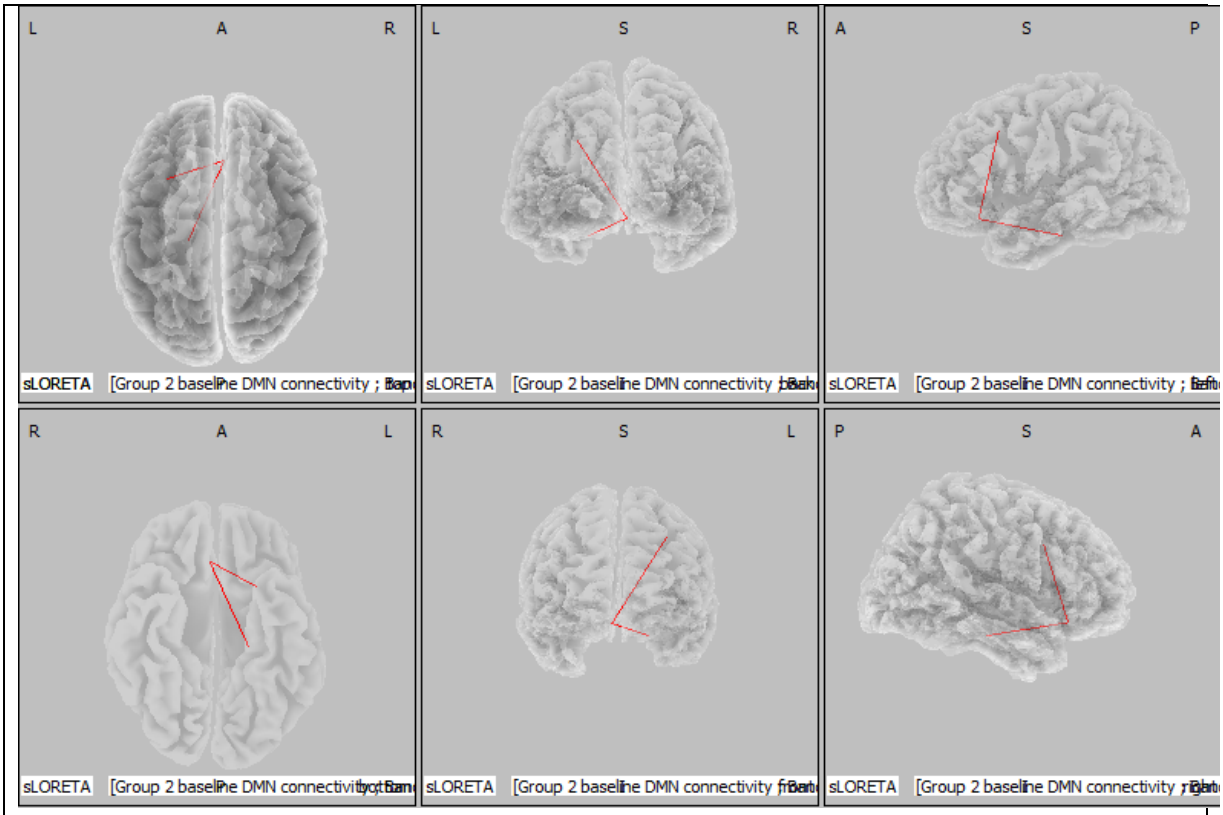
Narrowband Feedback Group



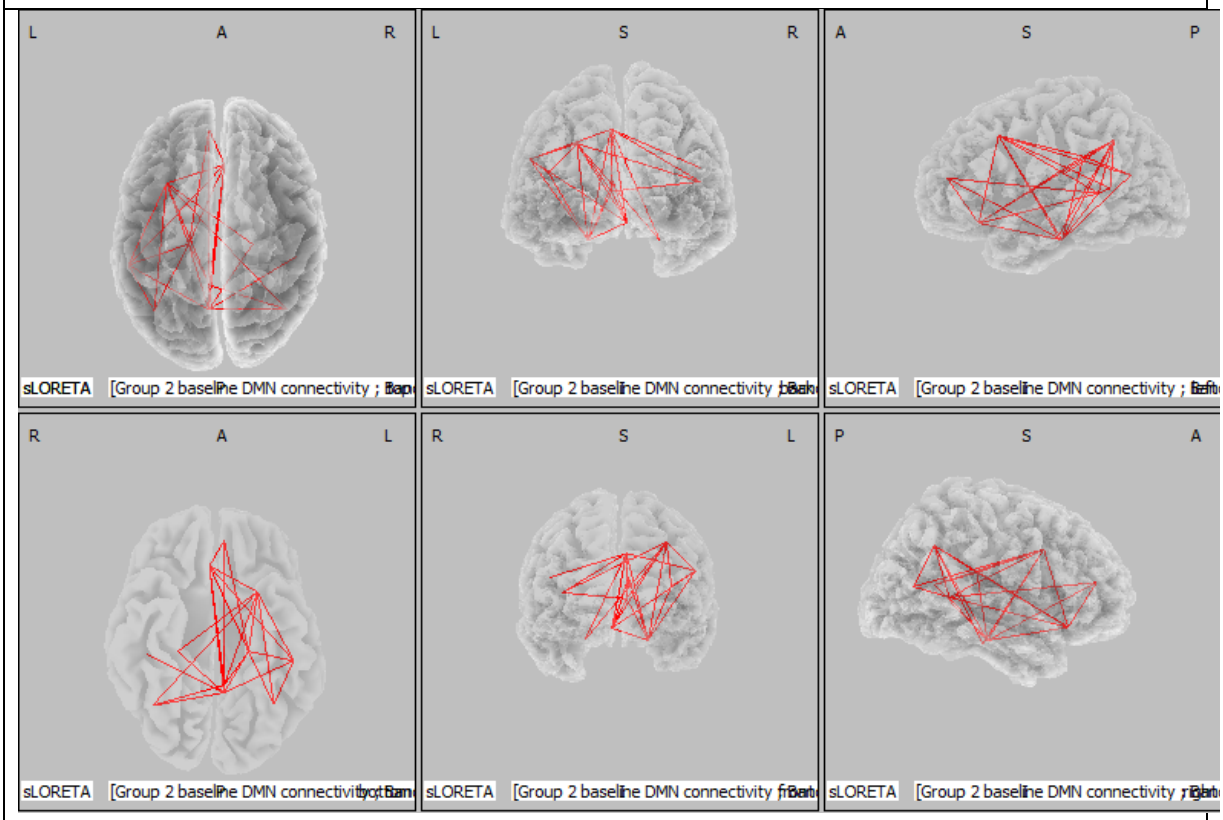
Delta band



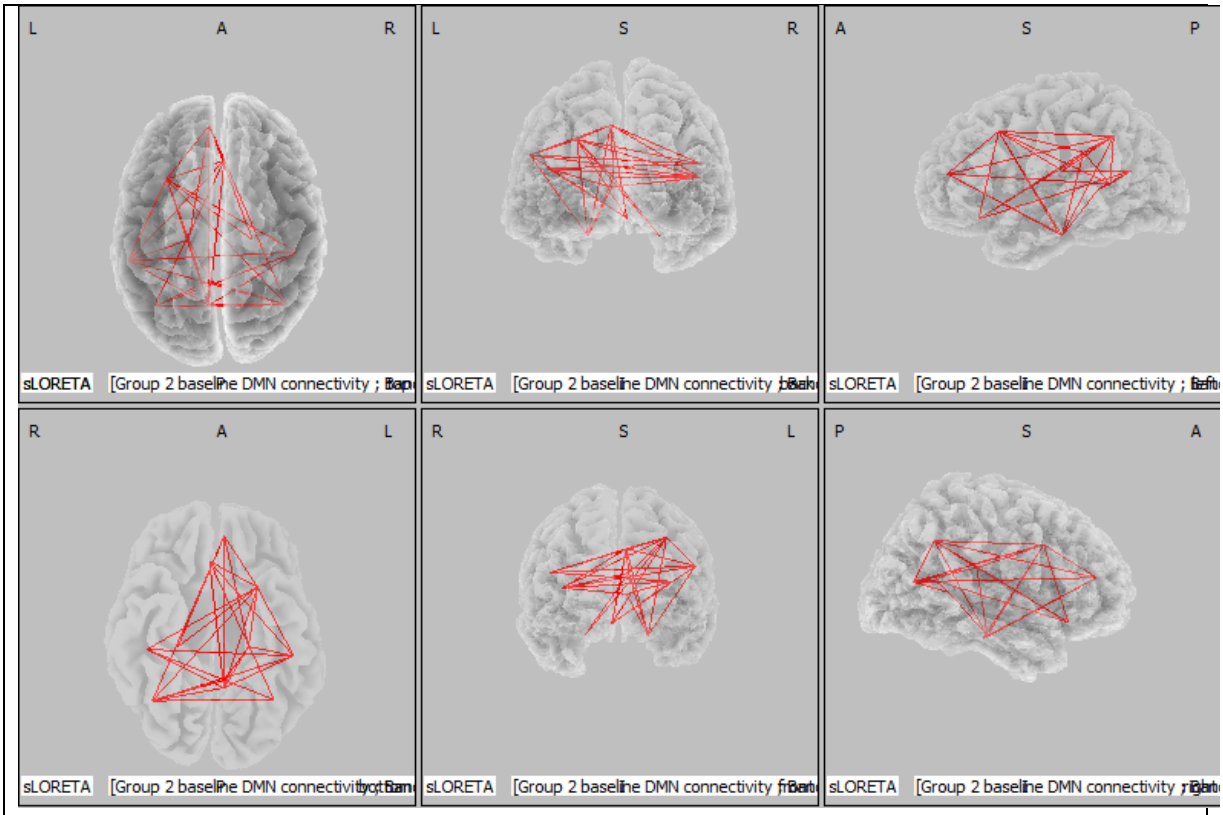
Theta band



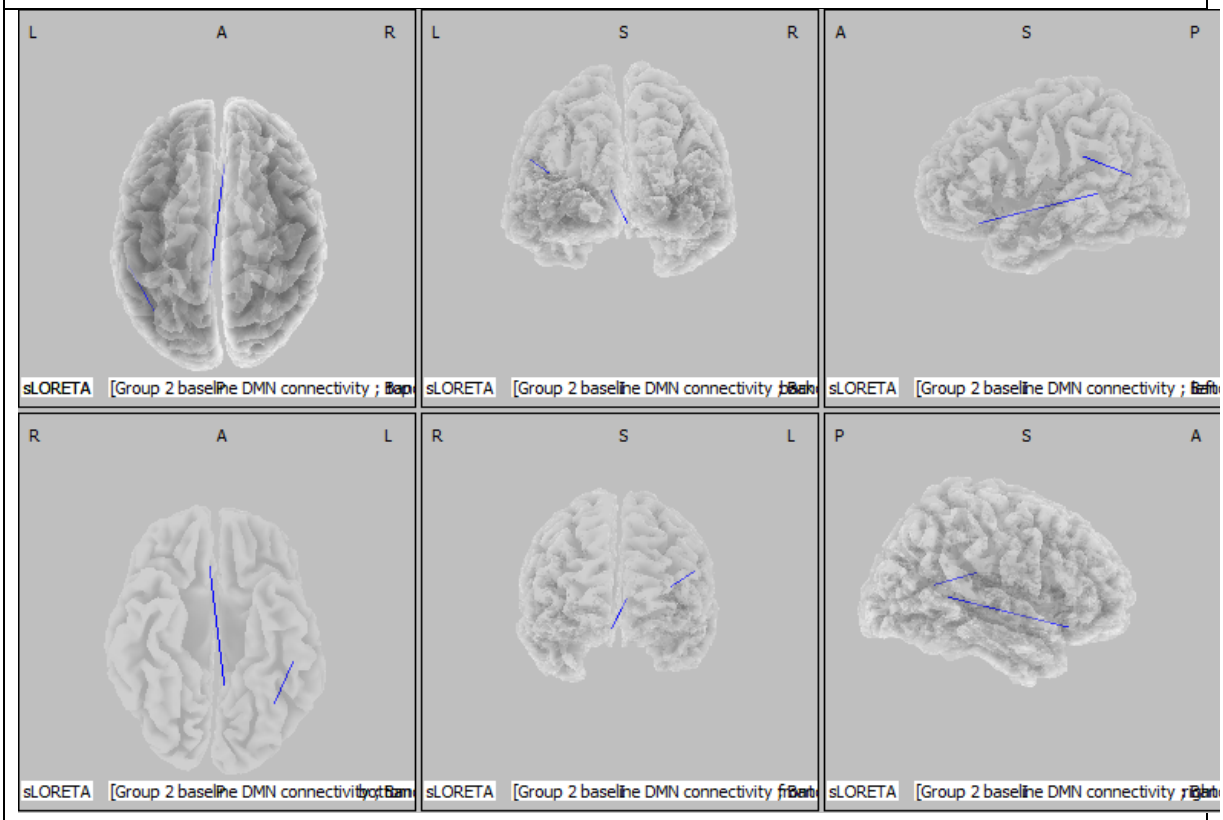
Alpha 1 band



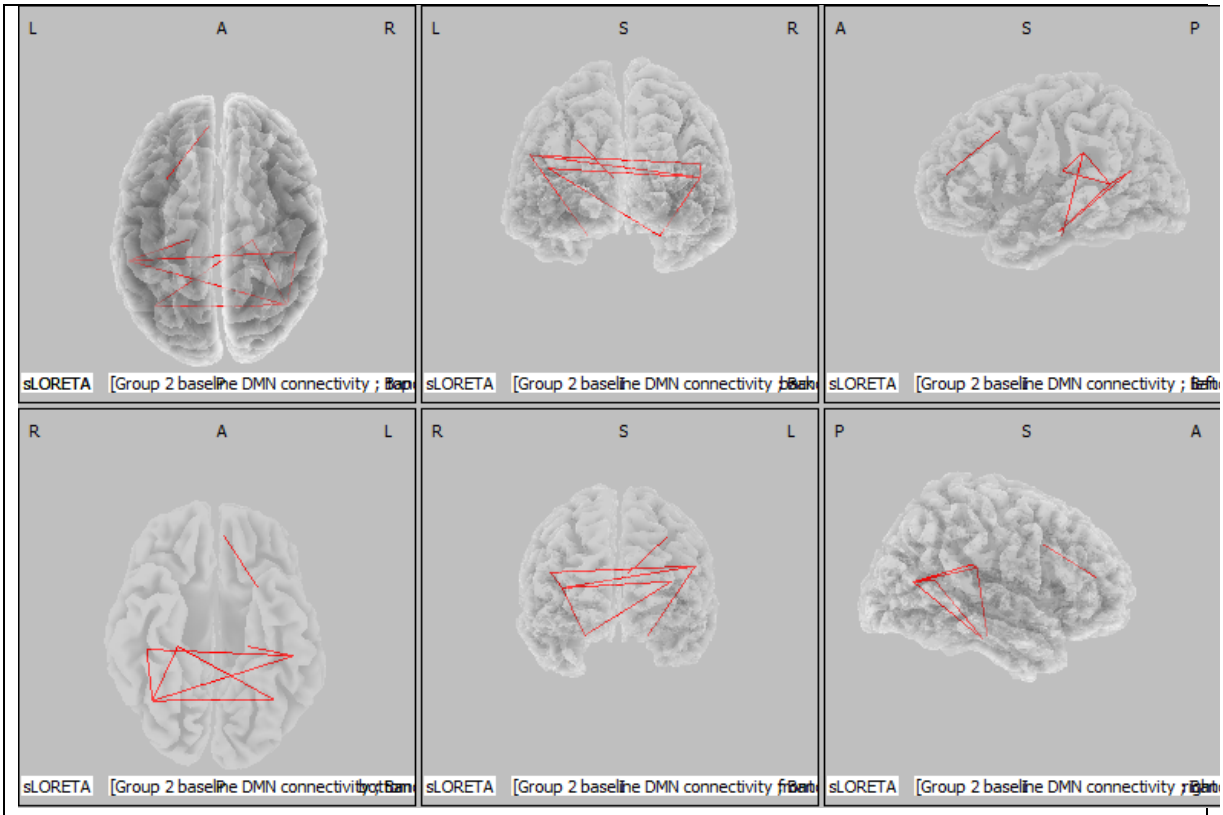
Alpha 2 band



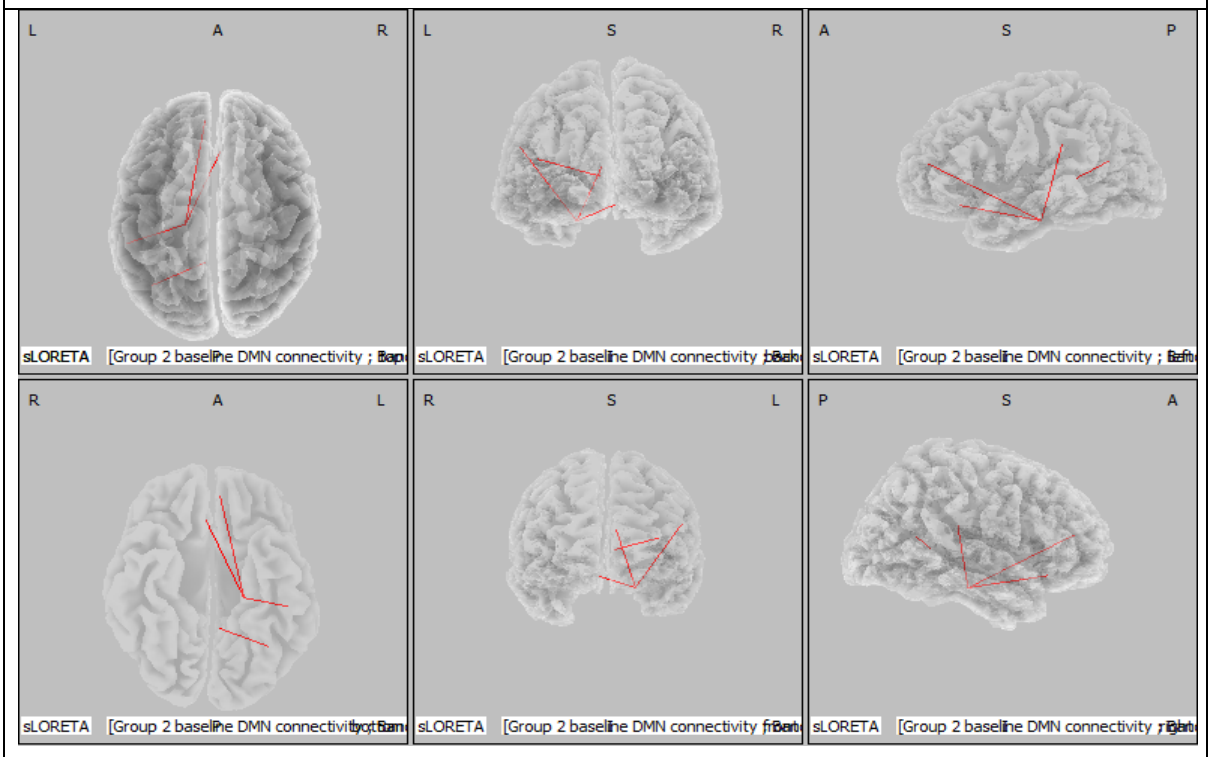
Beta 1 band



Beta 2 band



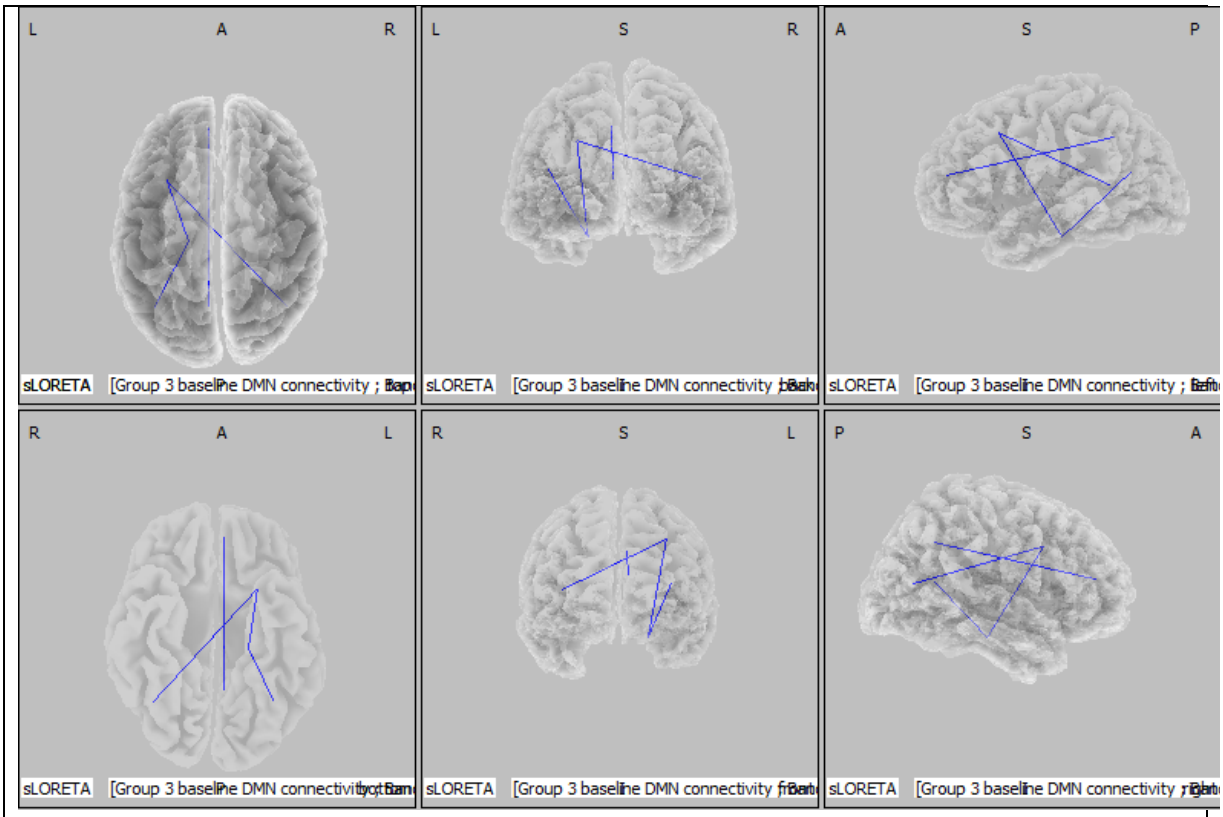
Beta 3 band



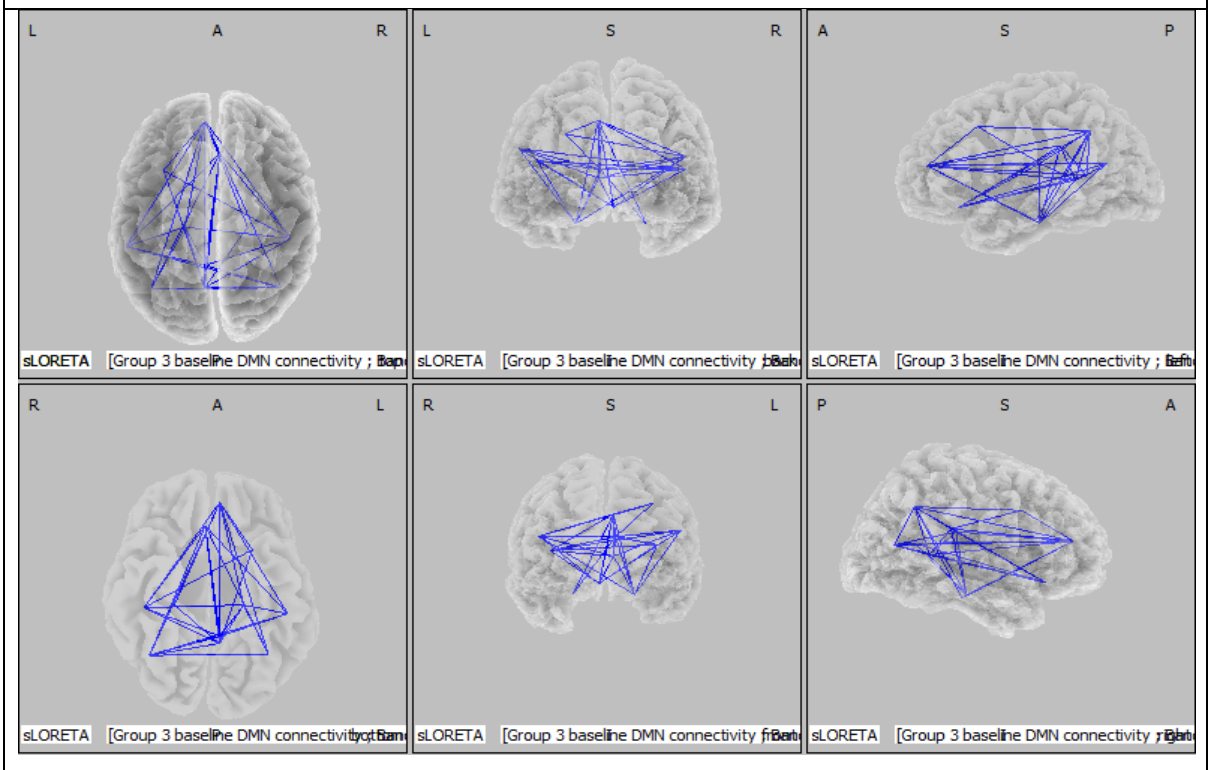
Omega band

Figure C-7: Maps of phase lagged synchronisation of the DMN comparing match participants in the narrowband feedback group at baseline with 'normal brain' controls

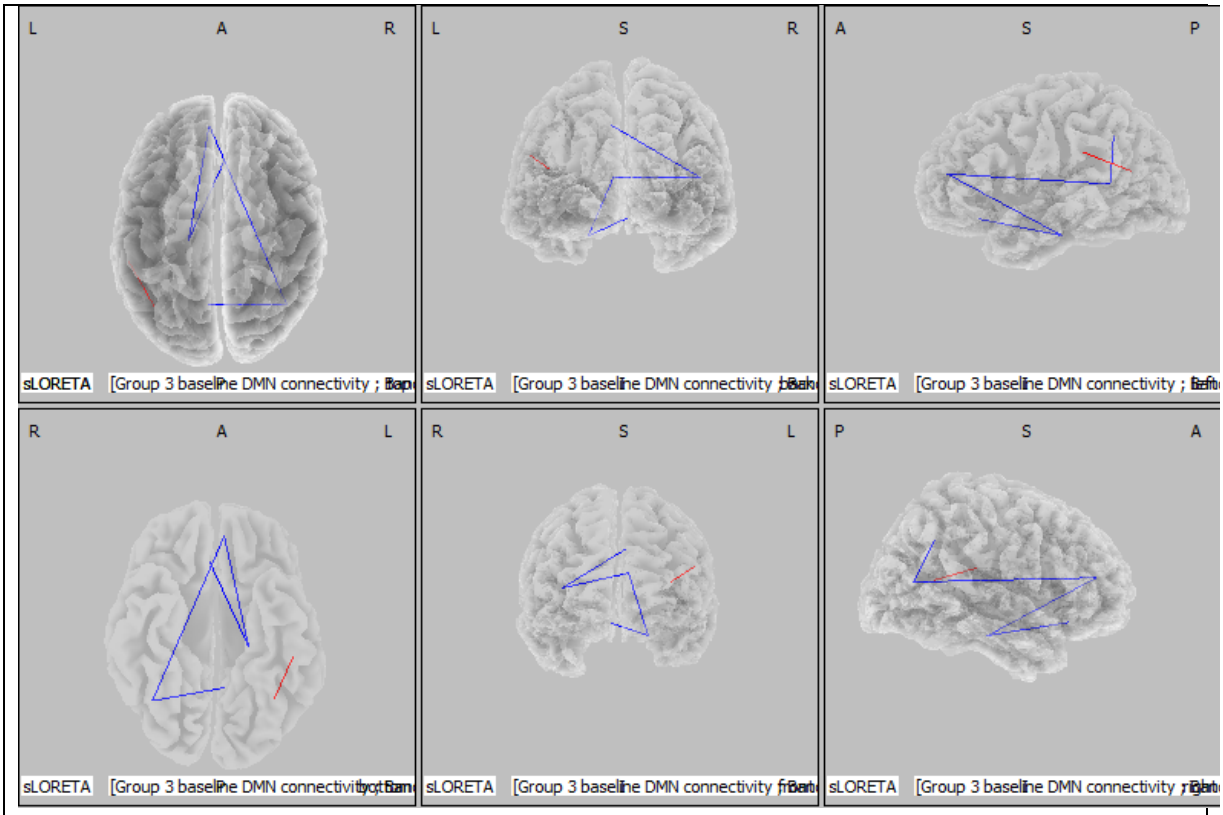
Placebo Feedback Group



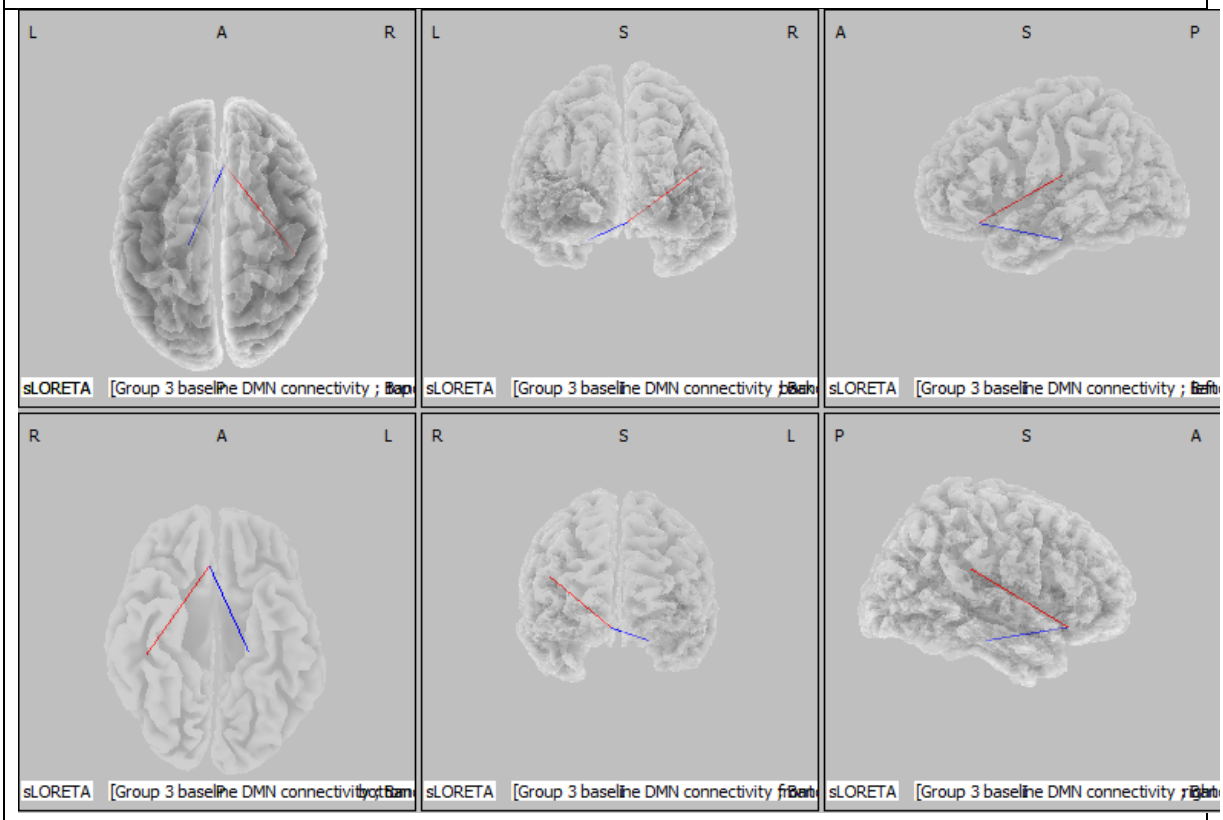
Delta band



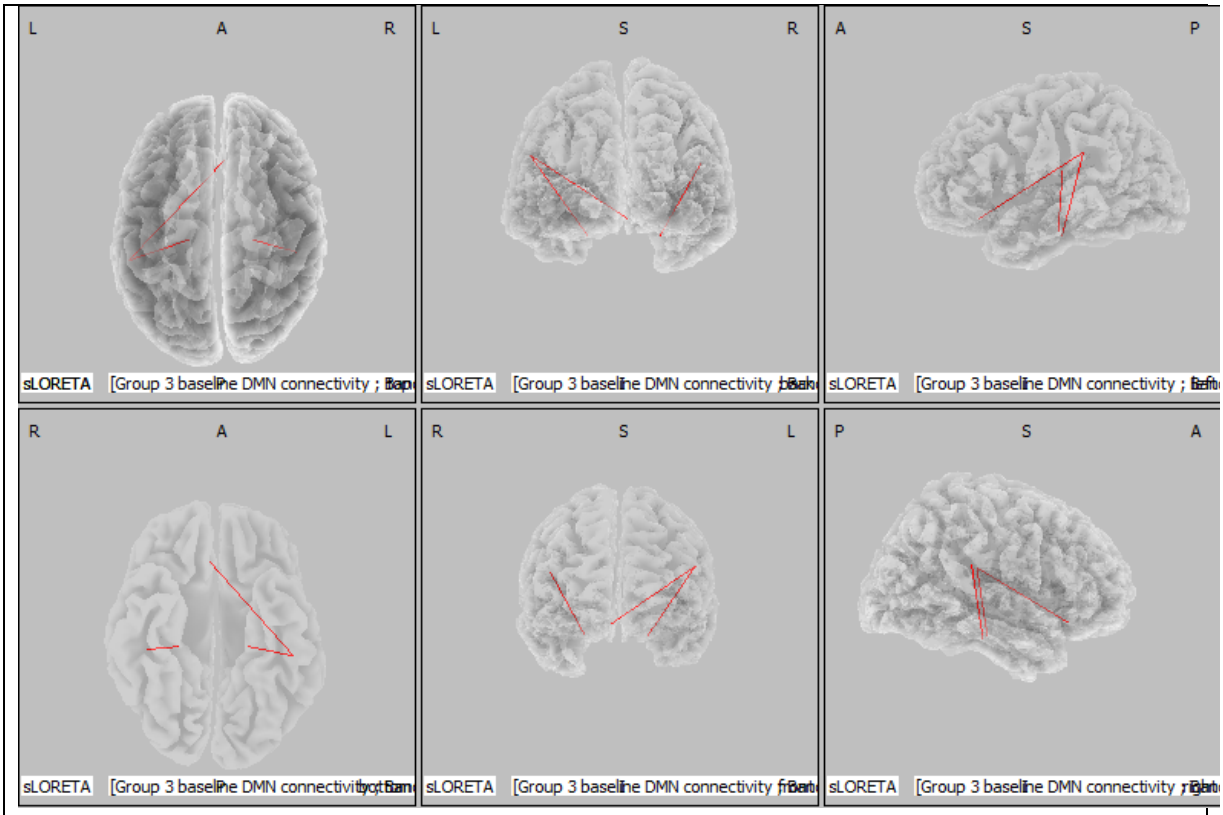
Theta band



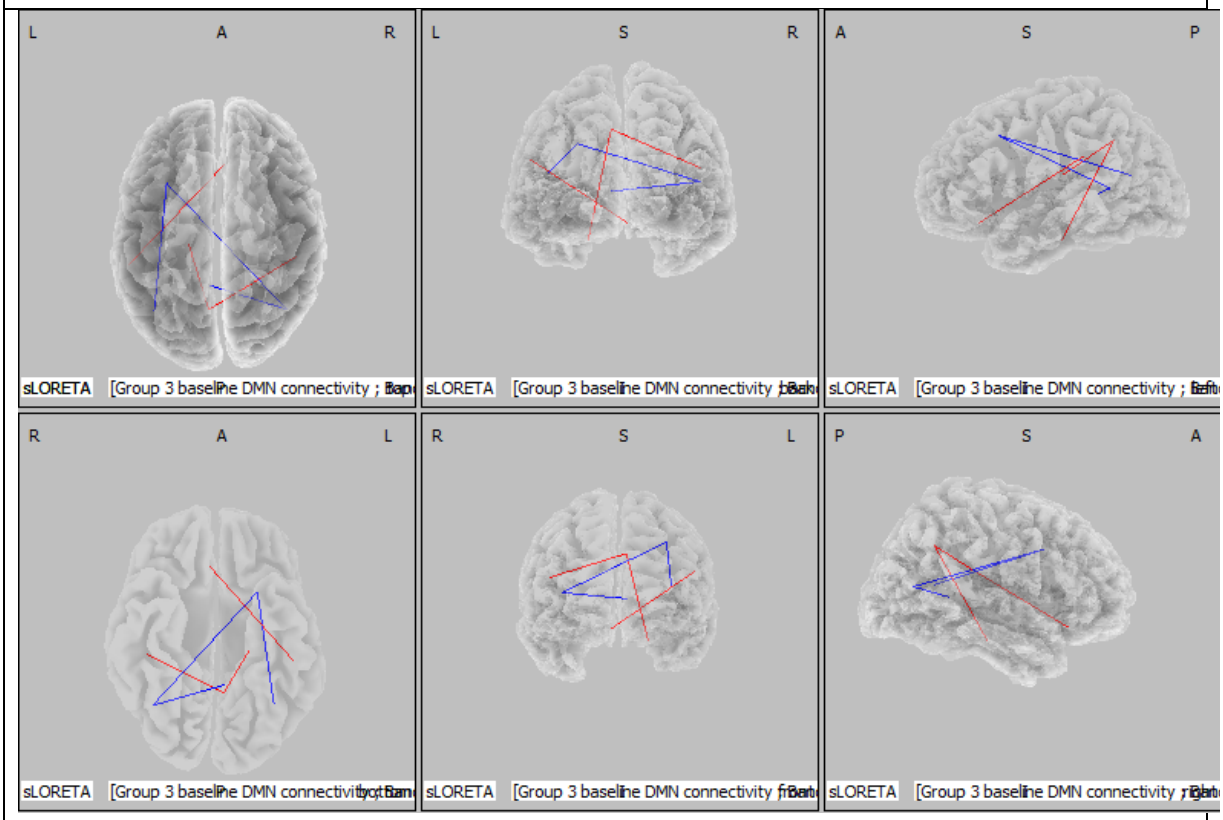
Alpha 1 band



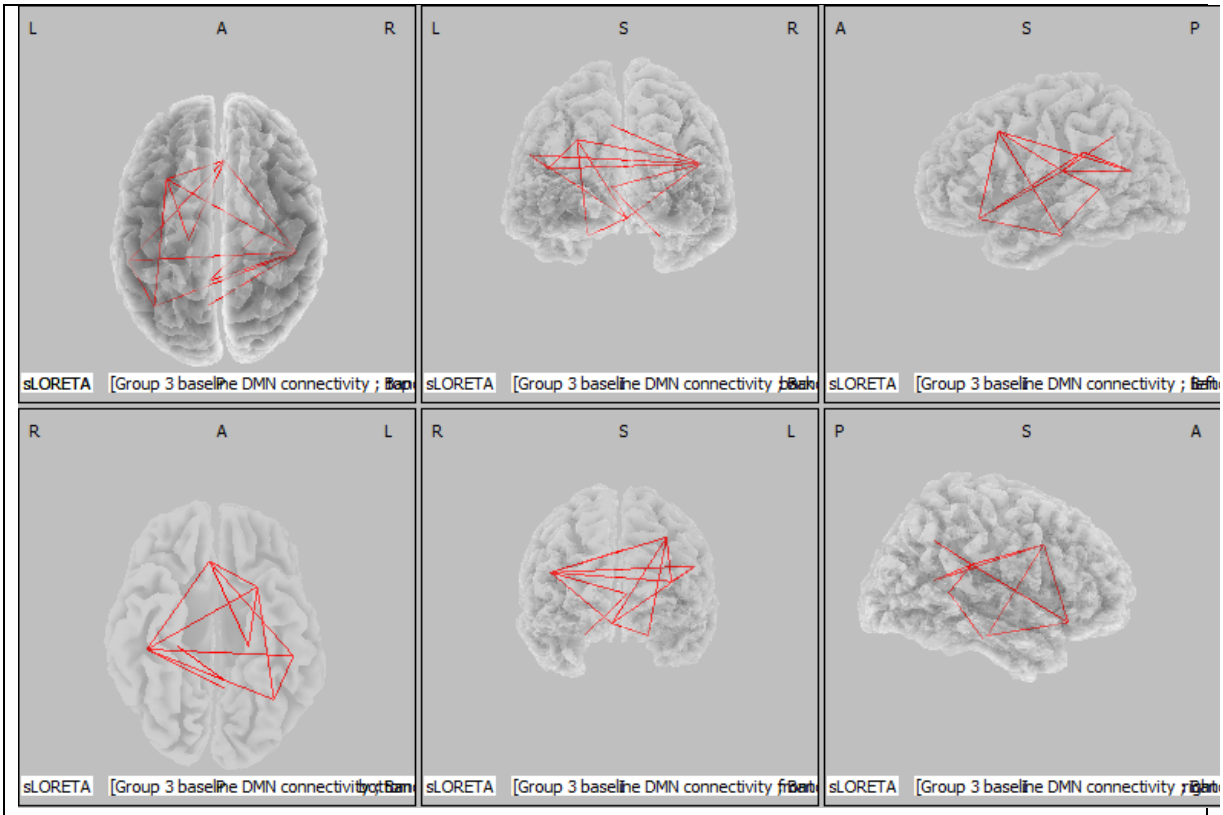
Alpha 2 band



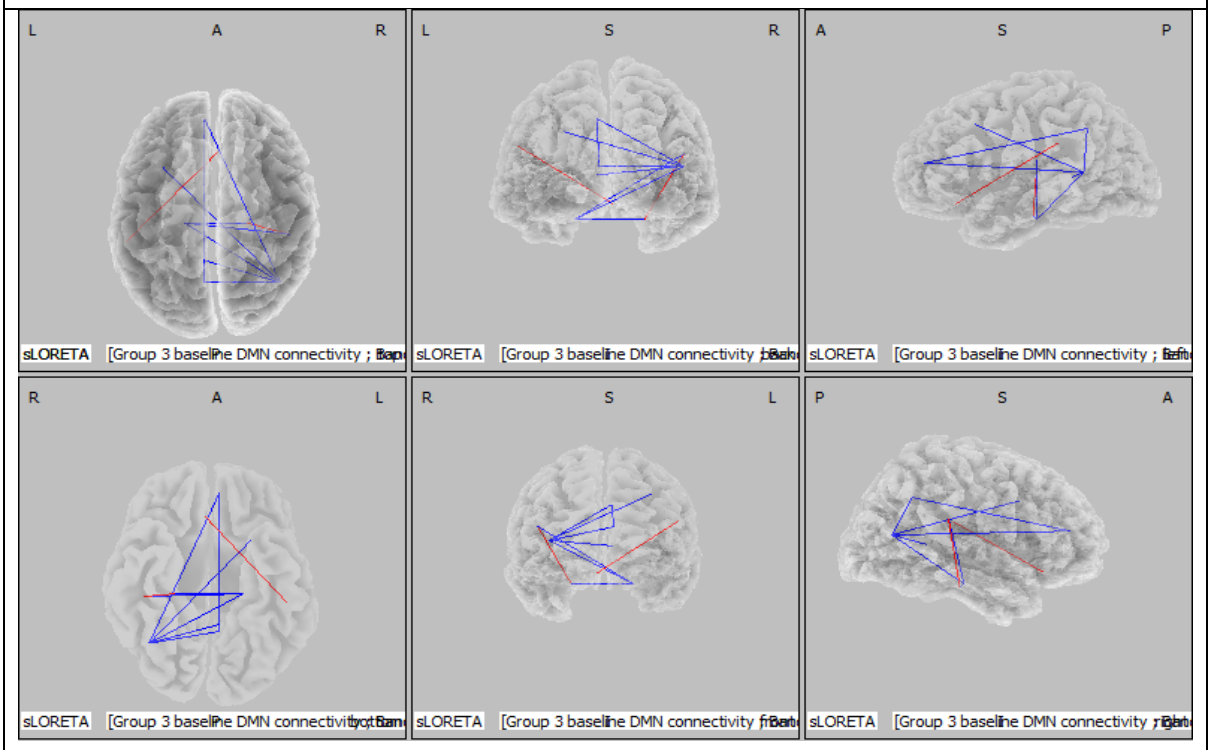
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure C-8: Maps of phase lagged synchronisation of the DMN comparing match participants in the placebo feedback group at baseline with 'normal brain' controls

Appendix C6: Change from Baseline to Immediate Follow up in RBANS Separated by RBANS Form

Tables C-6 to C-8 below show the immediate follow up score on the RBANS and change from baseline.

Broadband Feedback Group

Table C-6: Change in RBANS score from baseline to immediate follow up in the broadband feedback group separated by RBANS form

	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
List Learning	26.1 (5.13)	3.4	20.1 (5.71)	0.5
Story Learning	15.6 (2.91)	3.3	12.9 (3.72)	0.8
Figure Copy	16.6 (2.73)	-1.2	16.8 (1.85)	-1
Line Orientation	17.7 (2.05)	0	15.9 (2.98)	-0.6
Picture Naming	9.8 (0.60)	0.5	9.6 (0.48)	0.4
Semantic Fluency	18.4 (5.06)	-1.2	18.6 (6.04)	2.5
Digit Span	10.0 (1.67)	0.2	10.0 (2.40)	0.1
Coding	37.3 (7.36)	1.1	33.4 (12.98)	1.3
List Recall	6.6 (2.06)	2.5	3.4 (2.18)	0.8
List Recognition	18.7 (2.24)	0.8	17.8 (2.77)	0.1
Story Recall	7.6 (2.46)	2.1	6.1 (3.48)	0.9
Figure Recall	11.1 (5.07)	-0.8	9.4 (4.61)	-1.4
Immediate Memory Index	97.7 (12.76)	16.1	83.8 (12.26)	6.3

	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
Visuospatial Index	98.5 (17.09)	-6.8	95.1 (17.84)	-4.4
Language Index	97.1 (11.11)	-0.4	98.8 (9.60)	7.3
Attention index	95.5 (9.7)	2.7	92.3 (15.2)	2.8
Delayed Memory index	96.7 (19.48)	10.3	85.6 (20.33)	3.6
Sum of Indices	485.5 (44.89)	21.9	455.5 (59.55)	15.5
Total Scale Index	95.5 (11.3)	5.8	88.4 (15.32)	4.5
Average last two 2-back	31.7 (16.14)	-3.9	30.5 (13.62)	-4.2

Narrowband Feedback Group

Table C-7: Change in RBANS score from baseline to immediate follow up in the narrowband feedback group separated by RBANS form

	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
List Learning	24.2 (4.93)	2	24.0 (3.51)	0.7
Story Learning	16.1 (4.12)	4.1	12.0 (4.24)	-2.7
Figure Copy	23.9 (18.10)	5.2	18.5 (1.26)	-0.8
Line Orientation	15.8 (2.55)	-1.3	17.7 (2.05)	0.7
Picture Naming	9.6 (0.64)	0.5	9.7 (0.47)	-0.3
Semantic Fluency	17.9 (3.73)	-1.5	22.2 (2.41)	5
Digit Span	8.4 (2.53)	-1.1	10.8 (2.48)	-0.8
Coding	40.6 (6.88)	-0.6	48 (7.72)	-0.8
List Recall	4.8 (2.66)	0.7	3.3 (1.11)	-1.2

	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
List Recognition	17.5 (2.68)	-1.4	19.2 (1.07)	0.7
Story Recall	8.6 (2.80)	2.8	6.8 (3.29)	-1.3
Figure Recall	12.3 (3.33)	-0.3	12.8 (3.13)	0.2
Immediate Memory Index	94.3 (14.74)	14.5	80.7 (13.22)	-4
Visuospatial Index	98.9 (8.41)	-8.6	106.3 (12.46)	-2.7
Language Index	95.1 (11.46)	-1	103.0 (4.55)	9.3
Attention index	91.2 (9.53)	-4.5	105.8 (15.59)	-3.3
Delayed Memory index	93.9 (15.48)	3.5	93.8 (11.88)	0.7
Sum of Indices	473.4 (30.89)	3.7	489.7 (38.81)	0
Total Scale Index	92.3 (7.85)	1.1	96.3 (11.32)	-0.2
Average last two 2-back	42.5 (18.00)	5	61.7 (24.65)	6.8

Placebo Feedback Group

Table C-8: Change in RBANS score from baseline to immediate follow up in the placebo feedback group separated by RBANS form

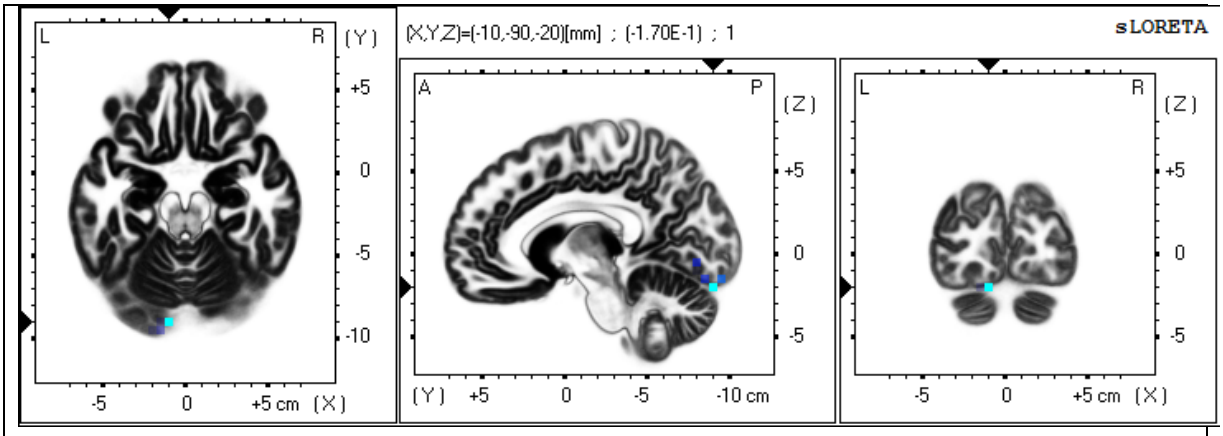
	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
List Learning	25.4 (3.20)	2.2	24.5 (4.07)	0.3
Story Learning	16.3 (4.09)	4.5	11.8 (3.85)	-2
Figure Copy	18.1 (2.50)	-0.5	17.7 (0.75)	-0.2

	Form A Mean(SD)	Change from Baseline	Form B Mean(SD)	Change from Baseline
Line Orientation	15.8 (4.52)	-1.1	16.0 (2.94)	0.2
Picture Naming	10.0 (0.00)	0.8	9.8 (0.37)	0.2
Semantic Fluency	19.6 (4.31)	-0.3	21.7 (2.49)	4
Digit Span	11.3 (2.38)	0.9	9.0 (2.45)	-1.3
Coding	43.4 (7.16)	2	40.5 (5.41)	1.8
List Recall	4.9 (2.02)	0.4	2.8 (1.21)	-1.3
List Recognition	18.3 (1.65)	-0.3	18.2 (1.46)	-0.2
Story Recall	9.7 (1.65)	3.4	5.3 (2.13)	-1.7
Figure Recall	14.5 (2.99)	1.1	11.3 (3.90)	1.8
Immediate Memory Index	95.6 (11.38)	16.1	81.8 (11.19)	-3.7
Visuospatial Index	101.2 (21.47)	-2.8	94.7 (12.93)	-2.7
Language Index	98.5 (9.45)	1.9	102.5 (5.32)	6.8
Attention index	102.3 (11.63)	5.3	90.3 (12.26)	-3.5
Delayed Memory index	97.9 (10.23)	5.2	83 (10.05)	-2.7
Sum of Indices	495.4 (39.45)	25.7	452.3 (19.37)	-5.7
Total Scale Index	98.1 (10.51)	6.4	86.7 (4.42)	-1.7
Average last two 2-back	59.7 (23.77)	-4.2	39.4 (8.80)	11.3

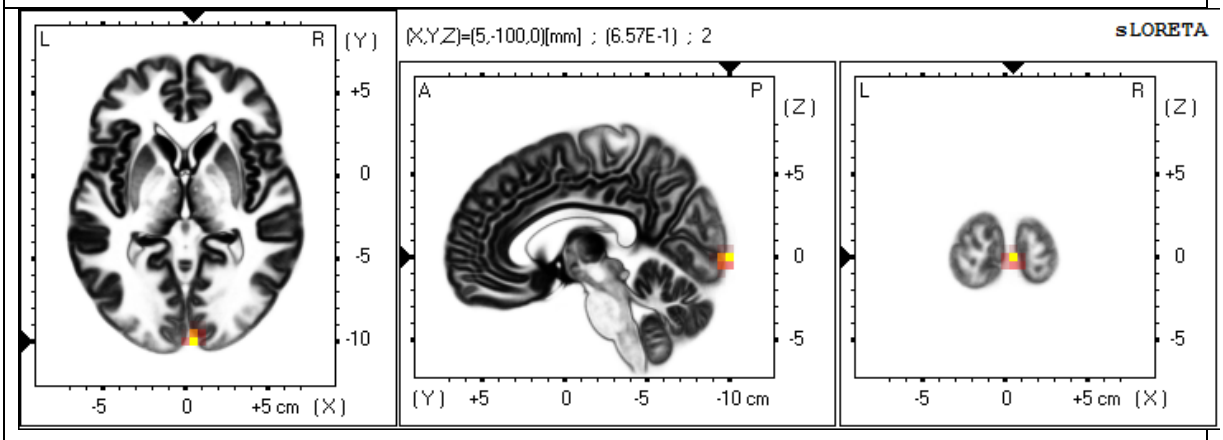
Appendix C7: Change From Baseline to Immediate Follow up in Current Density

Figures C-9 to C-11 illustrate the voxel with the highest magnitude change in each group in each frequency band, comparing the immediate follow up resting state recording to the baseline recording. Blue indicates voxels with decreased activity after training and red voxels indicate higher activity after training.

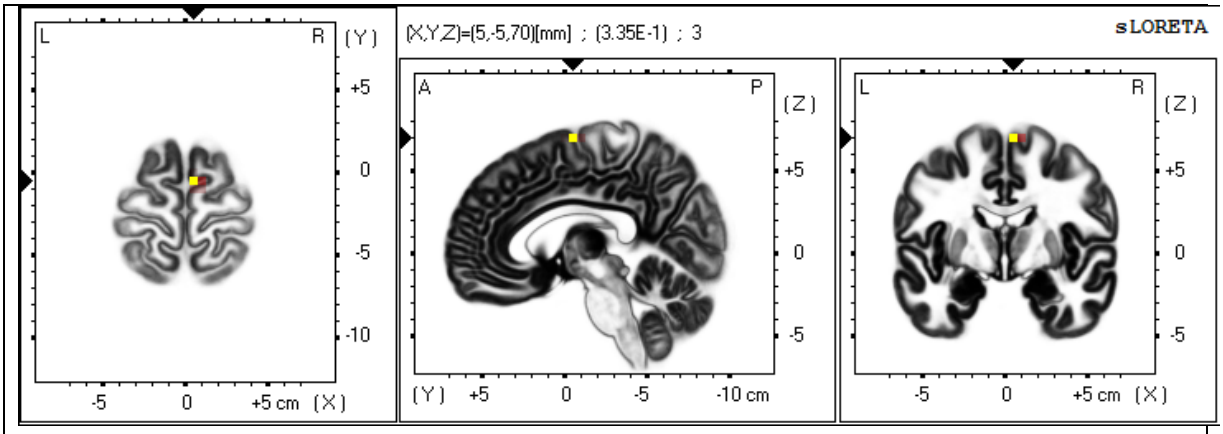
Broadband Feedback Group



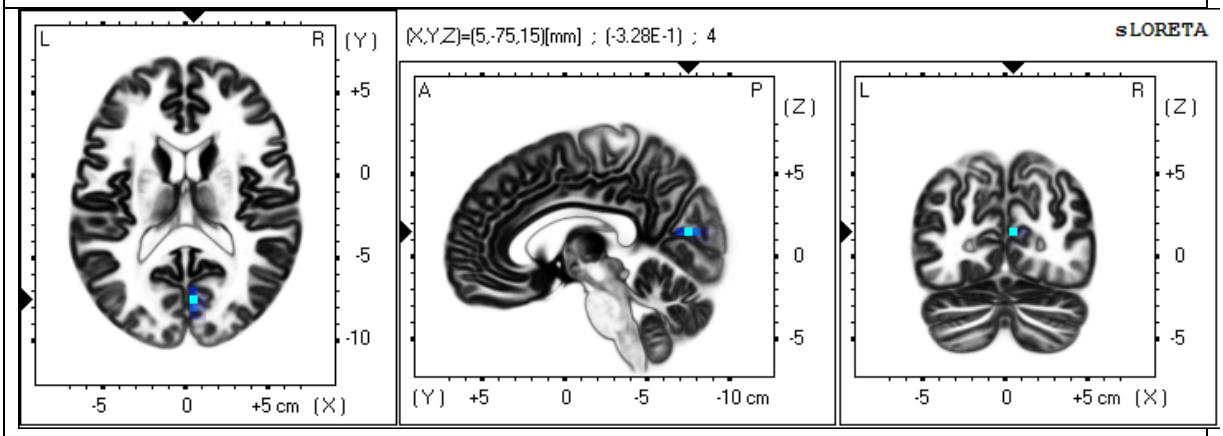
Delta band



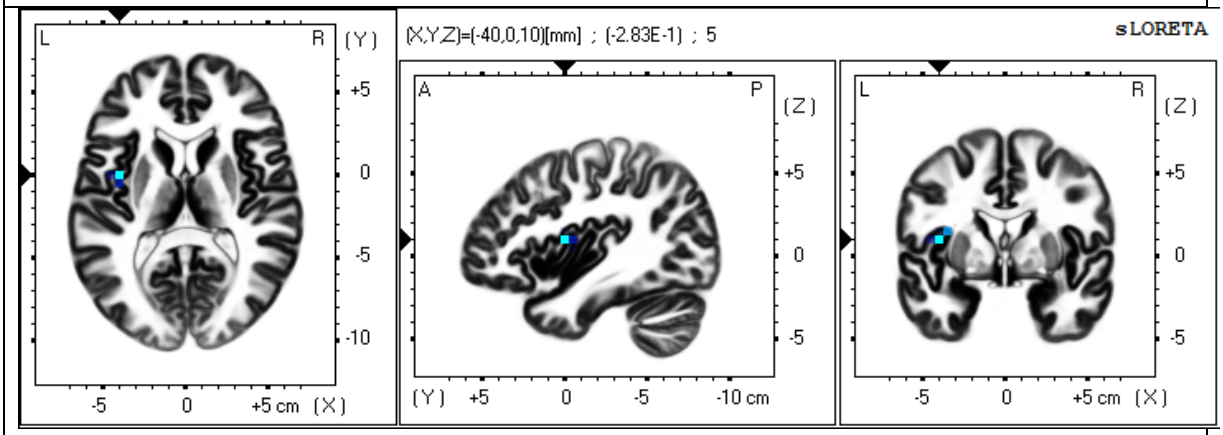
Theta band



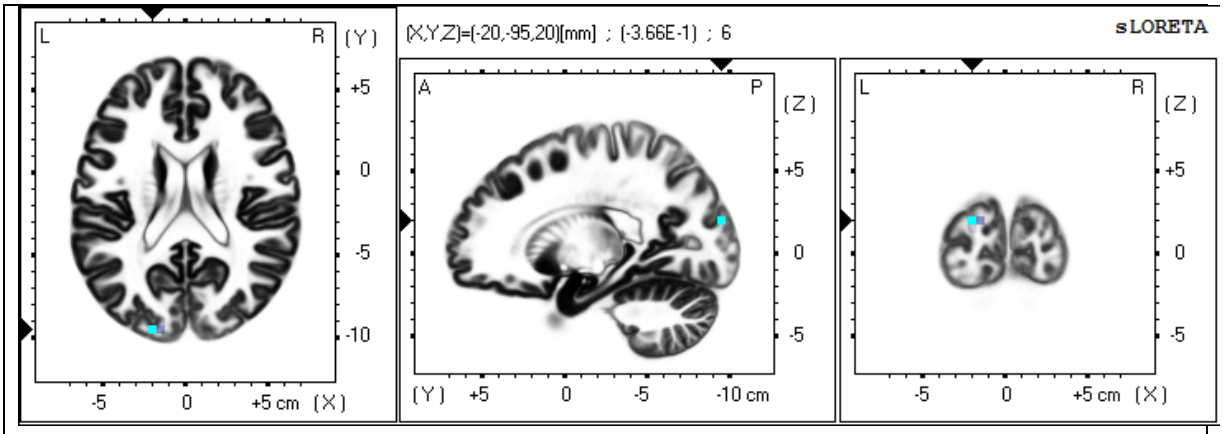
Alpha 1 band



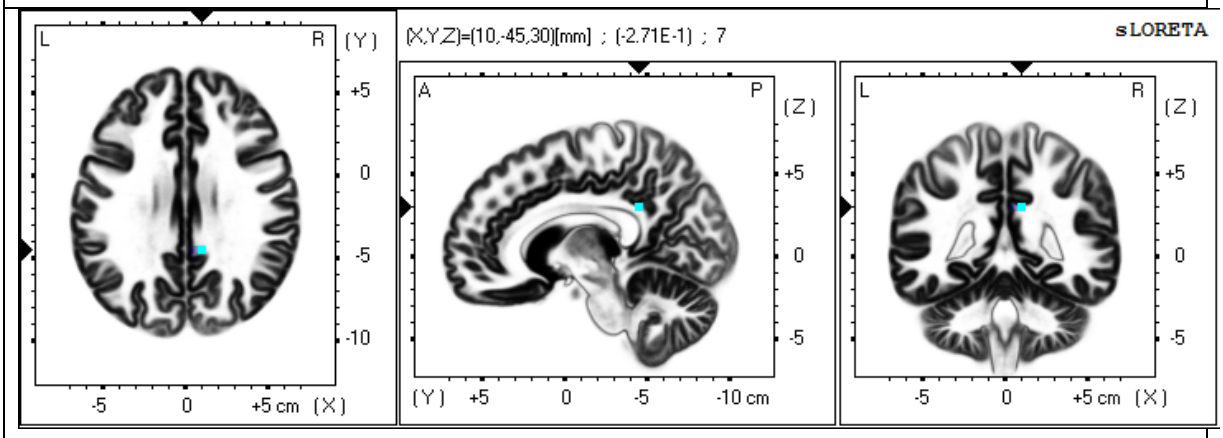
Alpha 2 band



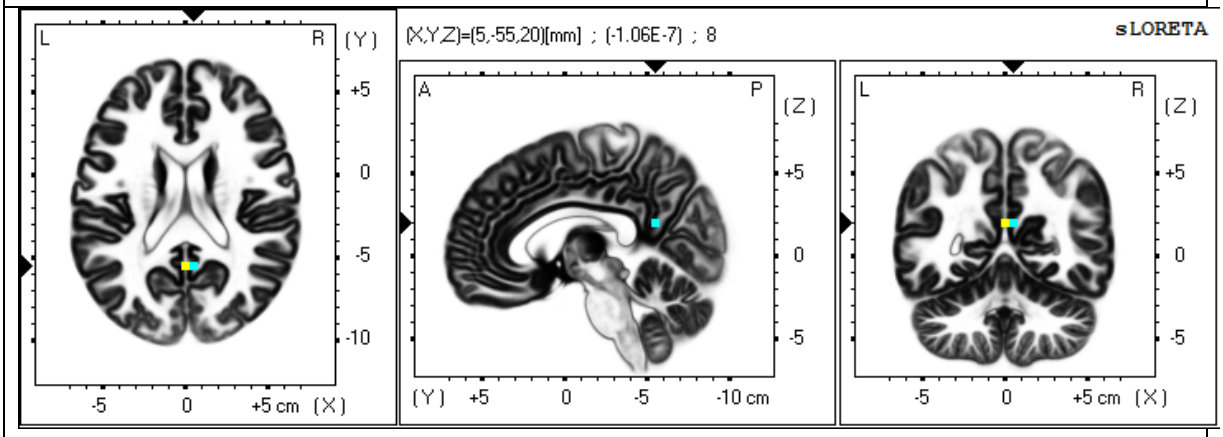
Beta 1 Band



Beta 2 band



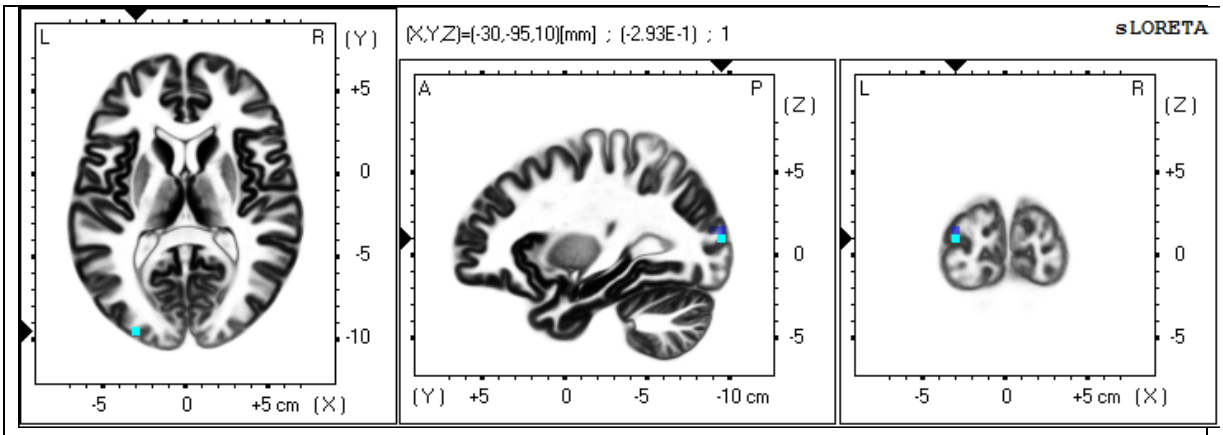
Beta 3 band



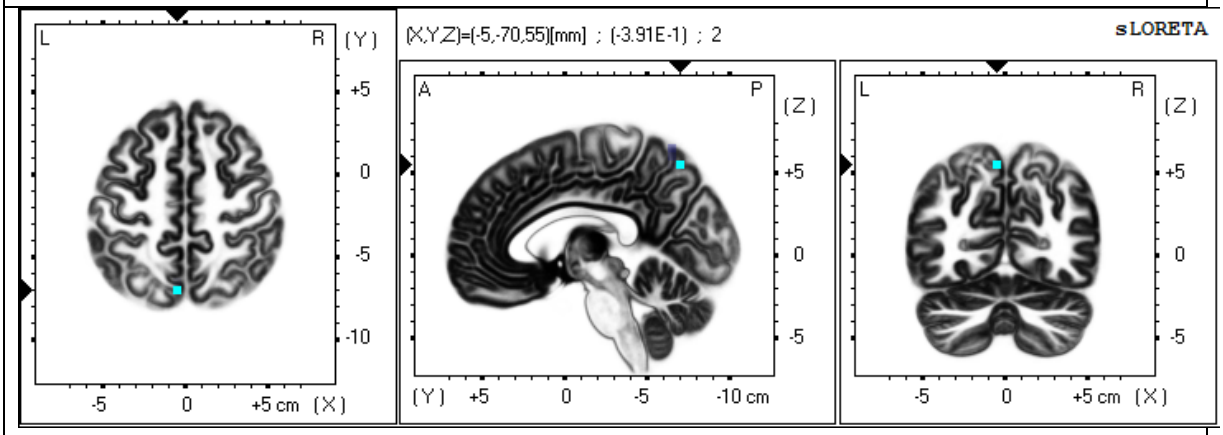
Omega Band

Figure C-9: Maps of change in current density comparing immediate follow up resting state recording to the baseline resting state recording in the broadband feedback group

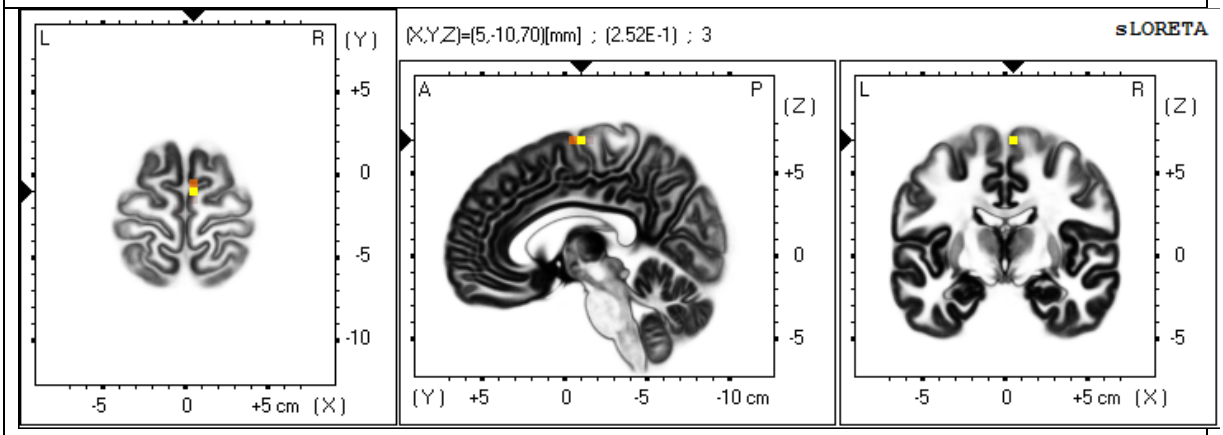
Narrowband Feedback Group



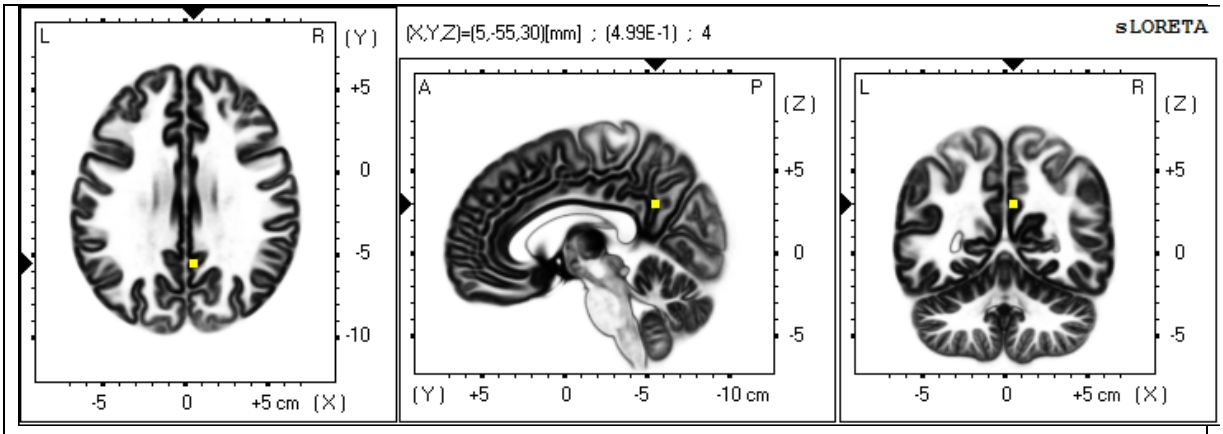
Delta band



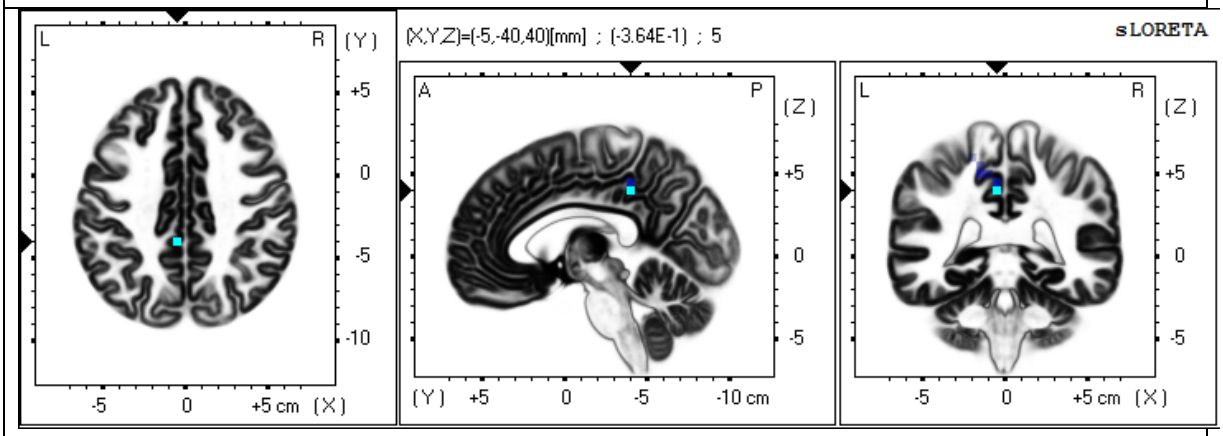
Theta band



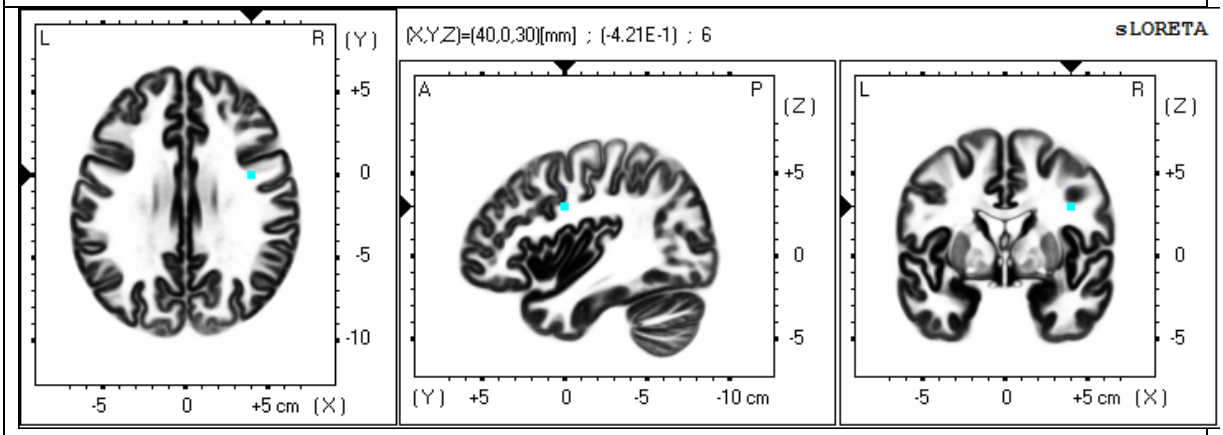
Alpha 1 band



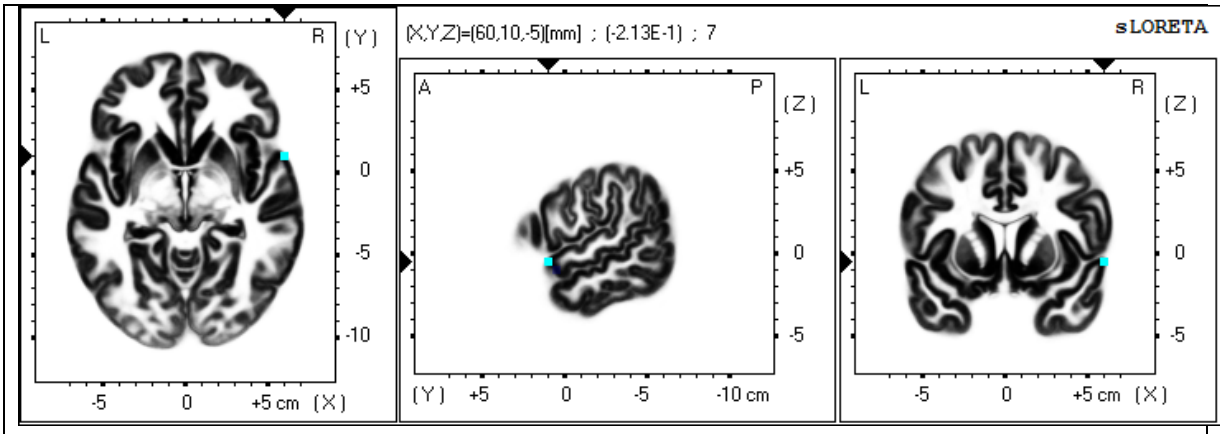
Alpha 2 band



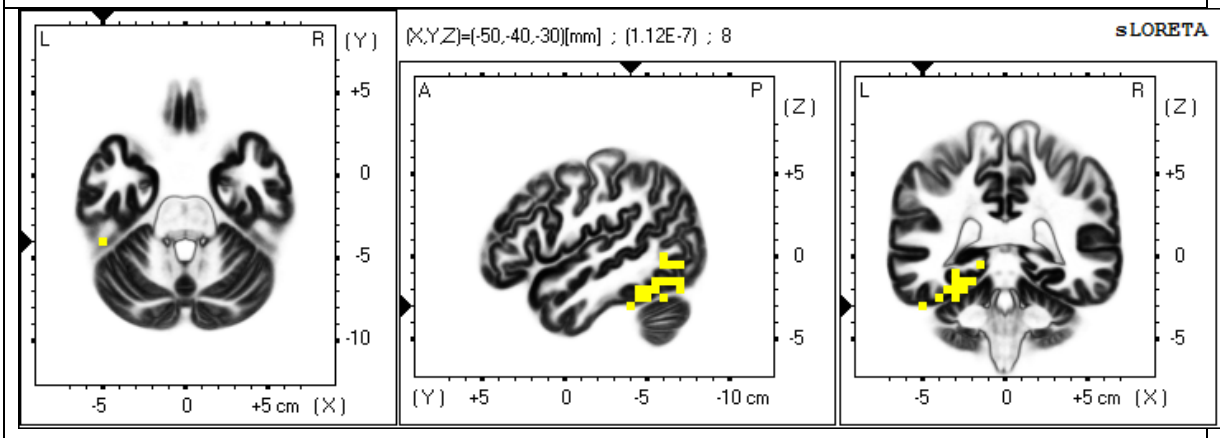
Beta 1 band



Beta 2 band



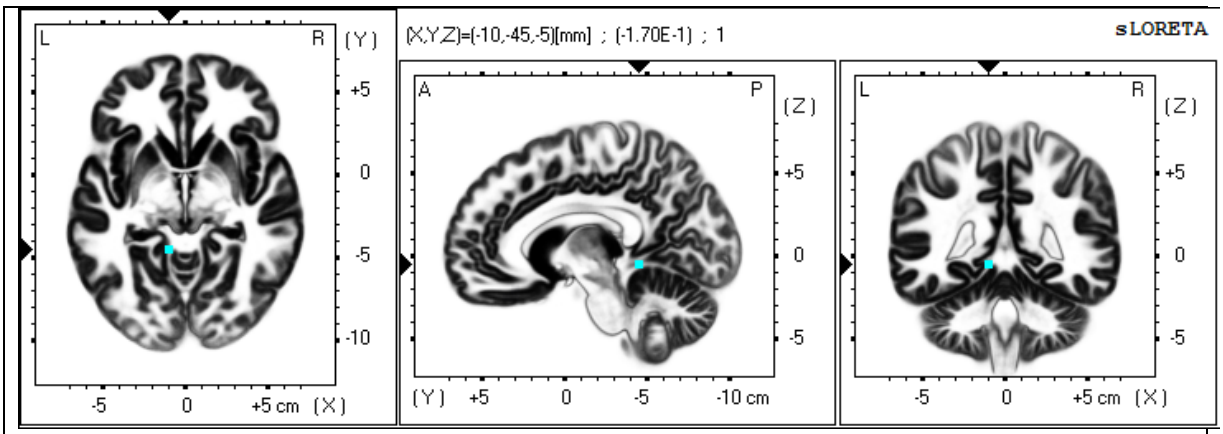
Beta 3 band



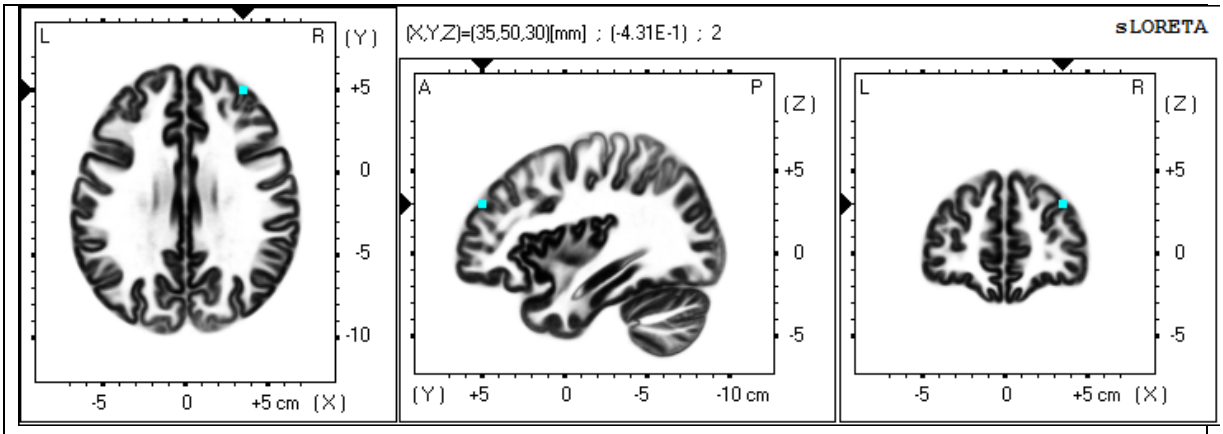
Omega band

Figure C-10: Maps of change in current density comparing immediate follow up resting state recording to the baseline resting state recording in the narrowband feedback group

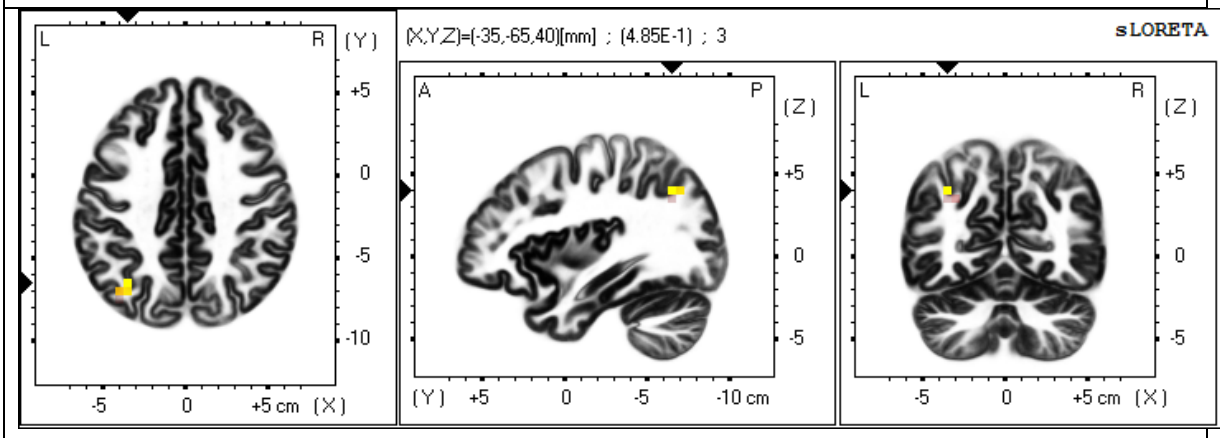
Placebo Feedback



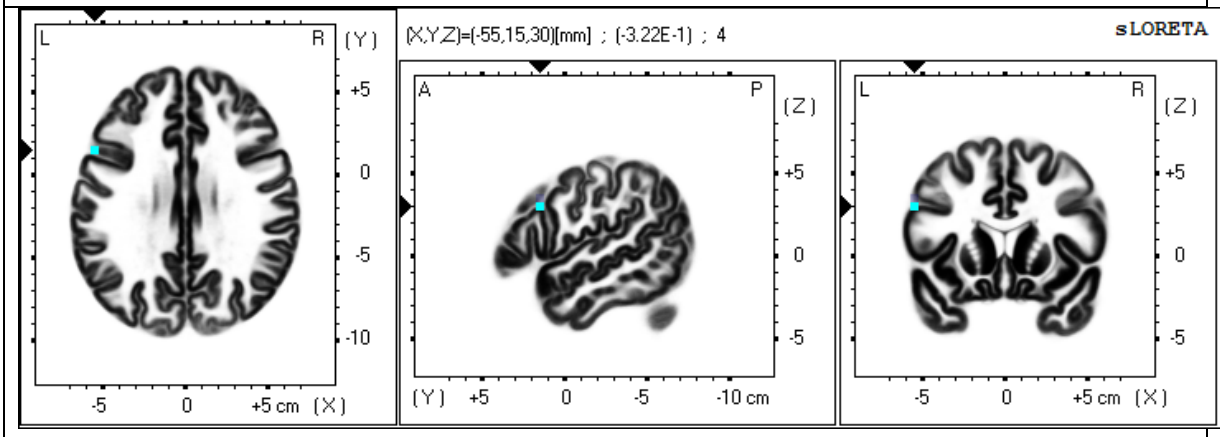
Delta band



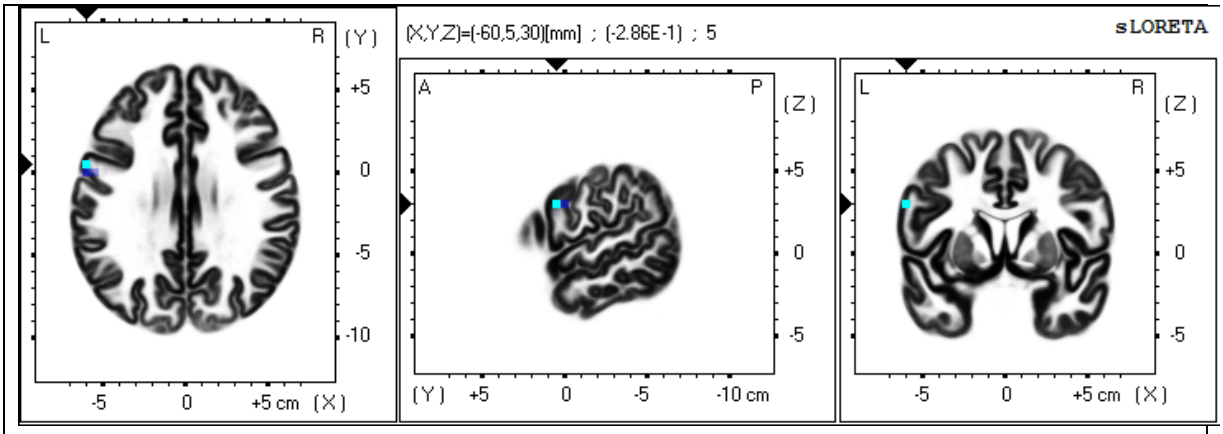
Theta band



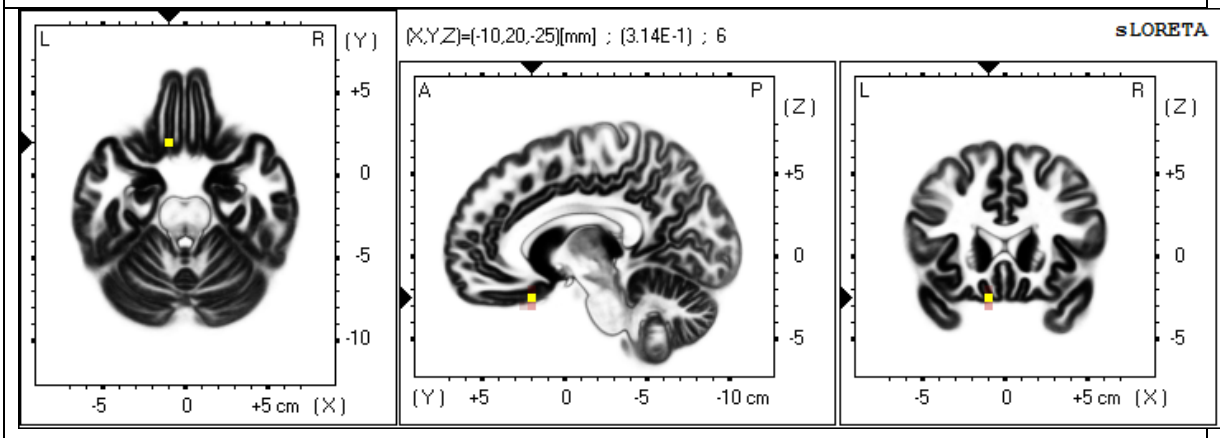
Alpha 1 band



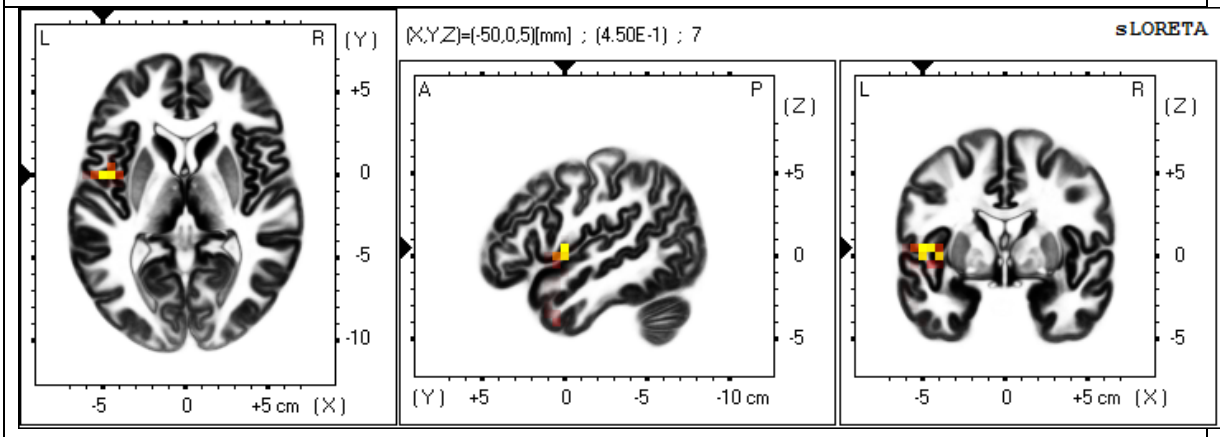
Alpha 2 band



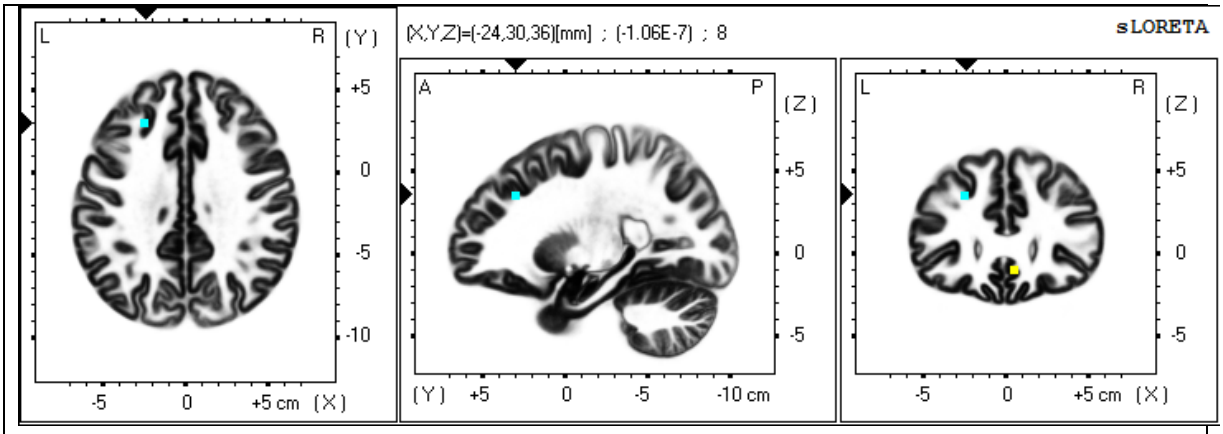
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

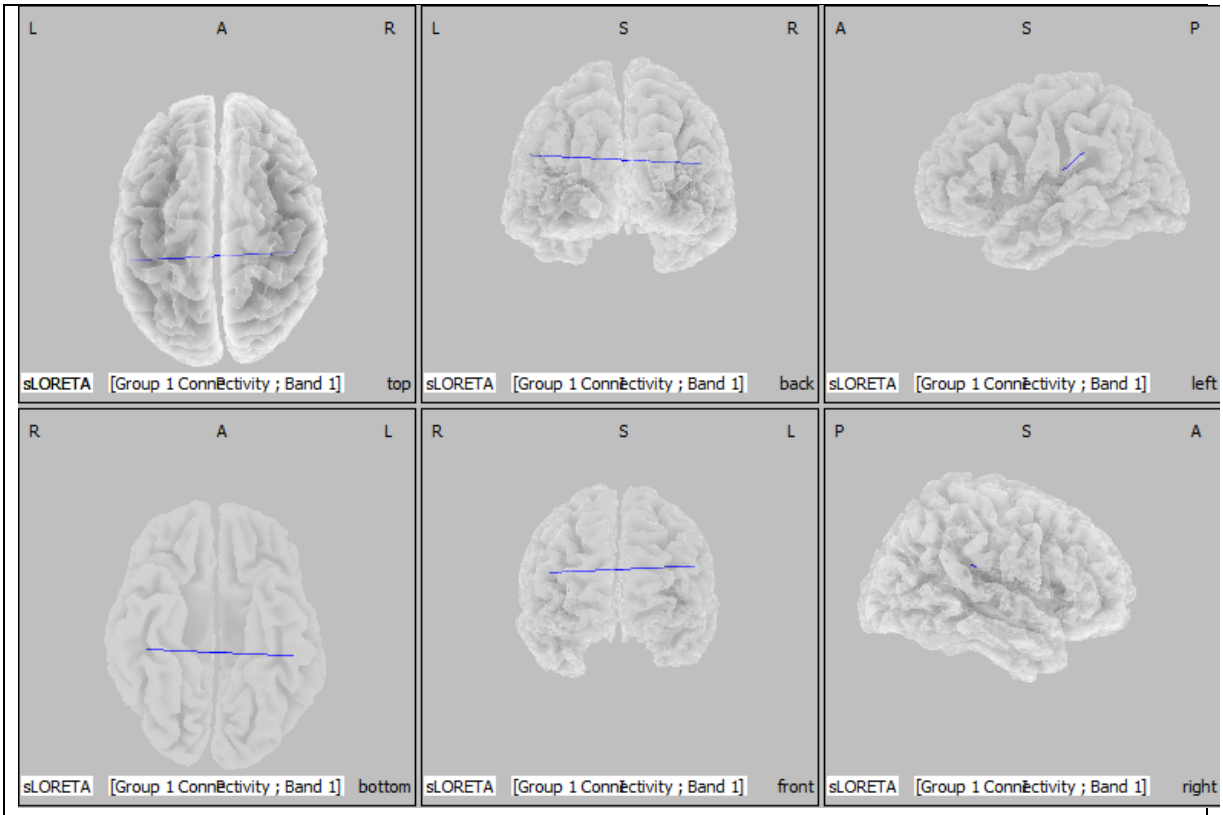
Figure C-11 Maps of change in current density comparing immediate follow up resting state recording to the baseline resting state recording in the placebo feedback group

Appendix C8: Change from Baseline to Immediate Follow Up in Phase Lagged Synchronisation of the DMN

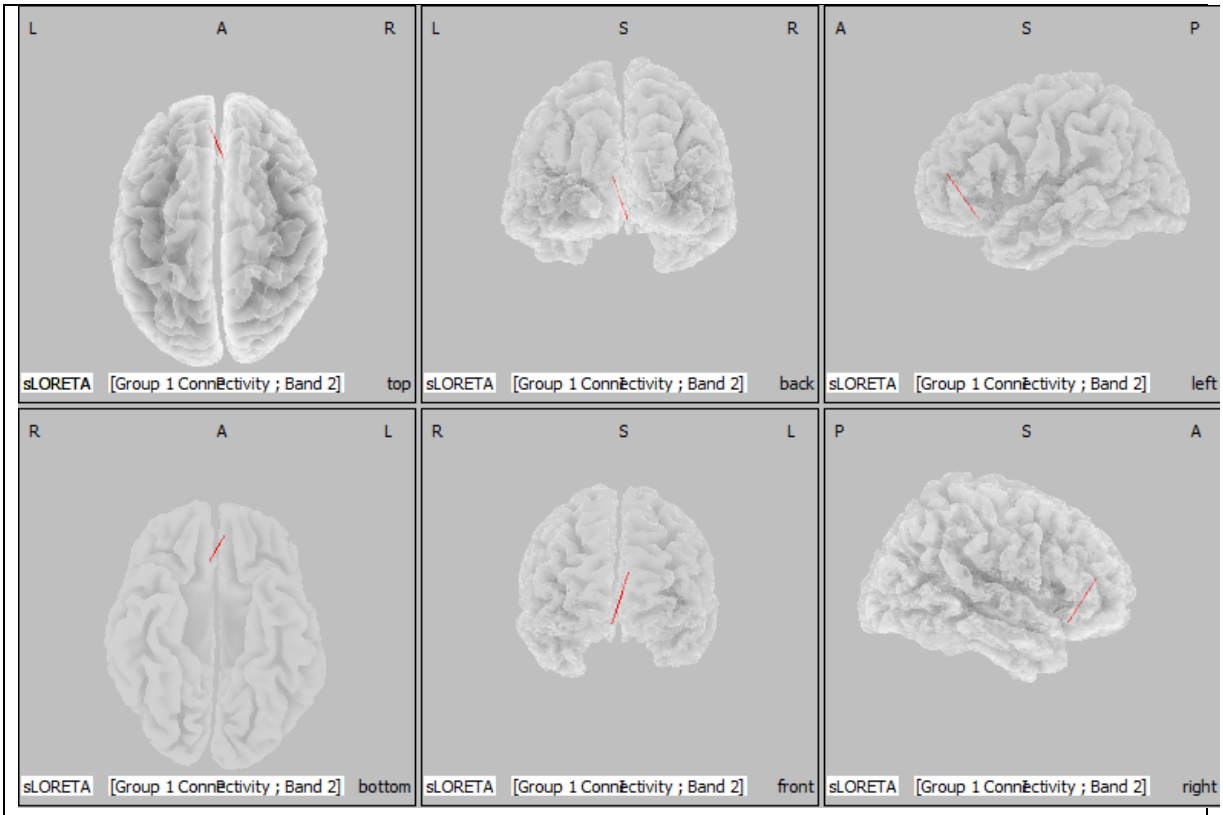
Figures C-12 to C-14 below show changes in the phase lagged synchronisation of the default mode network between baseline and immediate follow up. Blue lines represent decreases in connectivity from baseline and red lines indicate increases in connectivity from baseline. Bands not shown have no changes at that level of significance.

Broadband Feedback Group

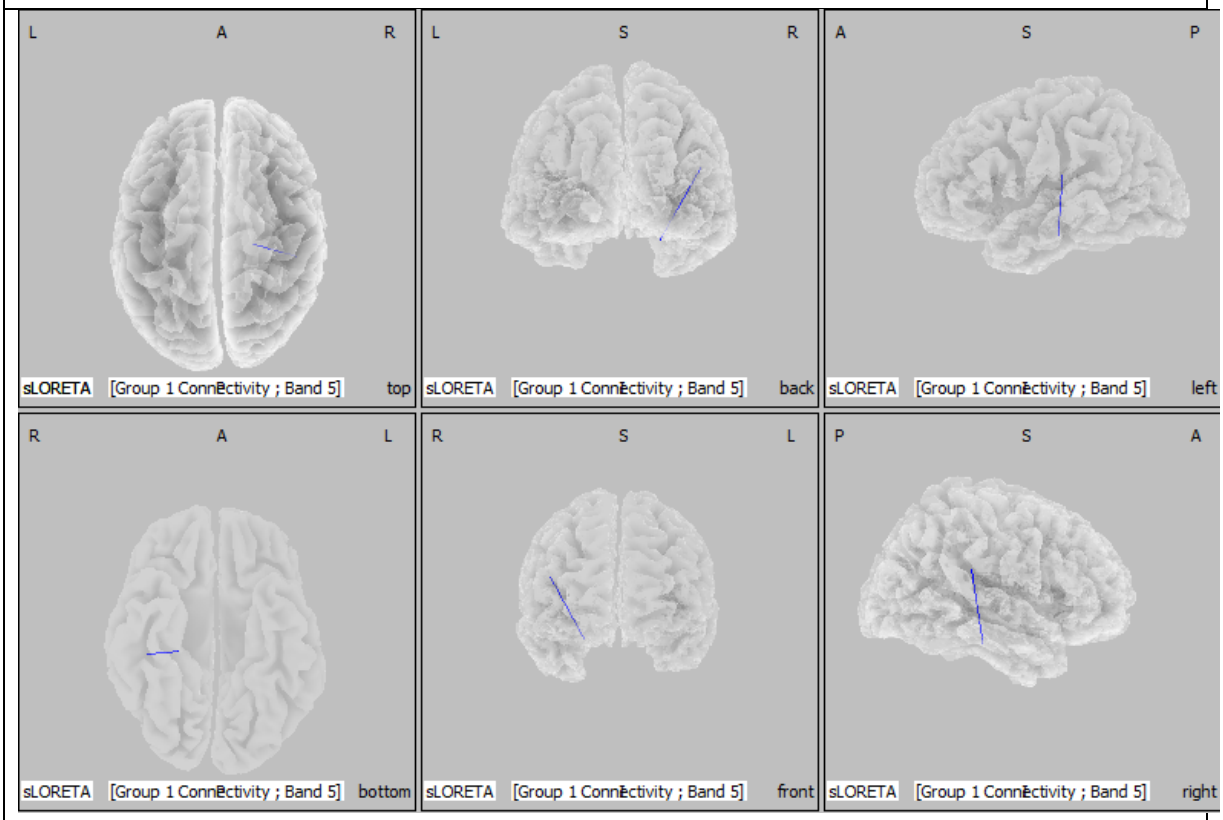
The following change have a significance of p=0.408



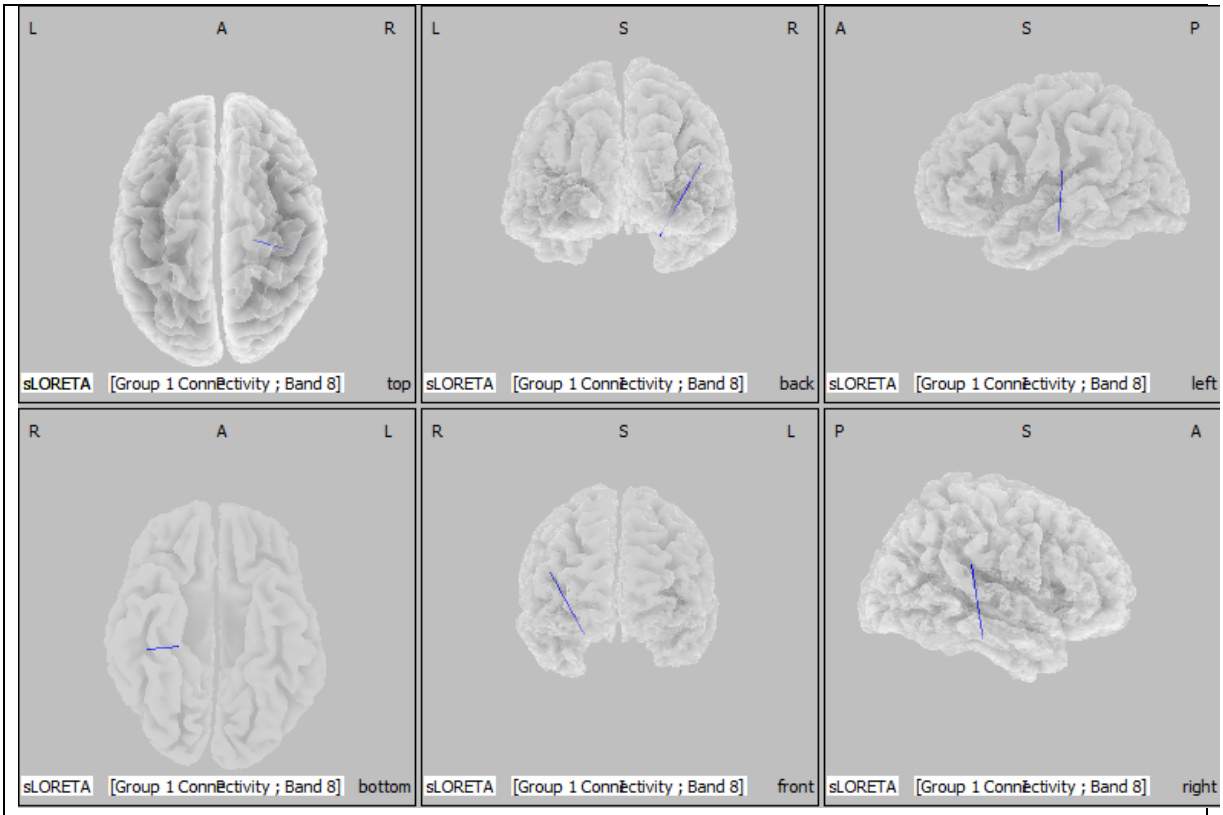
Delta band



Theta band



Beta 1 band

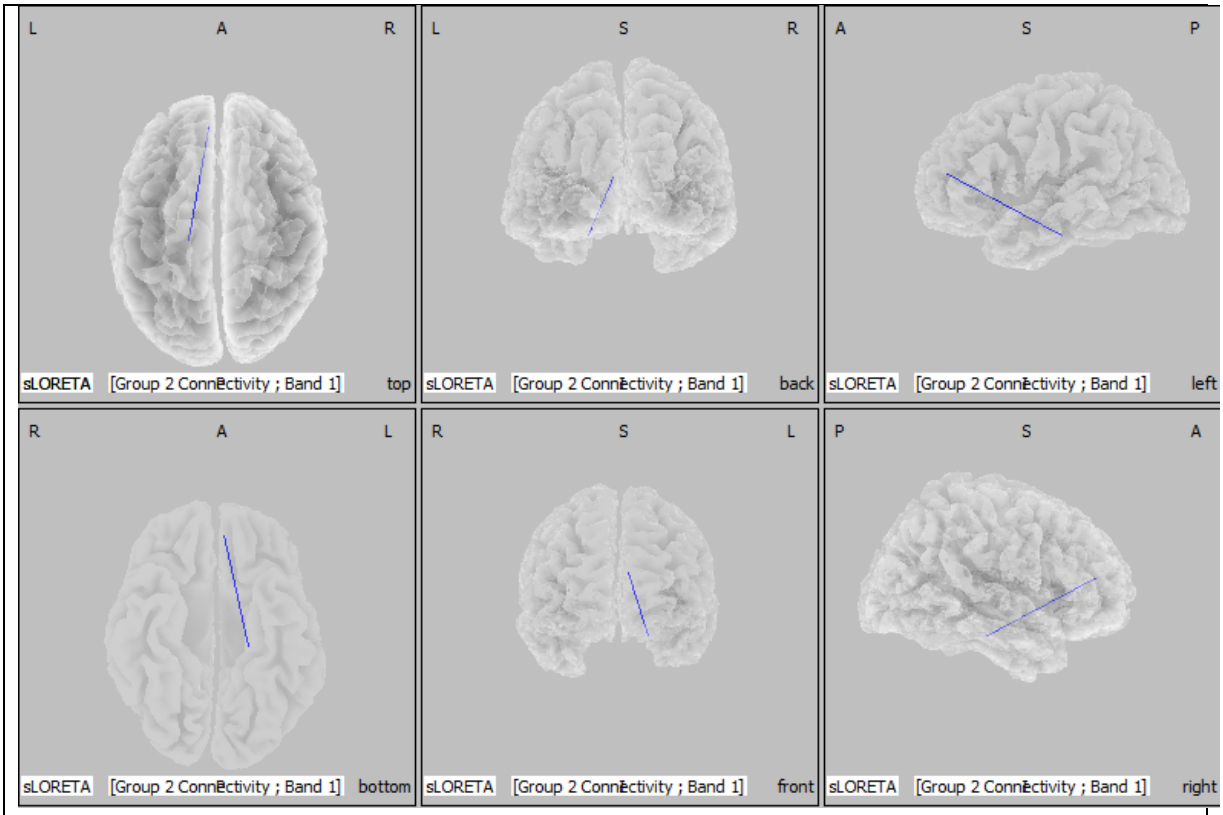


Omega Band

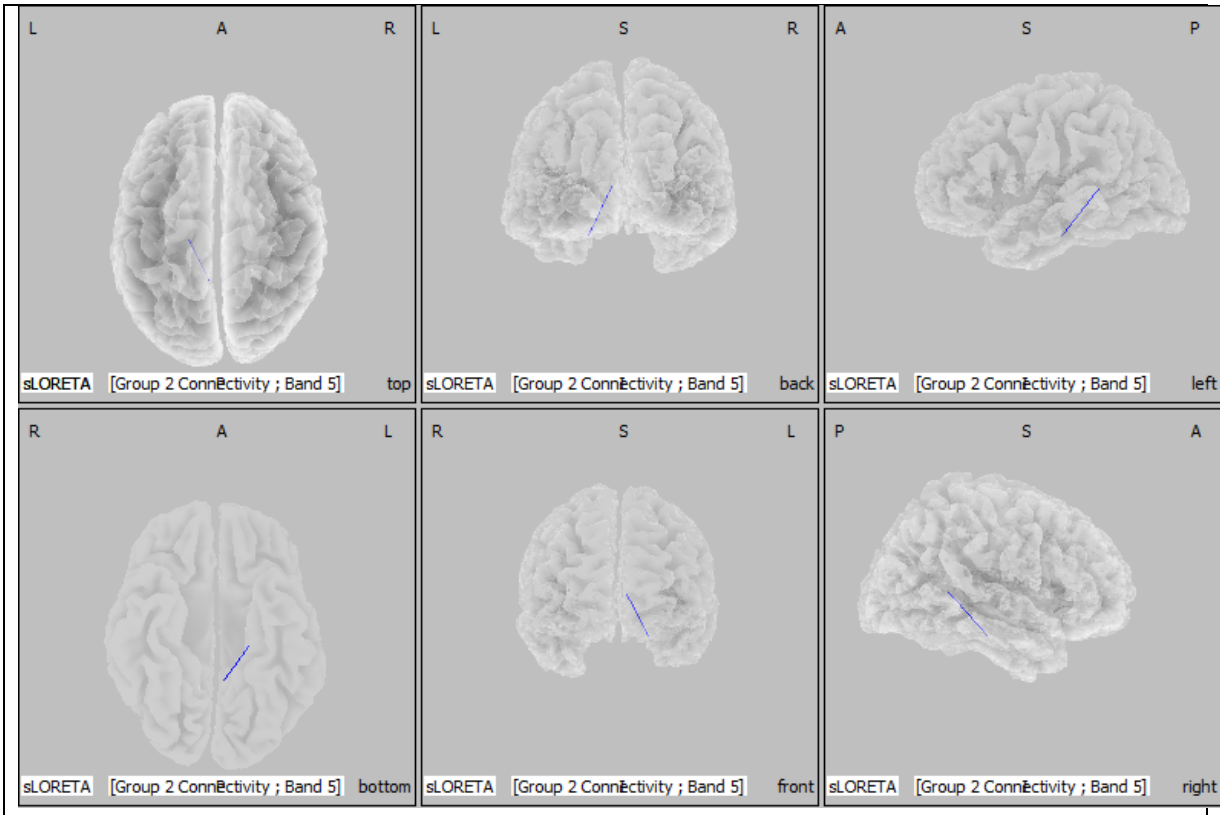
Figure C-12: Maps of change in phase lagged synchronisation of the DMN comparing immediate follow up resting state recording to the baseline resting state recording in the broadband feedback group

Narrowband Feedback Group

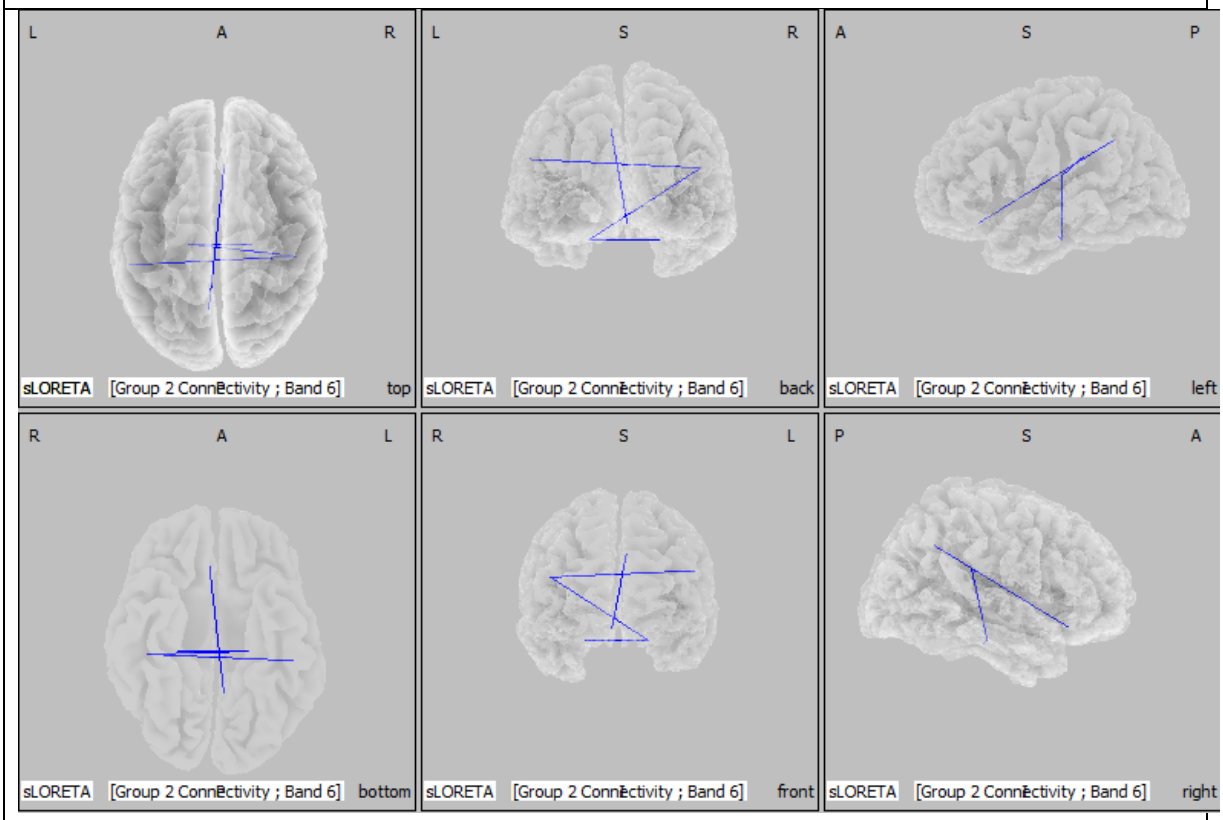
The following changes have a significance of p=0.163



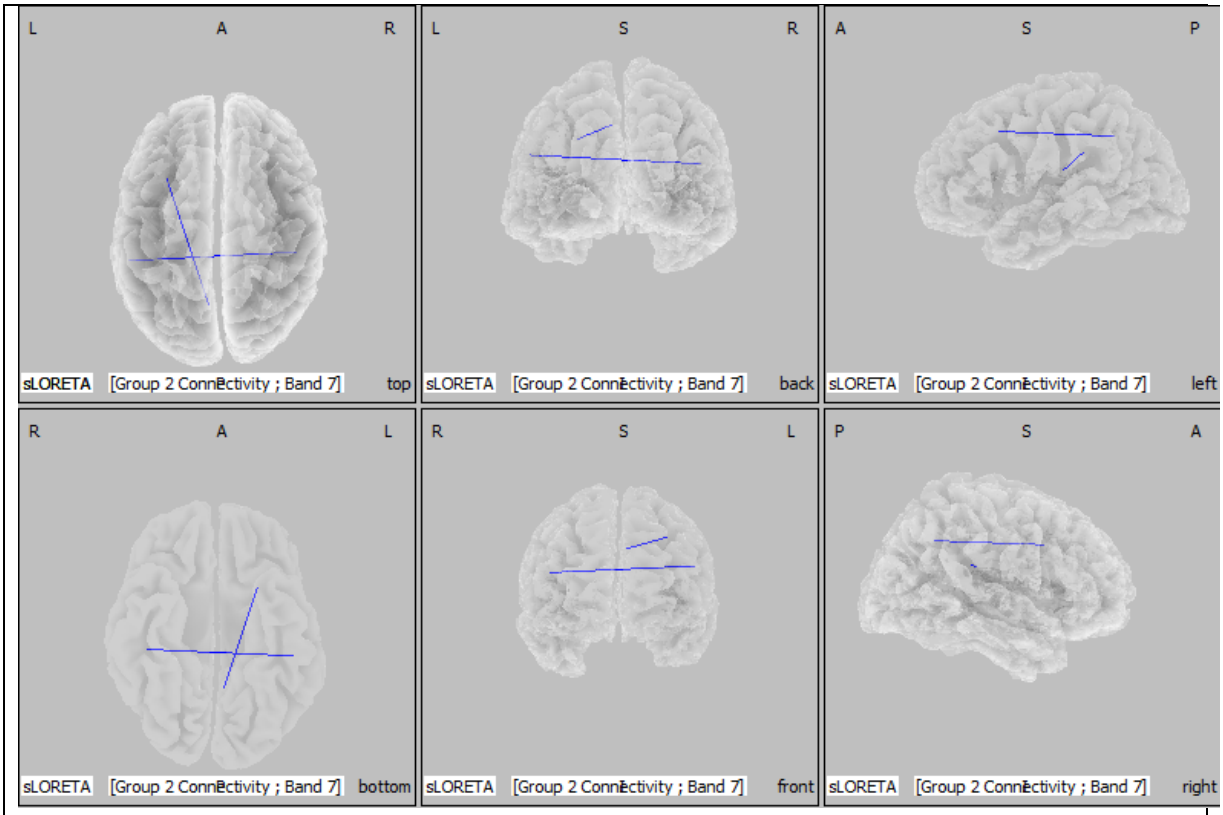
Delta band



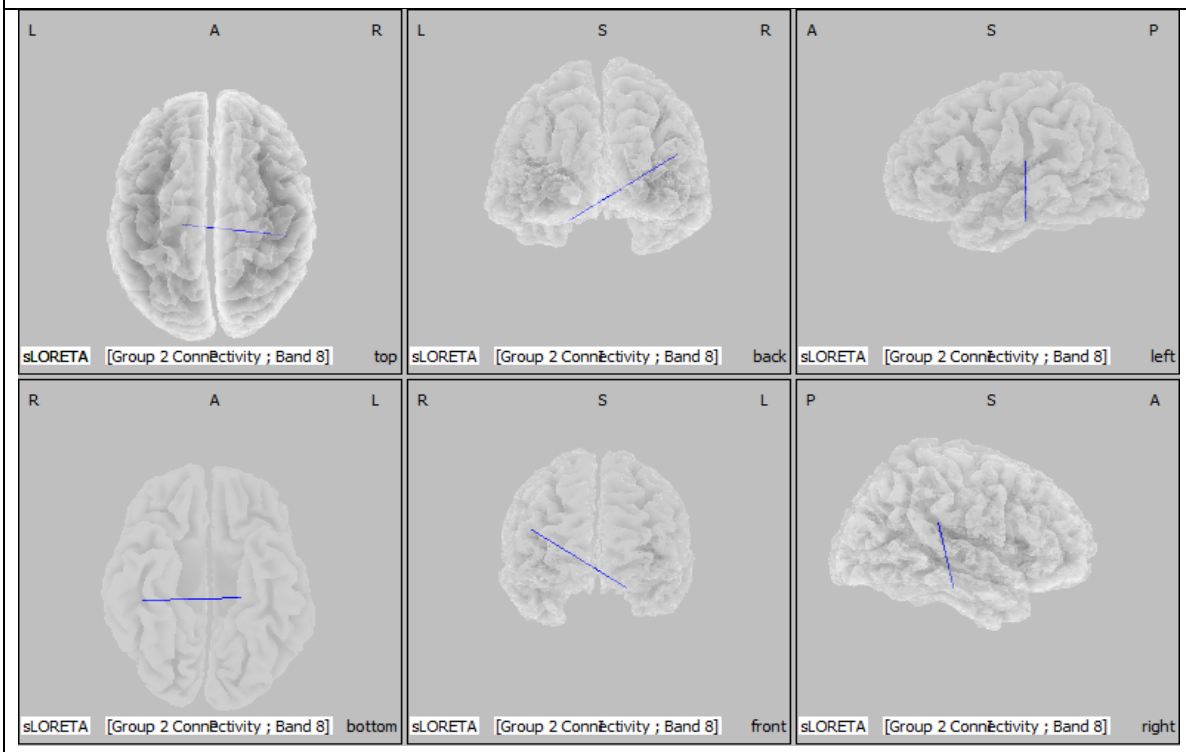
Beta 1 band



Beta 2 band



Beta 3 band

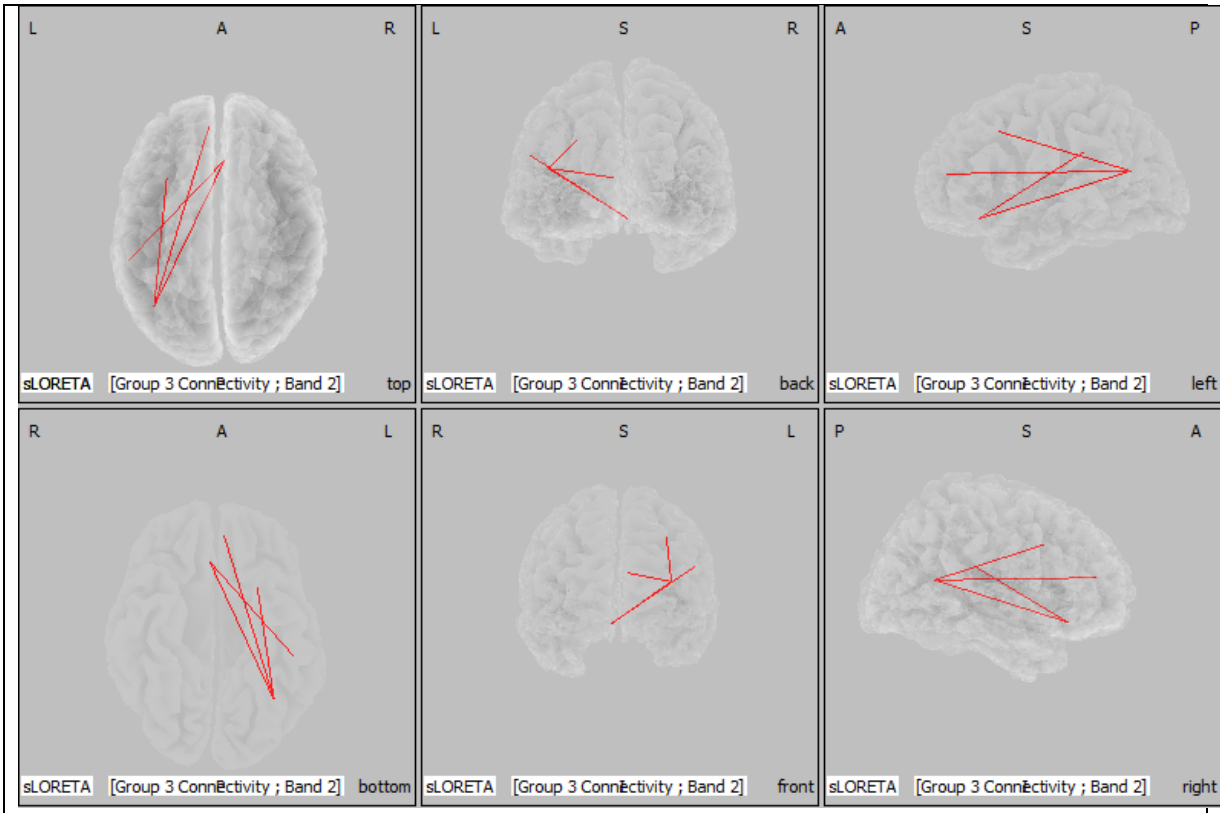


Omega band

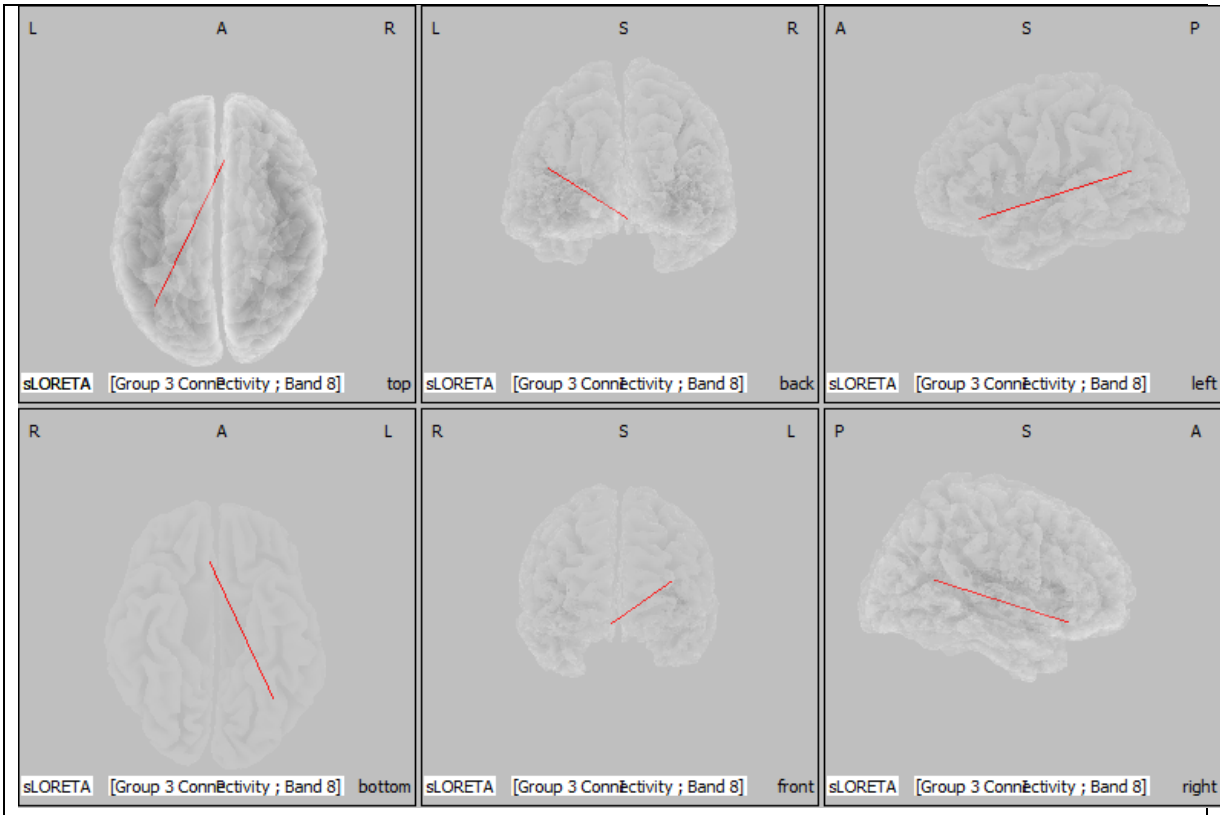
Figure C-13: Maps of change in phase lagged synchronisation of the DMN comparing immediate follow up resting state recording to the baseline resting state recording in the narrowband feedback group

Placebo Feedback Group

The following changes have a significance of p=0.307.



Theta band



Omega band

Figure C-14: Maps of change in phase lagged synchronisation of the DMN comparing immediate follow up resting state recording to the baseline resting state recording in the placebo feedback group

Appendix C9: Change in activity and connectivity indices for In-training Data

Figures C-15 to C-34 below show the changes in the measured indices for each participant in each group. The changes in these measures are non-significant at a group level, significant changes at a group level are given in chapter 5.

Broadband Feedback Group PCC Current Density

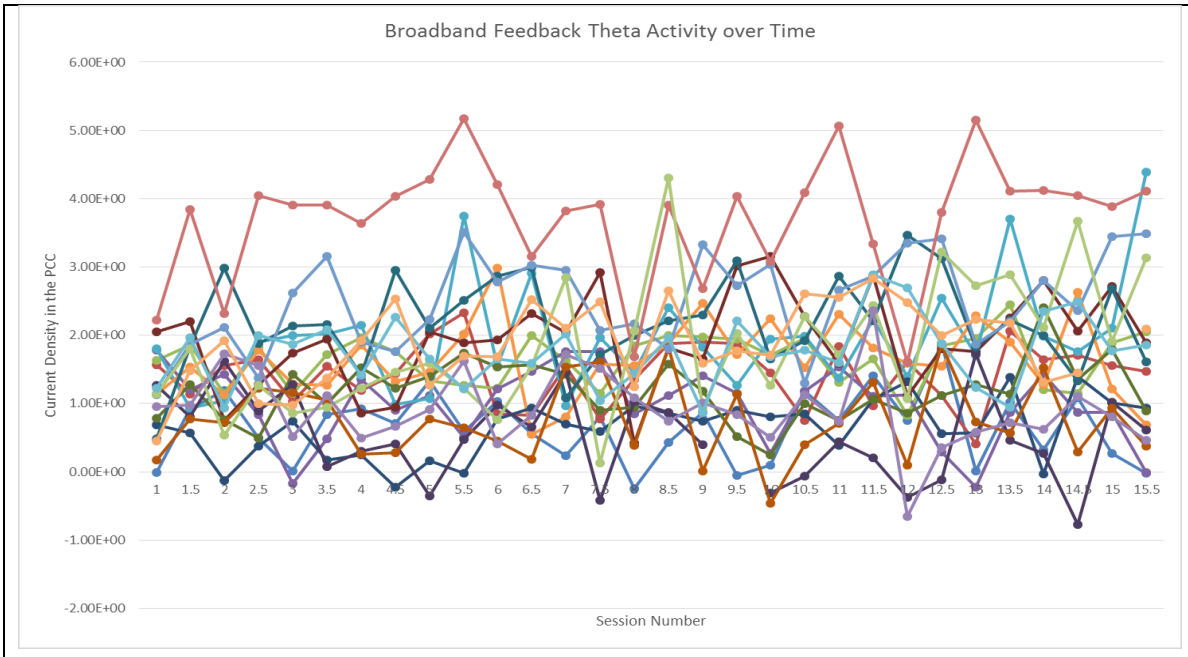


Figure C-15: Change in the theta current density in the PCC in the broadband feedback group in the in-training data

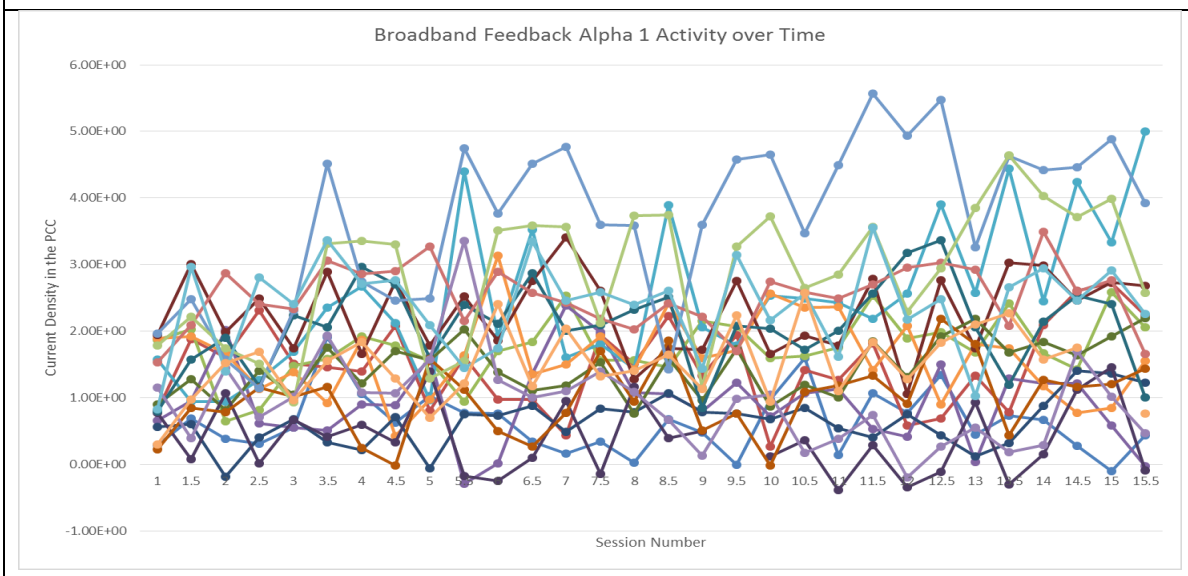


Figure C-16: Change in the alpha 1 current density in the PCC in the broadband feedback group in the in-training data

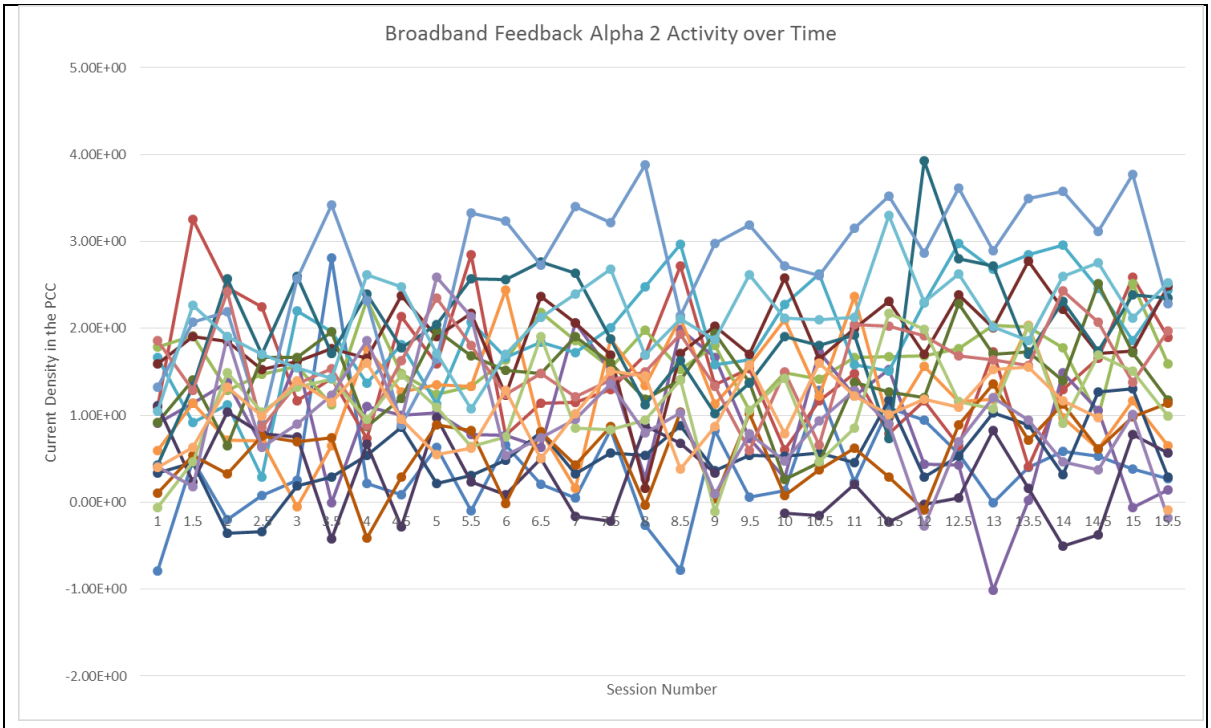


Figure C-17 Change in the alpha 2 current density in the PCC in the broadband feedback group in the in-training data

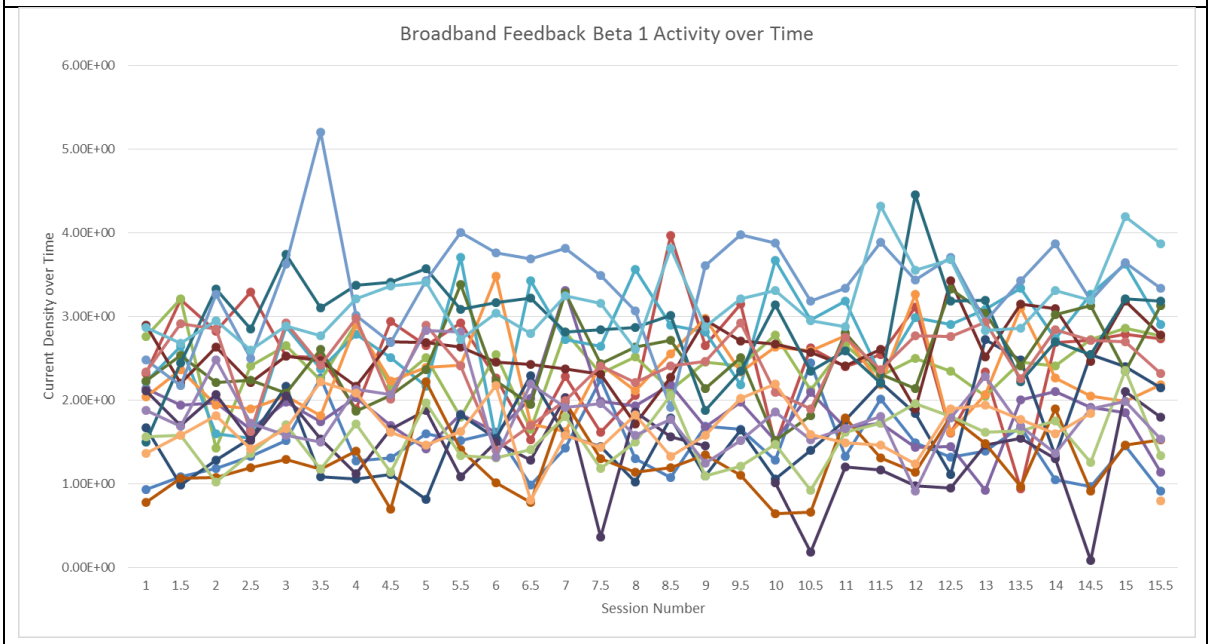


Figure C-18 Change in the beta 1 current density in the PCC in the broadband feedback group in the in-training data

Broadband Feedback Group Phase Lagged Synchronisation of the PCC to MTL

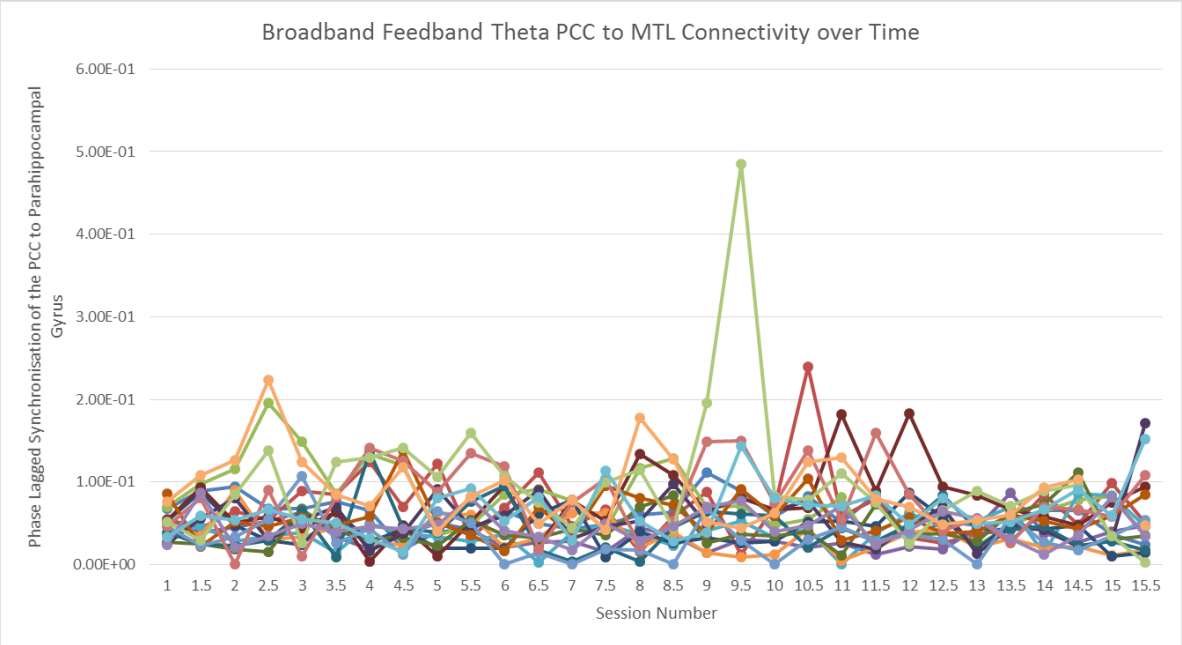


Figure C-19: Change in the theta phase lagged synchronisation between PCC and the parahippocampal gyrus in the broadband feedback group in the in-training data

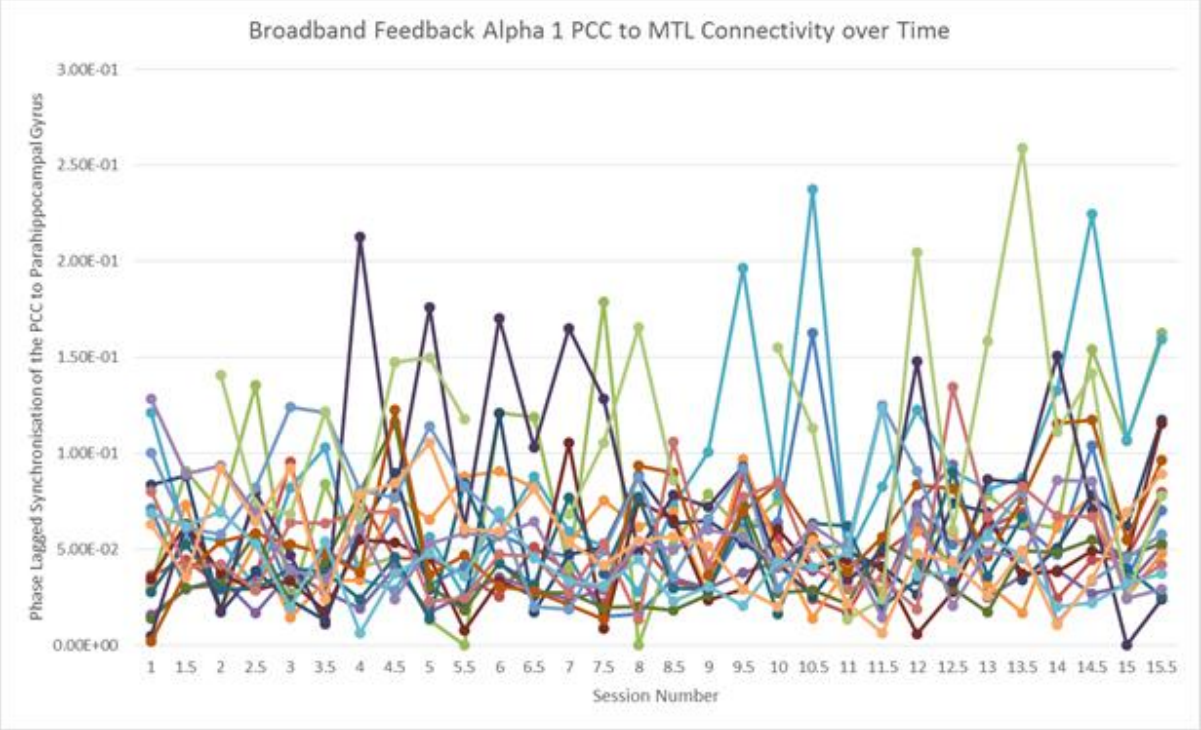


Figure C-20: Change in the alpha 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the broadband feedback group in the in-training data

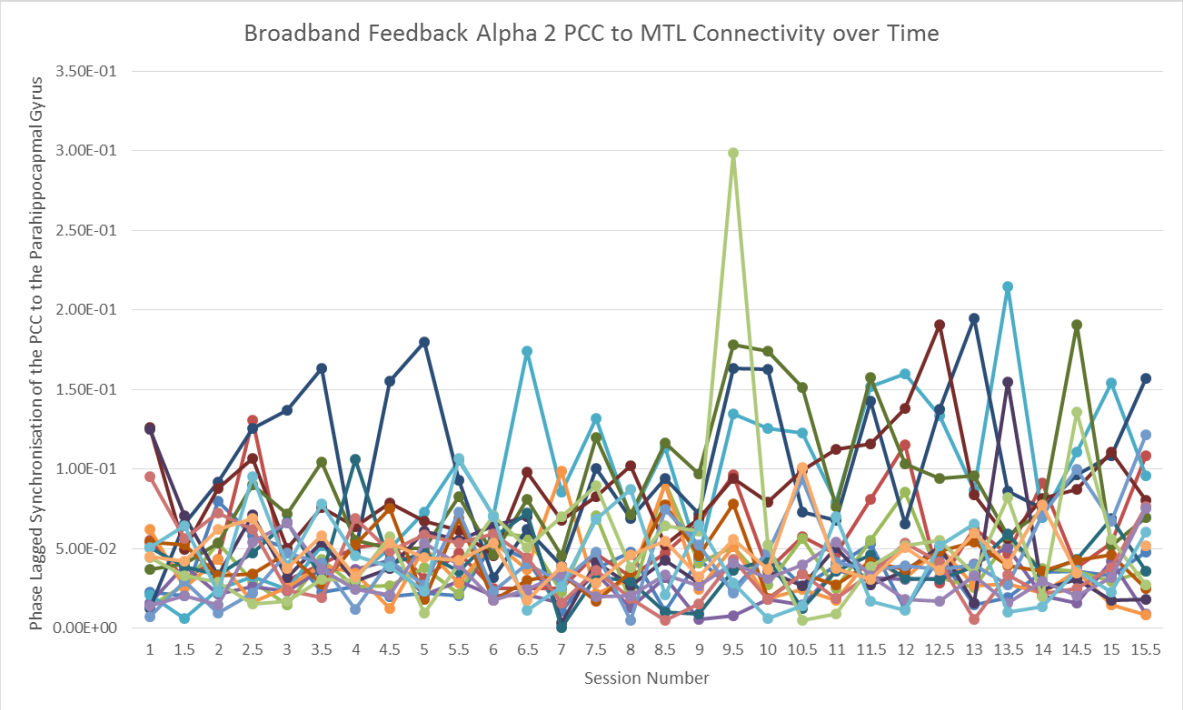


Figure C-21: Change in the beta 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the broadband feedback group in the in-training data

Narrowband Feedback Group PCC Current Density

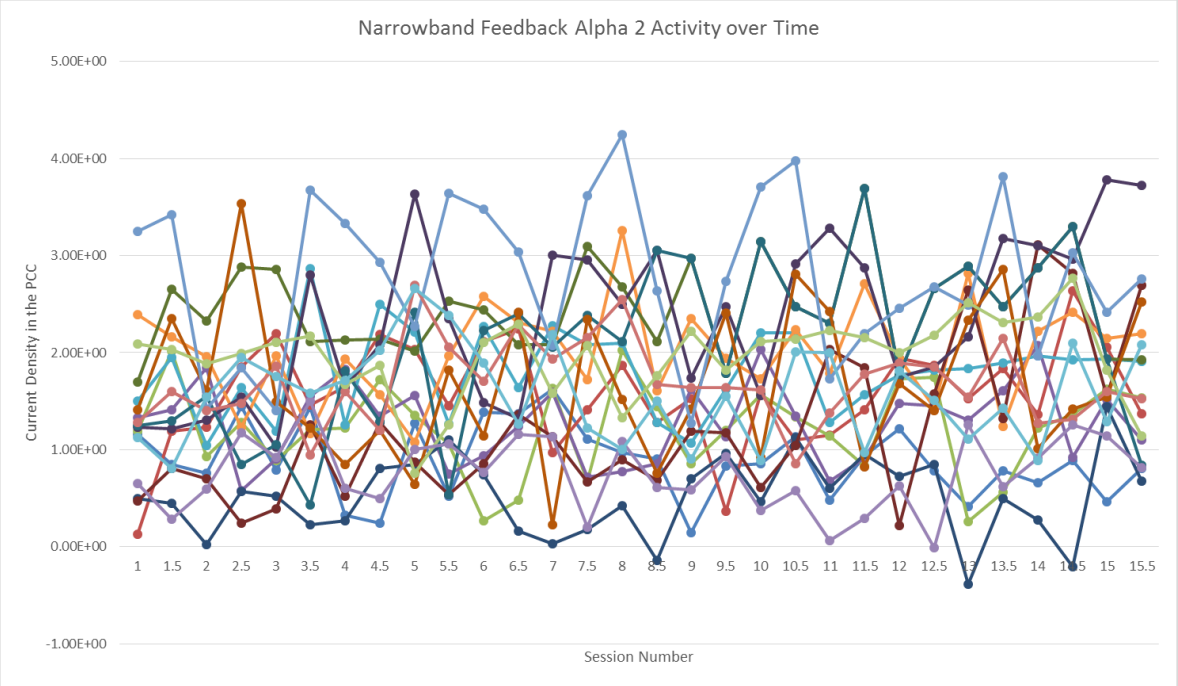


Figure C-22 Change in the alpha 2 current density in the PCC in the narrowband feedback group in the in-training data

Narrowband Feedback Group Phase Lagged Synchronisation of the PCC to MTL

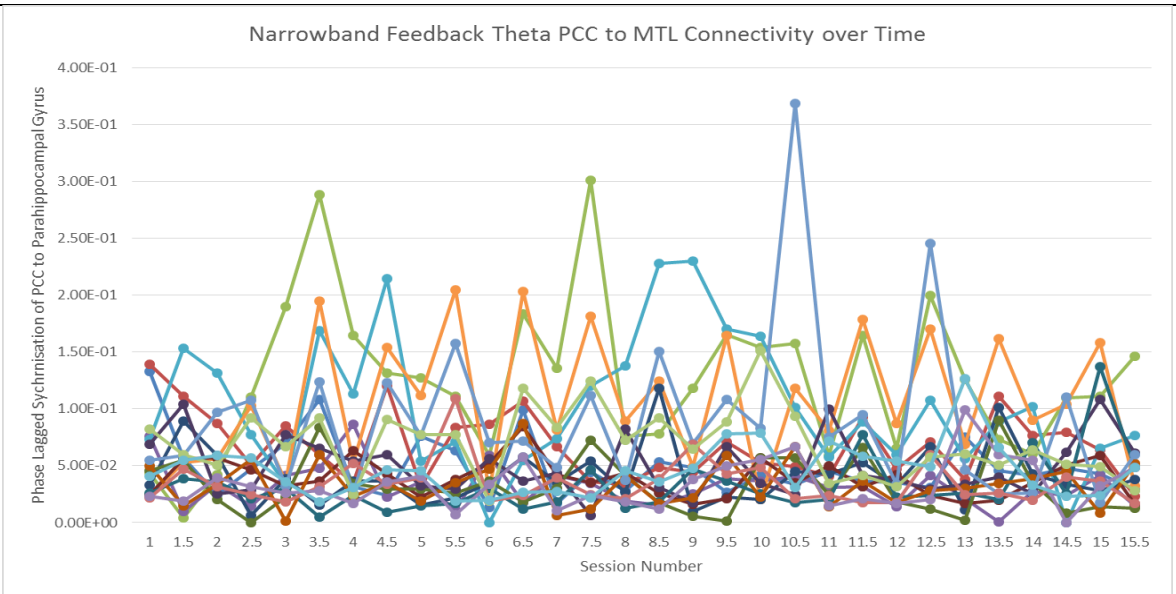


Figure C-23: Change in the theta phase lagged synchronisation between PCC and the parahippocampal gyrus in the narrowband feedback group in the in-training data

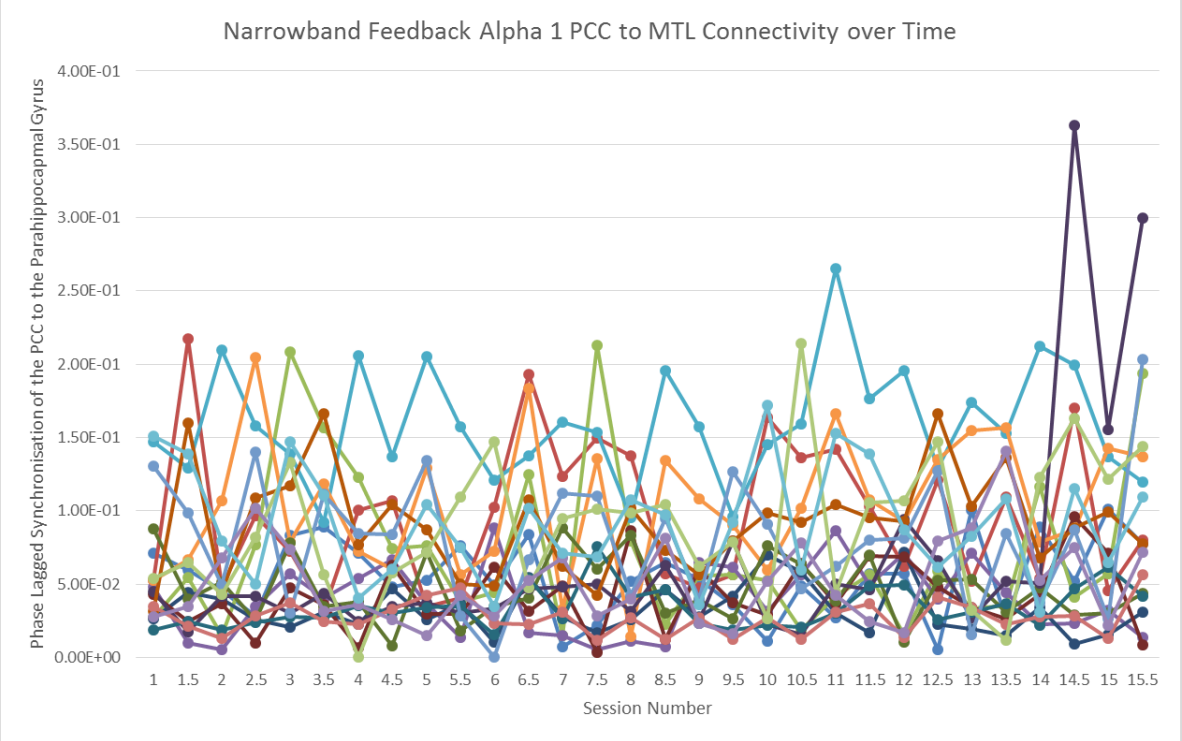


Figure C-24: Change in the alpha 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the narrowband feedback group in the in-training data

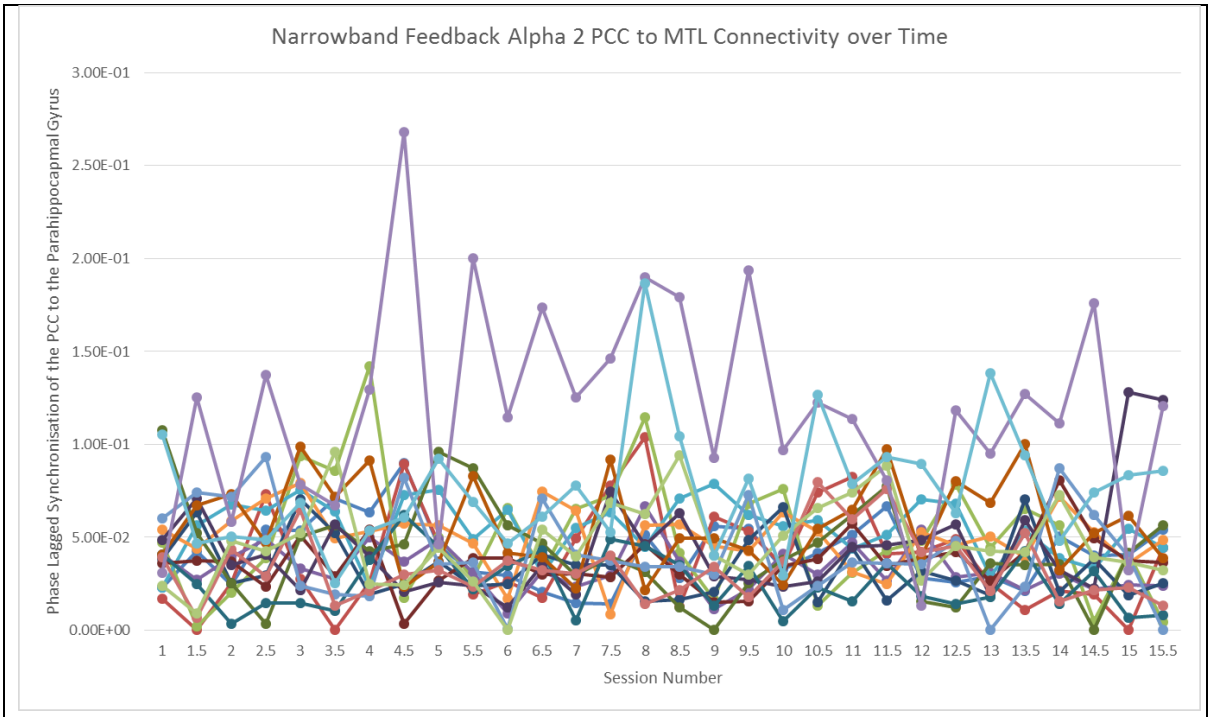


Figure C-25: Change in the alpha 2 phase lagged synchronisation between PCC and the parahippocampal gyrus in the narrowband feedback group in the in-training data

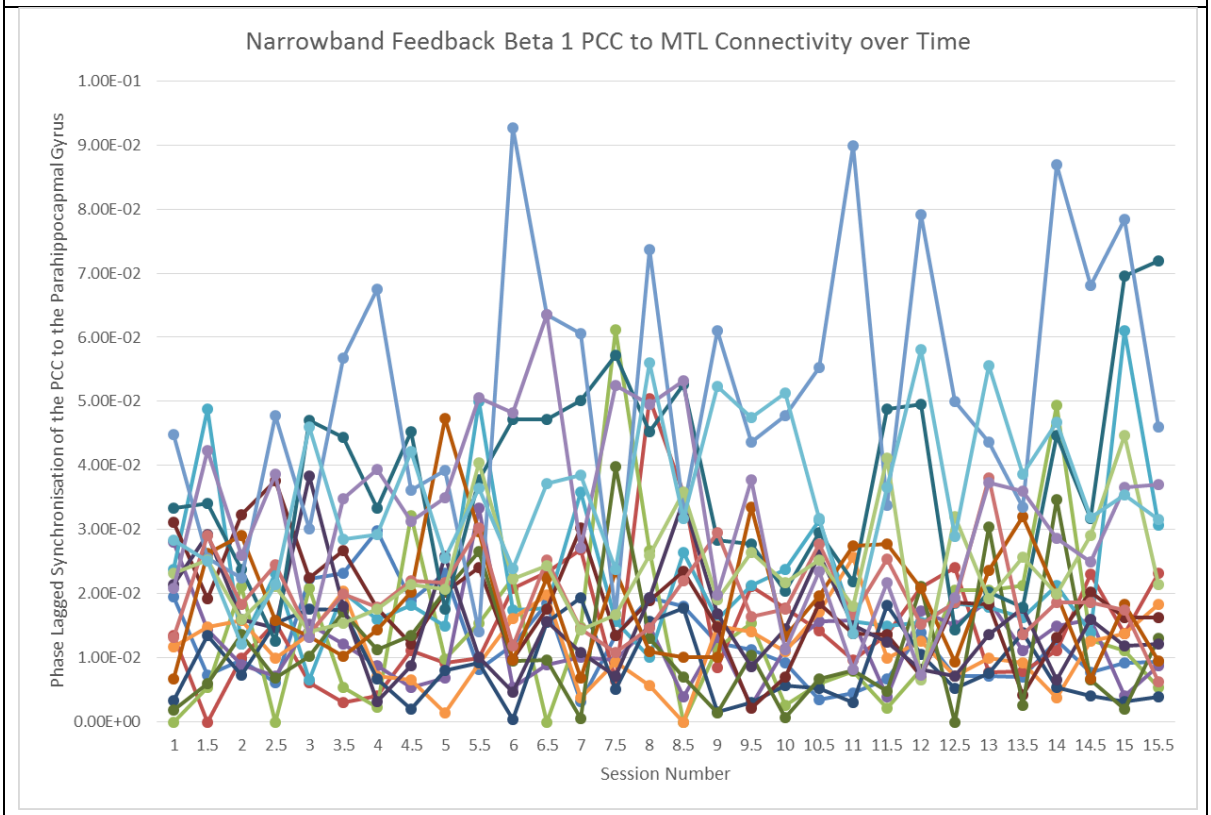


Figure C-26: Change in the beta 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the narrowband feedback group in the in-training data

Placebo Feedback Group PCC Current Density

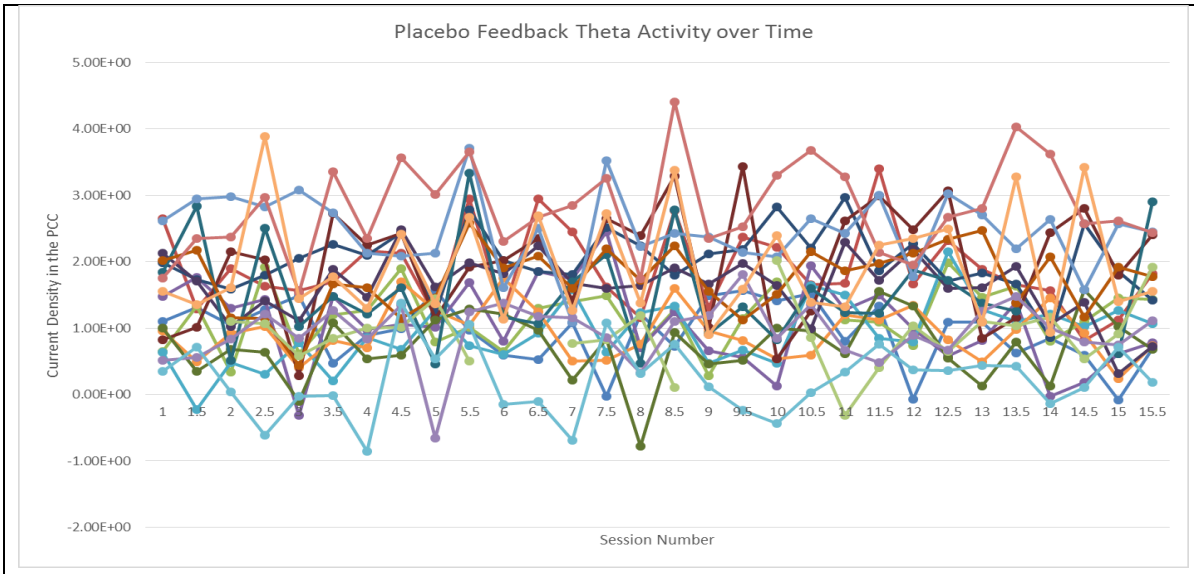


Figure C-27: Change in the theta current density in the PCC in the placebo feedback group in the in-training data

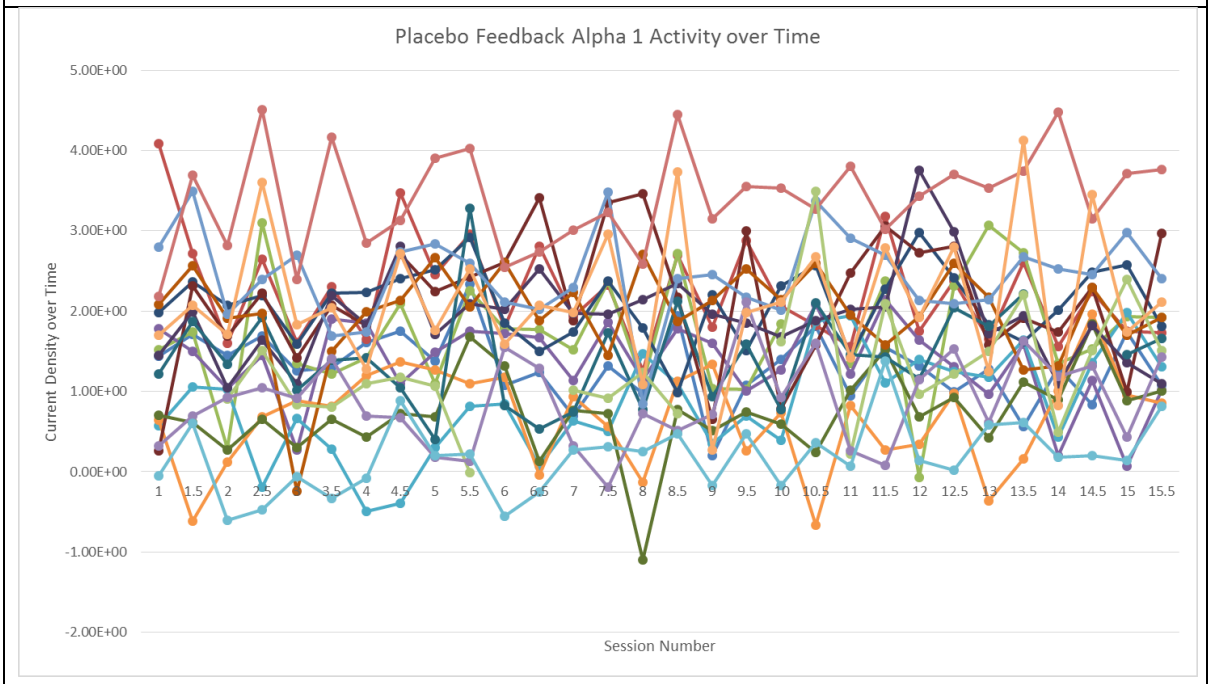


Figure C-28: Change in the alpha 1 current density in the PCC in the placebo feedback group in the in-training data

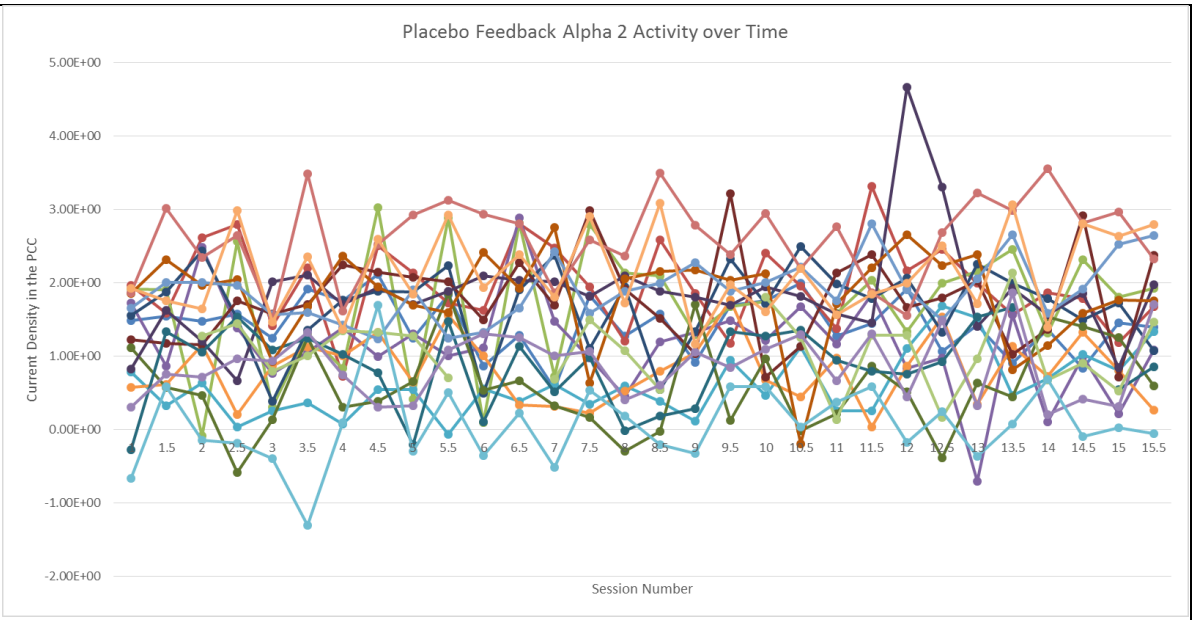


Figure C-29: Change in the alpha 2 current density in the PCC in the placebo feedback group in the in-training data

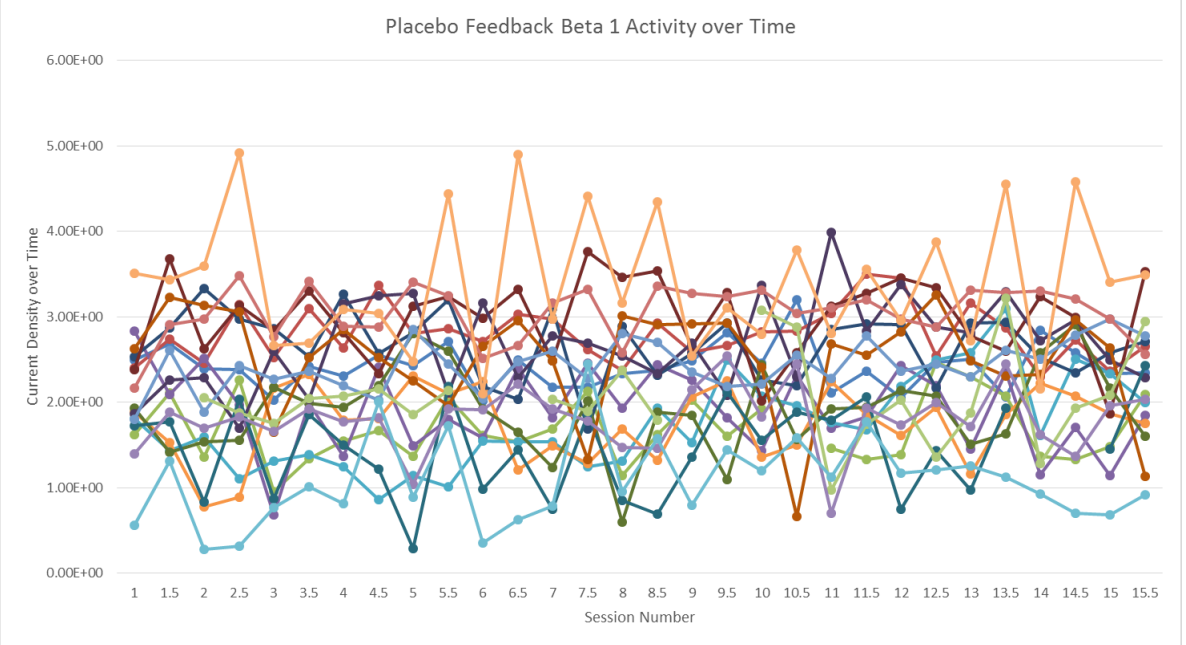


Figure C-30: Change in the beta 1 current density in the PCC in the placebo feedback group in the in-training data

Placebo Feedback Group Phase Lagged Synchronisation of the PCC to MTL

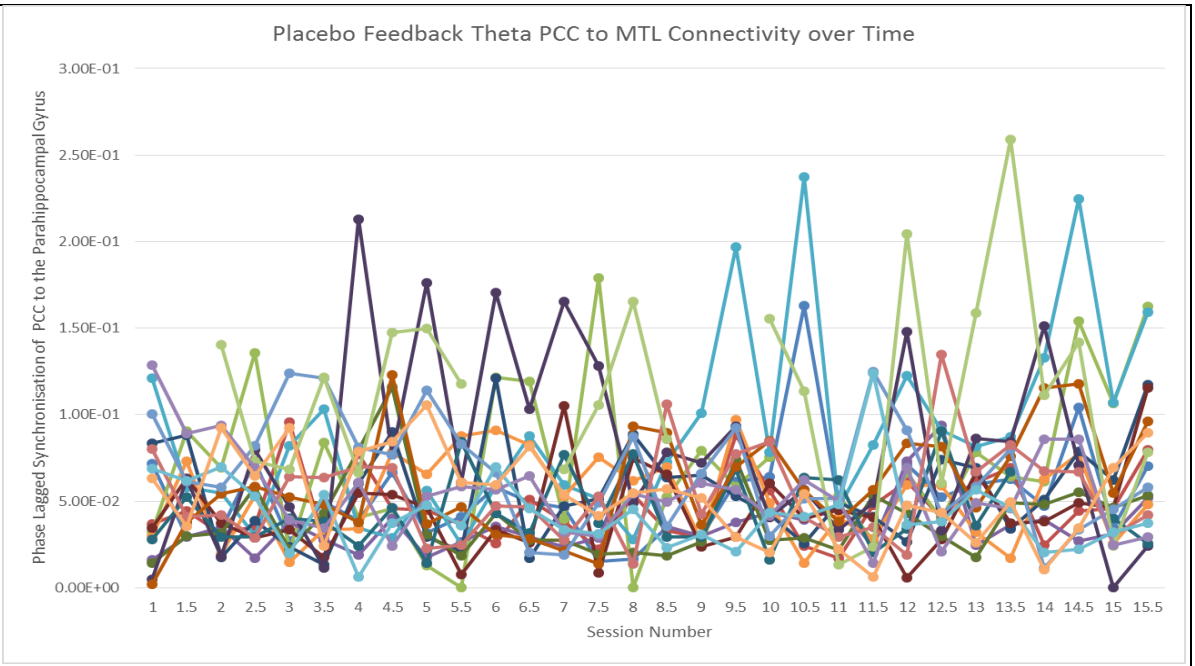


Figure C-31: Change in the theta phase lagged synchronisation between PCC and the parahippocampal gyrus in the placebo feedback group in the in-training data

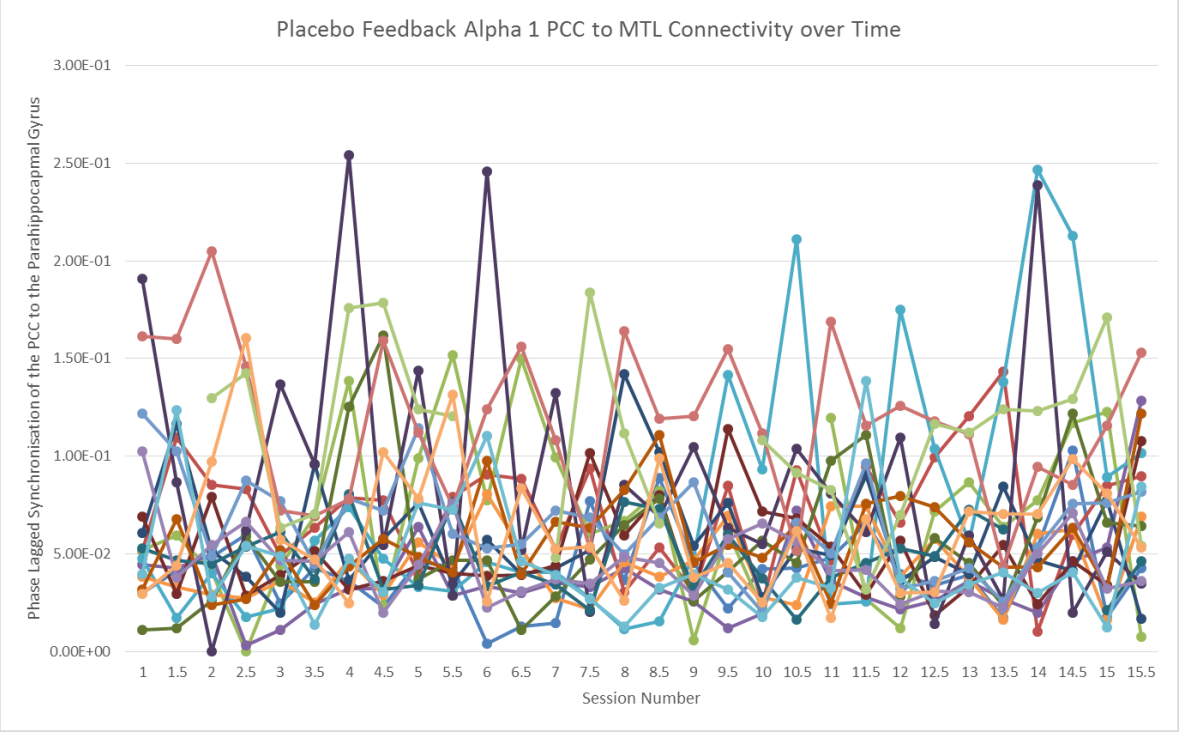


Figure C-32: Change in the alpha 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the placebo feedback group in the in-training data

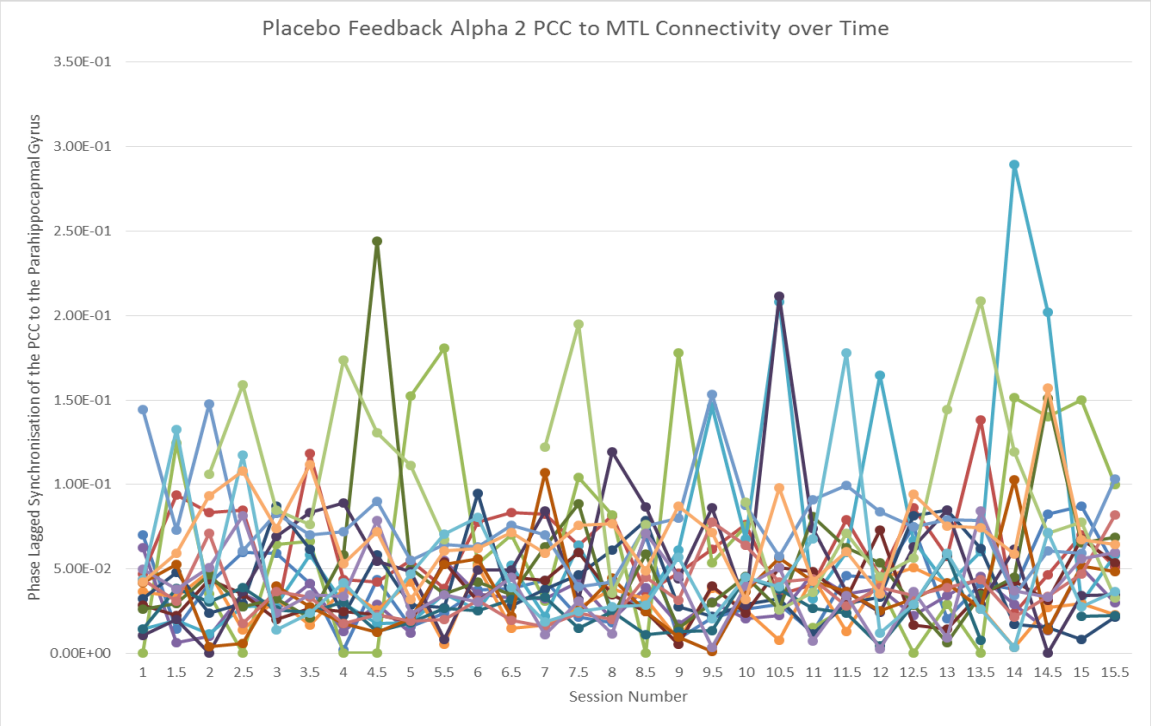


Figure C-33: Change in the alpha 2 phase lagged synchronisation between PCC and the parahippocampal gyrus in the placebo feedback group in the in-training data

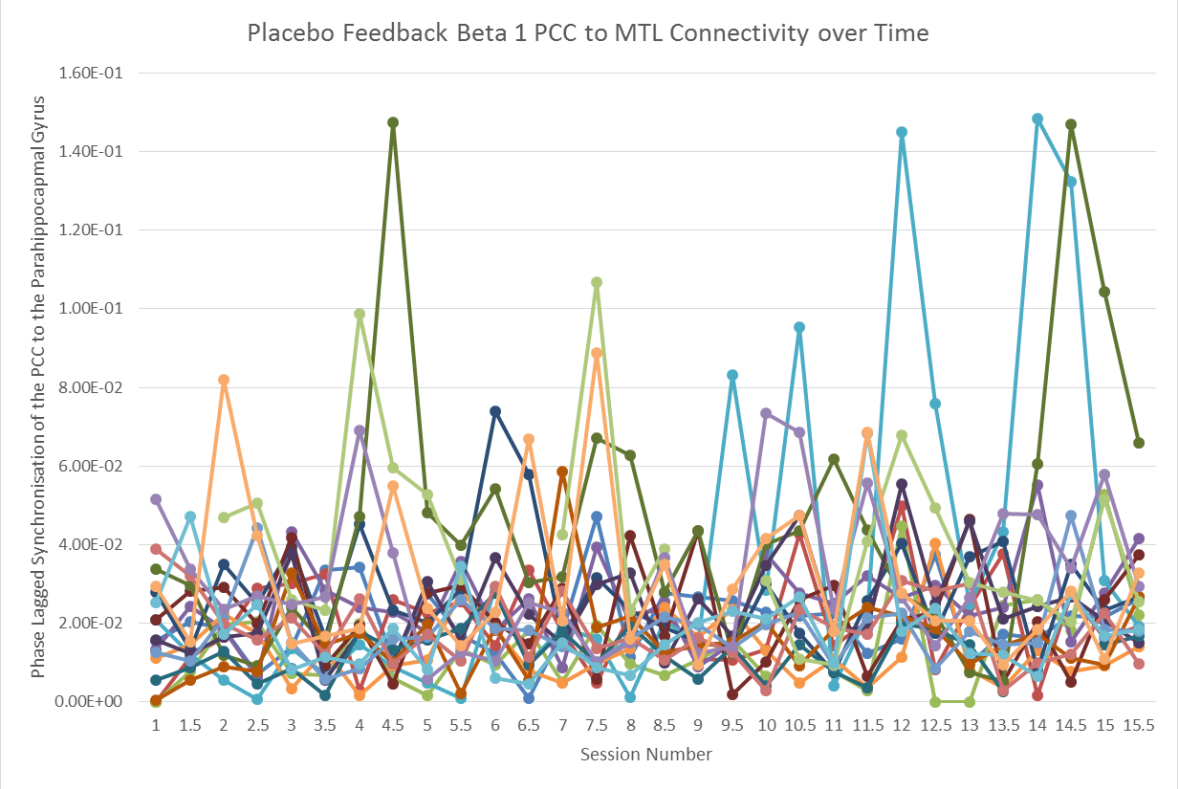


Figure C-34: Change in the beta 1 phase lagged synchronisation between PCC and the parahippocampal gyrus in the placebo feedback group in the in-training data

Appendix C10: Change in Baseline to 6 Week Follow Up RBANS Scores Separated by Initial Form

Table C-9 to C-11 show the changes of the 6 week follow up test from baseline of RBANS subtests and cognitive indices separated by whether the participants started on RBANS form A or B.

Broadband Feedback Group

Table C-9: Change in RBANS scores comparing the 6 week follow up to the baseline score in the broadband feedback group

	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
List Learning	25.2 (6.05)	2.5	23.0 (4.72)	3.4
Story Learning	16.1 (2.21)	3.8	14.6 (4.58)	2.5
Figure Copy	17.9 (1.14)	0.1	17.8 (1.85)	0
Line Orientation	18.0 (2.14)	0.3	16.4 (2.12)	-0.1
Picture Naming	9.5 (0.50)	0.2	9.6 (0.48)	0.4
Semantic Fluency	21.1 (5.24)	1.5	17.3 (4.71)	1.1
Digit Span	9.6 (2.37)	-0.2	9.6 (1.32)	-0.3
Coding	40.8 (7.93)	4.6	35 (11.06)	2.9
List Recall	4.8 (3.09)	0.7	3.8 (2.44)	1.1
List Recognition	18.2 (2.09)	0.3	18.6 (2.29)	1
Story Recall	7.2 (2.93)	1.7	7.5 (3.61)	2.3
Figure Recall	12.1 (5.58)	0.2	11.3 (5.63)	0.5
Immediate Memory Index	97.8 (10.97)	16.2	91.8 (11.30)	14.3
Visuospatial Index	106.3 (9.82)	1	101.4 (11.02)	1.9
Language Index	104.4 (10.13)	6.9	96.8 (6.87)	5.3

	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
Attention index	98.7 (12.35)	5.9	92.1 (8.61)	2.6
Delayed Memory index	93.1 (21.24)	6.7	89.5 (21.03)	7.5
Sum of Indices	500.3 (38.45)	36.7	471.5 (47.88)	31.5
Total Scale Index	99.4 (10.54)	9.7	92.1 (12.39)	8.3
Average last two 2-back	42.0 (20.27)	6.4	39.5 (20.10)	4.8

Narrowband Feedback Group

Table C-10: Change in RBANS scores comparing the 6 week follow up to the baseline score in the narrowband feedback group

	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
List Learning	24.3 (5.99)	2.1	24.3 (2.29)	1
Story Learning	15.4 (3.26)	3.4	19.0 (2.08)	4.3
Figure Copy	17.5 (2.43)	-1.2	17.7 (1.37)	-1.7
Line Orientation	16.7 (2.70)	-0.4	17.2 (1.21)	0.2
Picture Naming	9.5 (0.50)	0.4	9.8 (0.37)	-0.2
Semantic Fluency	20.3 (4.71)	0.8	19.2 (3.34)	2
Digit Span	9.5 (1.44)	0	11.8 (2.61)	0.2
Coding	43.3 (8.52)	2	51.3 (4.53)	2.5
List Recall	4.3 (2.70)	0.2	5.0 (3.06)	0.5
List Recognition	18.5 (1.92)	-0.4	18.3 (1.37)	-0.2
Story Recall	8.4 (2.50)	2.5	10.3 (1.37)	2.2

	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
Figure Recall	14.0 (2.66)	1.5	14.7 (1.97)	2
Immediate Memory Index	92.2 (15.16)	12.4	97.2 (7.20)	12.5
Visuospatial Index	99.5 (15.16)	-8.1	100.0 (7.81)	-9
Language Index	101.5 (9.26)	5.4	97.5 (6.37)	3.8
Attention index	98.7 (9.98)	3	111.8 (9.84)	2.7
Delayed Memory index	96.7 (16.39)	6.3	99.8 (14.55)	6.7
Sum of Indices	488.5 (37.26)	18.9	509.0 (19.53)	19.3
Total Scale Index	96.5 (9.47)	5.3	101.7 (5.37)	5.2
Average last two 2-back	43.9 (18.72)	6.3	69.1 (27.46)	14.3

Placebo Feedback Group

Table C-11: Change in RBANS scores comparing the 6 week follow up to the baseline score in the placebo feedback group

	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
List Learning	25.5 (3.82)	2.2	25.5 (3.55)	1.3
Story Learning	14.3 (4.39)	2.4	14.7 (3.40)	0.8
Figure Copy	18.0 (2.17)	-0.6	17.5 (1.98)	-0.3
Line Orientation	16.4 (4.18)	-0.6	16.2 (2.11)	0.3
Picture Naming	9.7 (0.45)	0.6	10.0 (0.00)	0.3
Semantic Fluency	20.6 (3.20)	0.7	17.5 (2.75)	-0.2
Digit Span	10.4 (1.82)	0	10.5 (3.1)	0.2
Coding	45.7 (8.62)	4.3	41.2 (7.54)	2.5

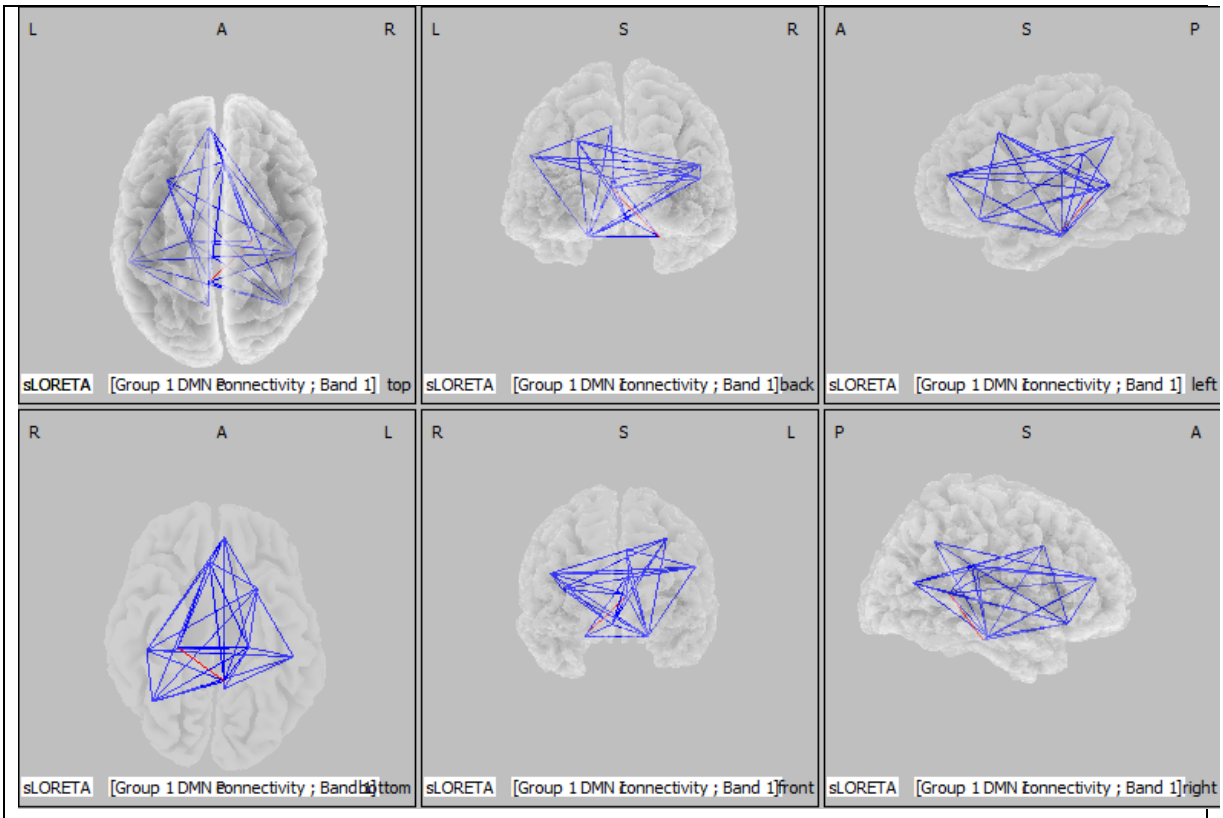
	RBANS A Mean (SD)	Difference from baseline	RBANS B Mean (SD)	Difference from baseline
List Recall	5.3 (1.66)	0.8	4.2 (1.57)	0
List Recognition	19.1 (1.38)	0.4	19.5 (0.50)	1.2
Story Recall	7.9 (2.57)	1.7	7.3 (1.97)	0.3
Figure Recall	13.5 (4.23)	0	12.3 (4.27)	2.8
Immediate Memory Index	89.6 (9.63)	10.1	91.2 (12.27)	5.7
Visuospatial Index	101.6 (19.79)	-2.4	95.5 (10.77)	-1.8
Language Index	99.6 (5.35)	3.1	95.0 (4.69)	-0.7
Attention index	102.4 (14.17)	5.4	97.2 (17.03)	3.3
Delayed Memory index	99.1 (12.84)	6.3	99.3 (5.09)	13.7
Sum of Indices	492.4 (50.61)	22.6	478.7 (26.61)	20.7
Total Scale Index	98 (13.54)	6.3	93.2 (6.89)	4.8
Average last two 2-back	64.2 (24.64)	0.4	41.9 (17.48)	13.8

Appendix C11: Change from Baseline to 6 Week Follow Up in the Phase Lagged Synchronisation of the DMN

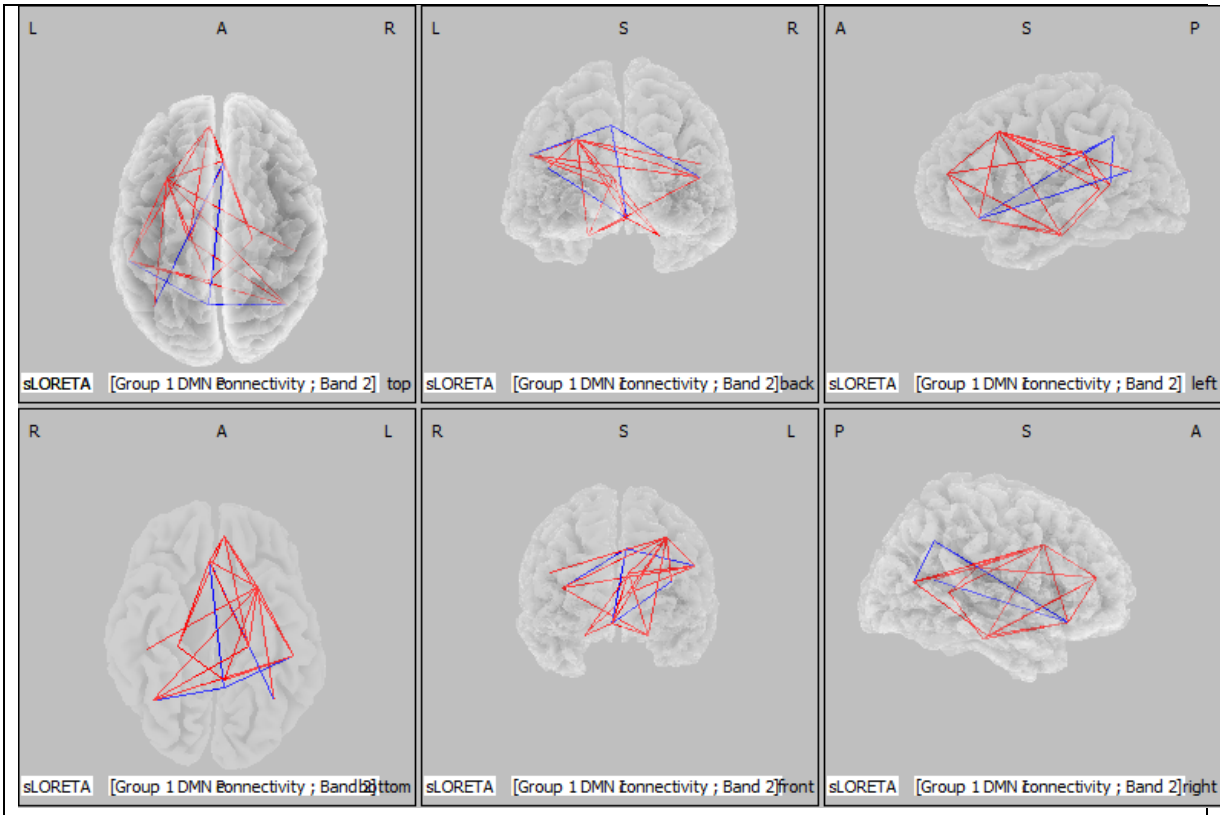
Figures C-35 to C-37 show the changes in the phase lagged synchronisation of the 11 default mode nodes, comparing the 6 week follow up recording to the pre training resting sate recording. Blue lines indicate lower connectivity at the 6 week follow up and red lines indicate increased connectivity at the 6 week follow up.

Broadband Feedback group

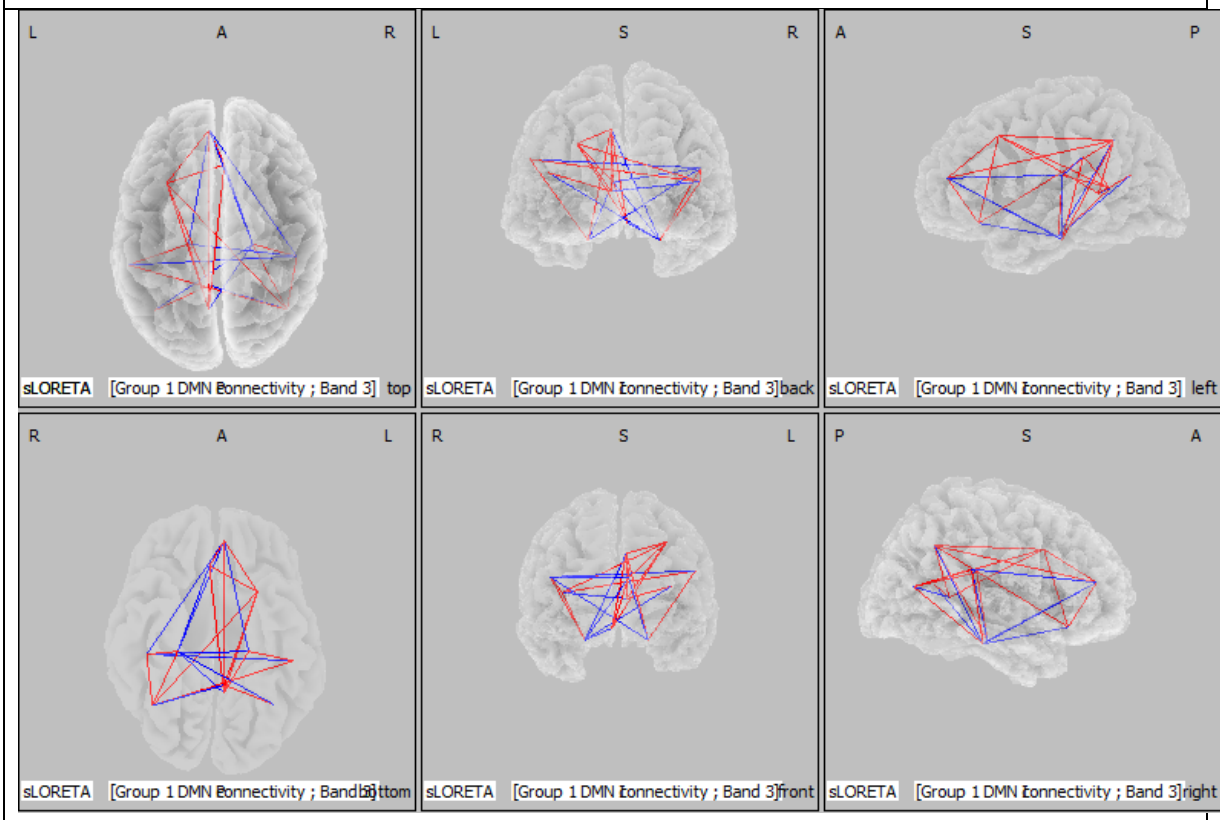
These images are not significant at p=0.68.



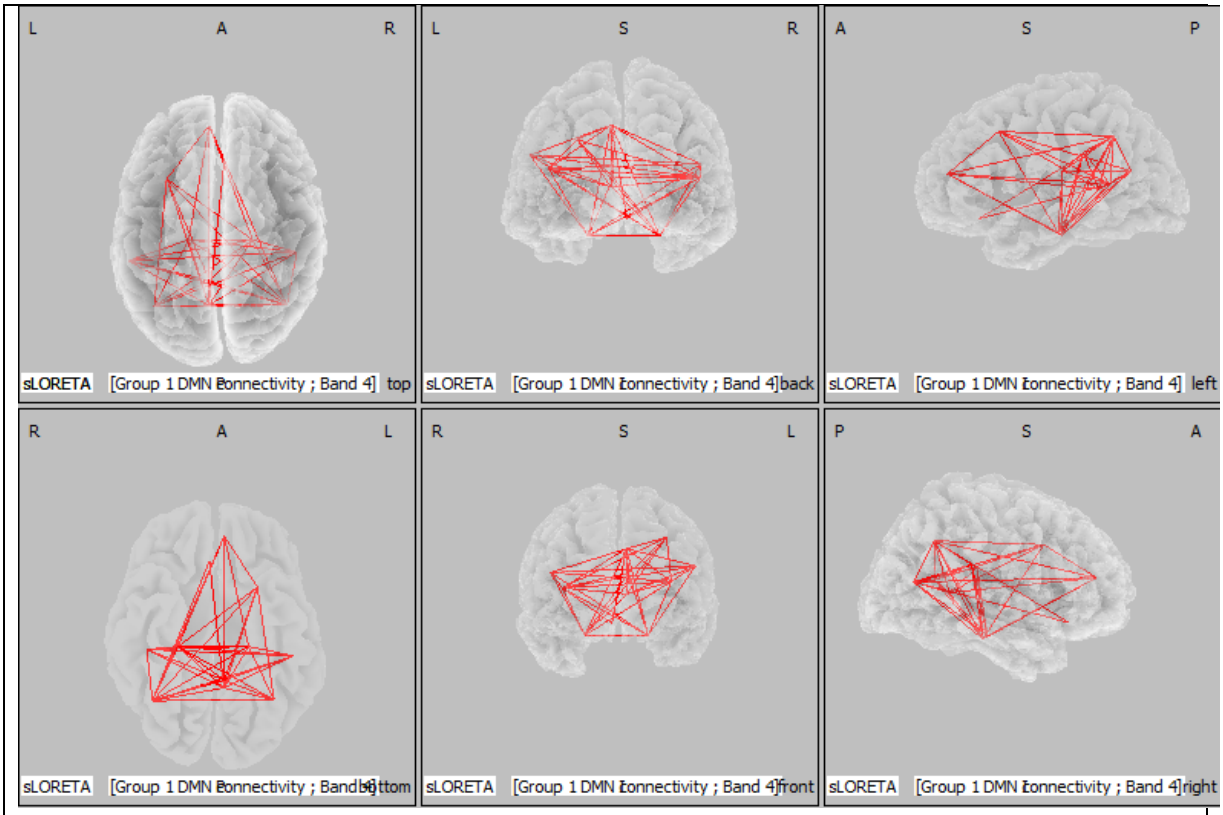
Delta band



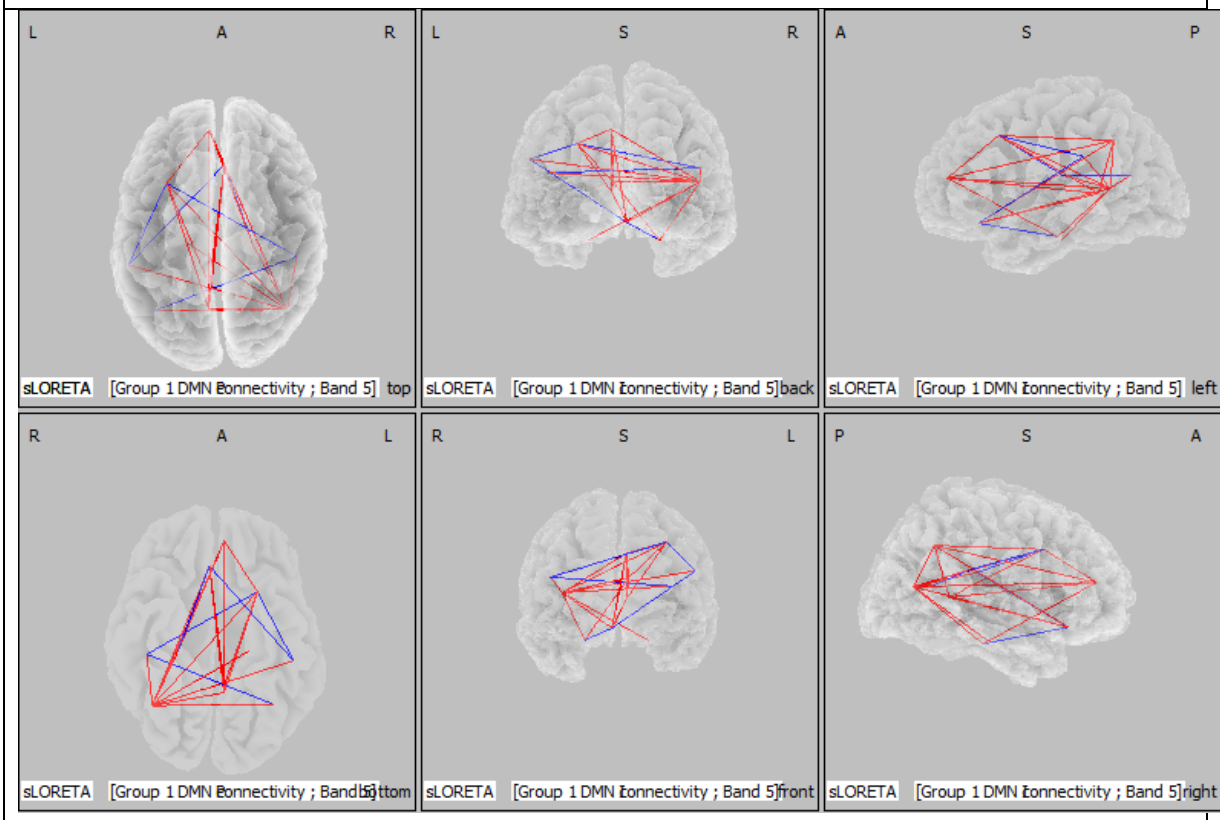
Theta band



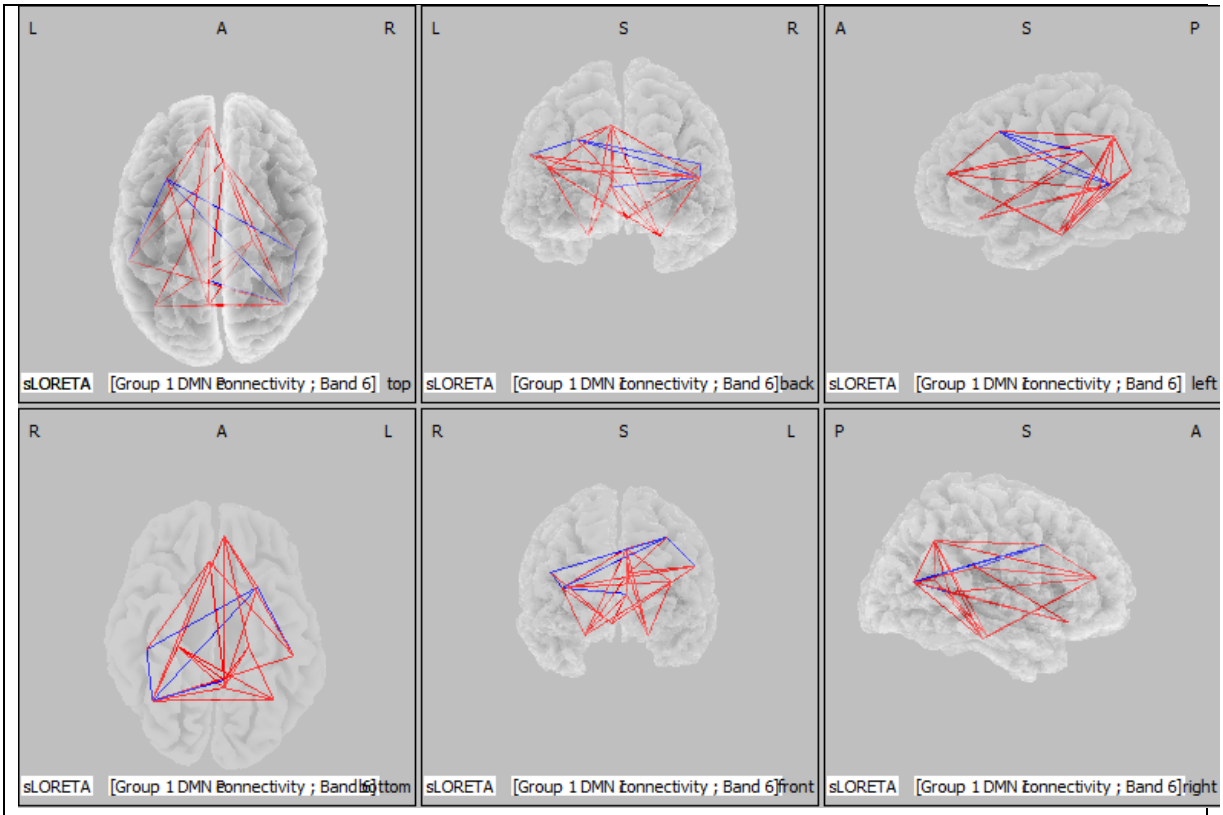
Alpha 1 band



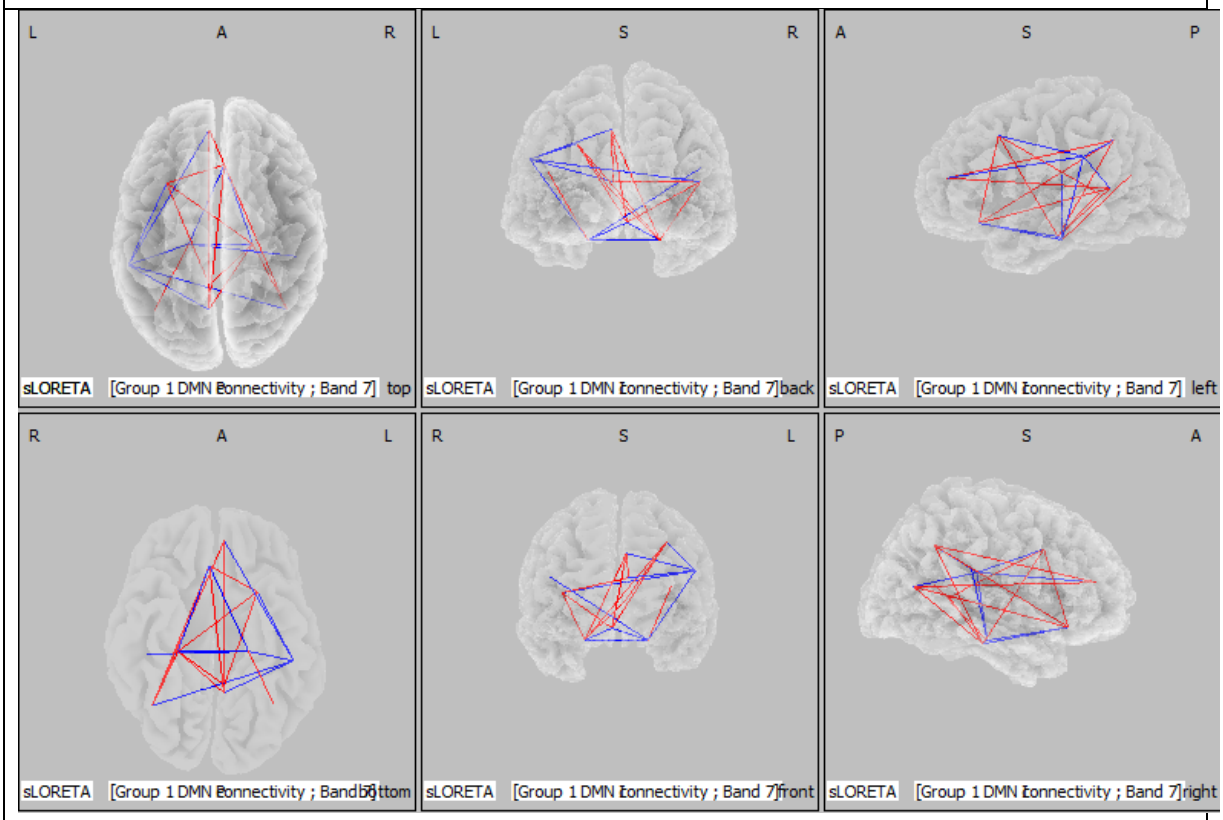
Alpha 2 band



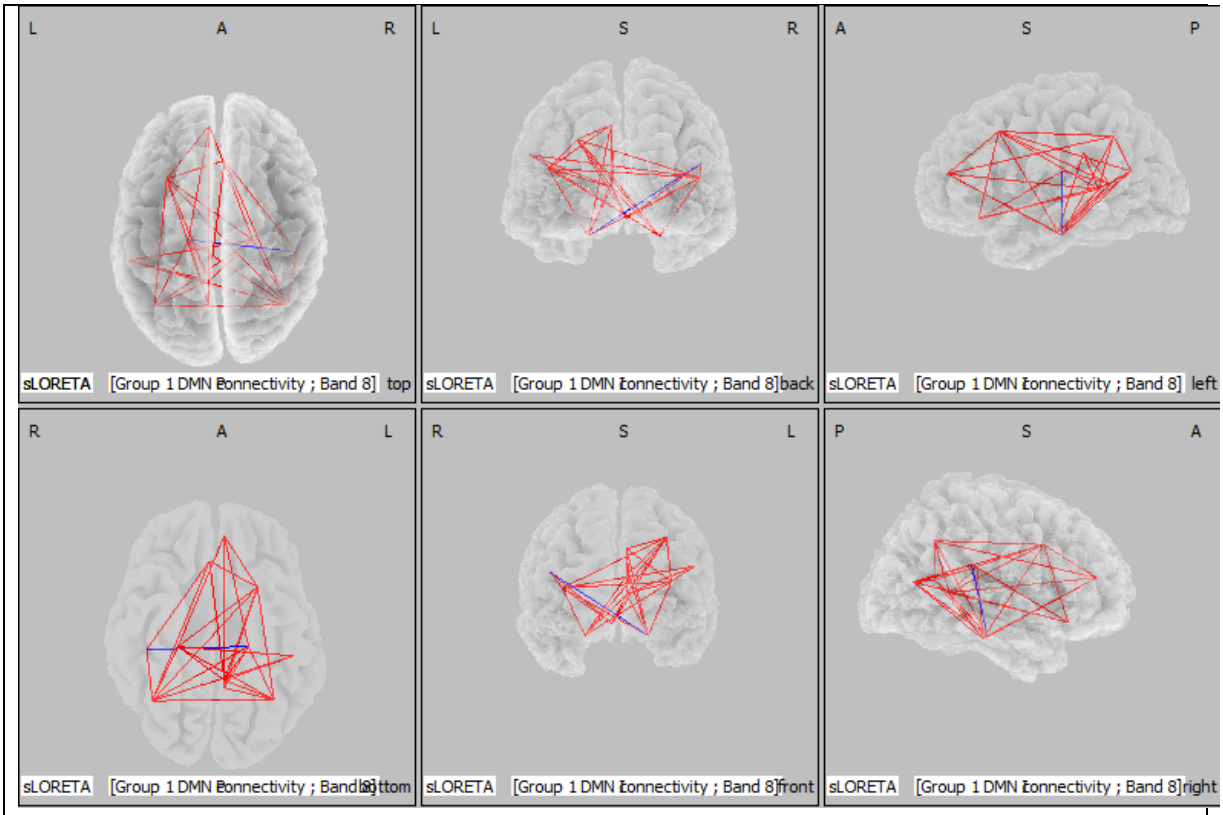
Beta 1 band



Beta2 band



Beta 3 band

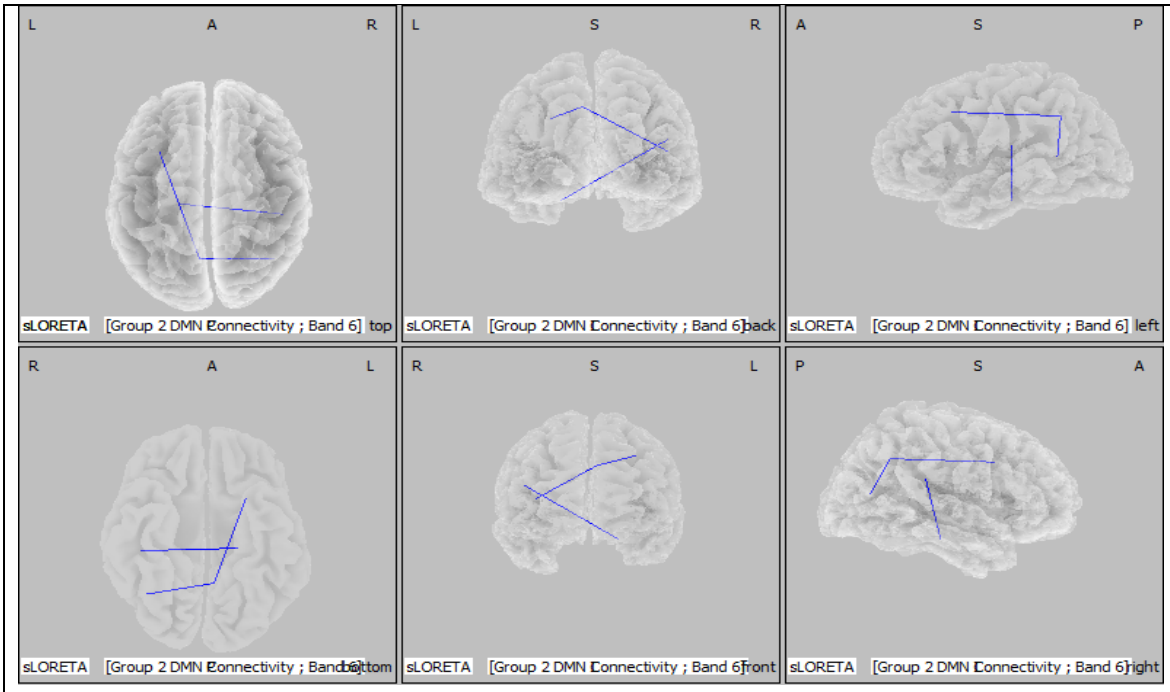


Omega band

Figure C-35: Maps of change in phase lagged synchronisation of the DMN comparing 6 week follow up resting state recording to the baseline resting state recording in the broadband feedback group

Narrowband Feedback group

This image is not significant at p=0.32. No other changes were found at this level of significance.

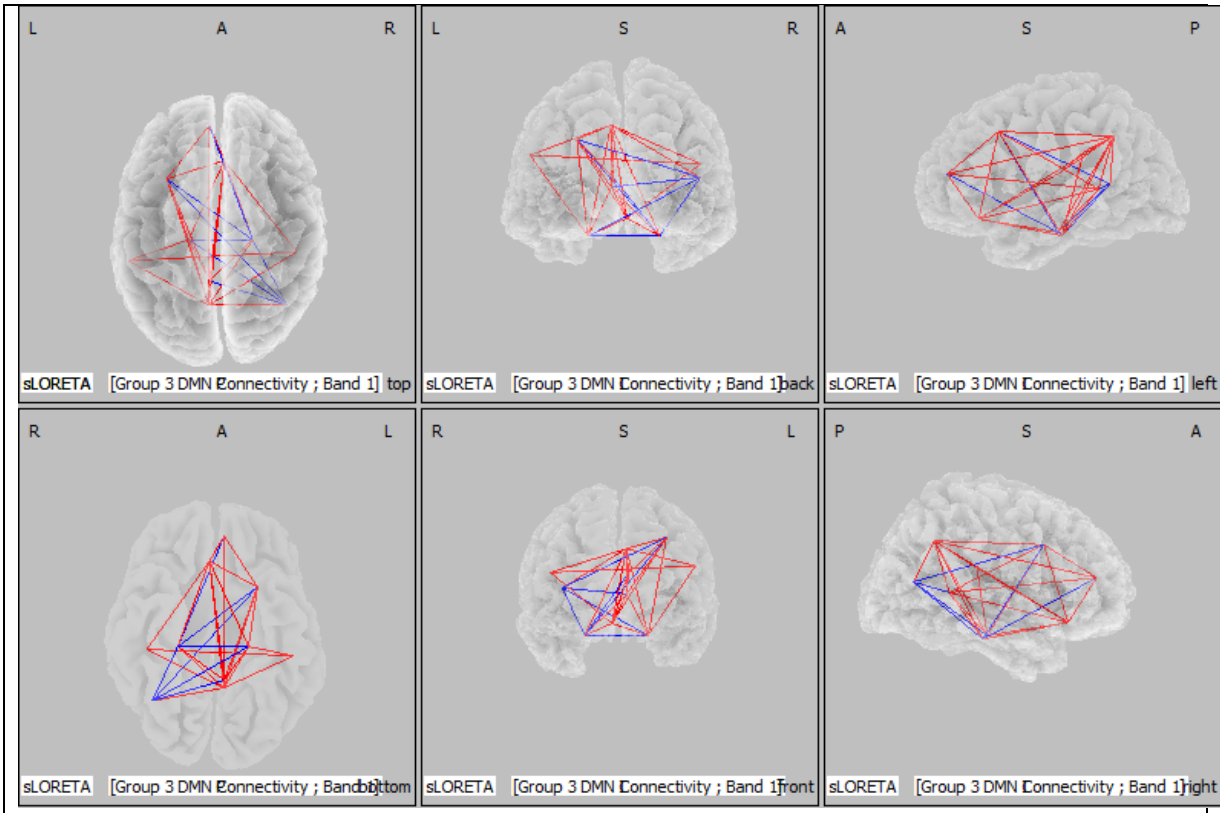


Beta 2 band

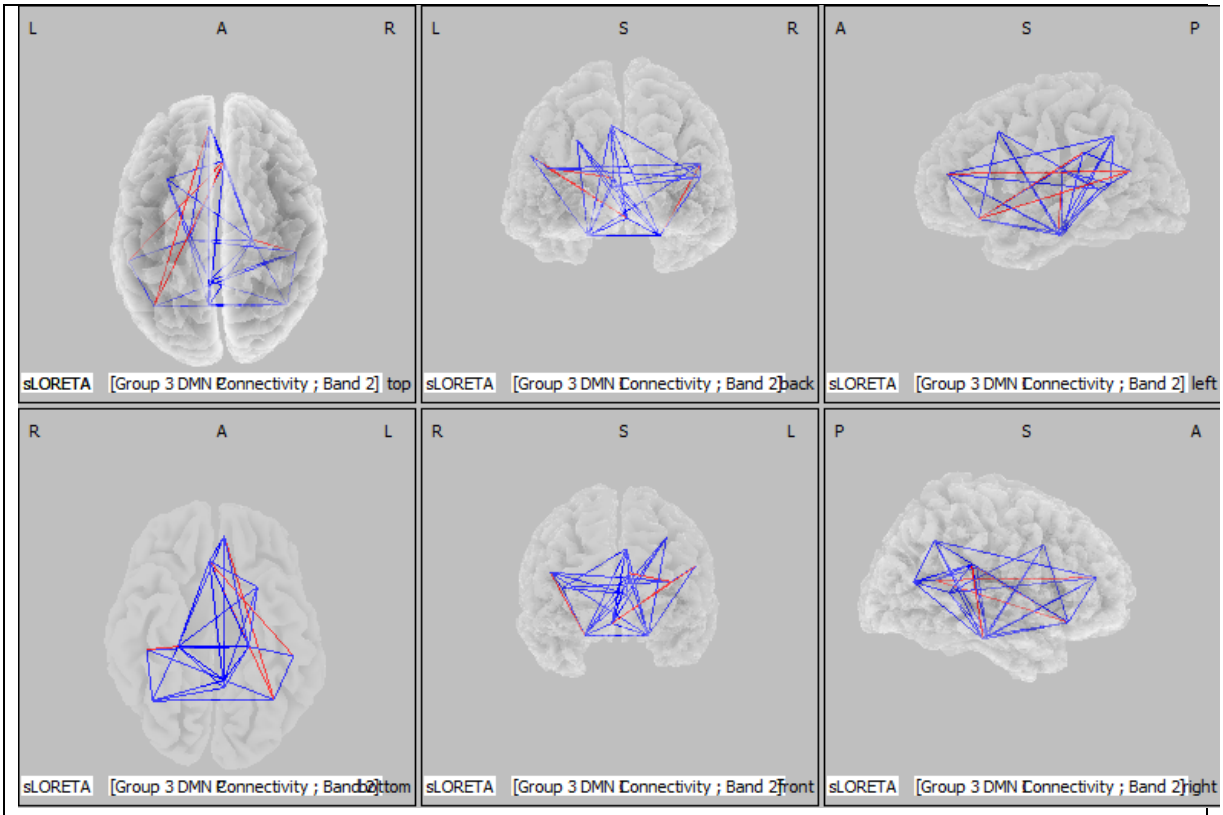
Figure C-36: Maps of change in phase lagged synchronisation of the DMN comparing 6 week follow up resting state recording to the baseline resting state recording in the narrowband feedback group

Placebo Feedback Group

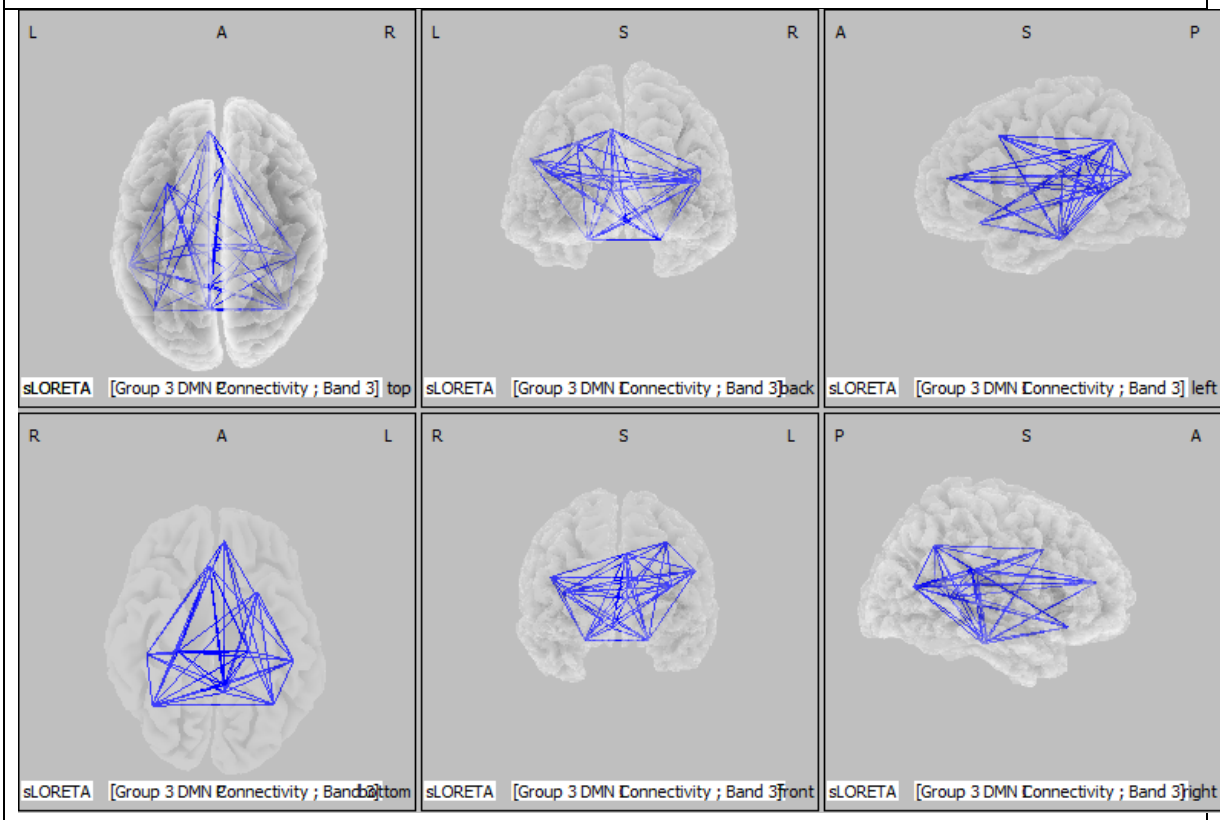
These images are not significant at p=0.088.



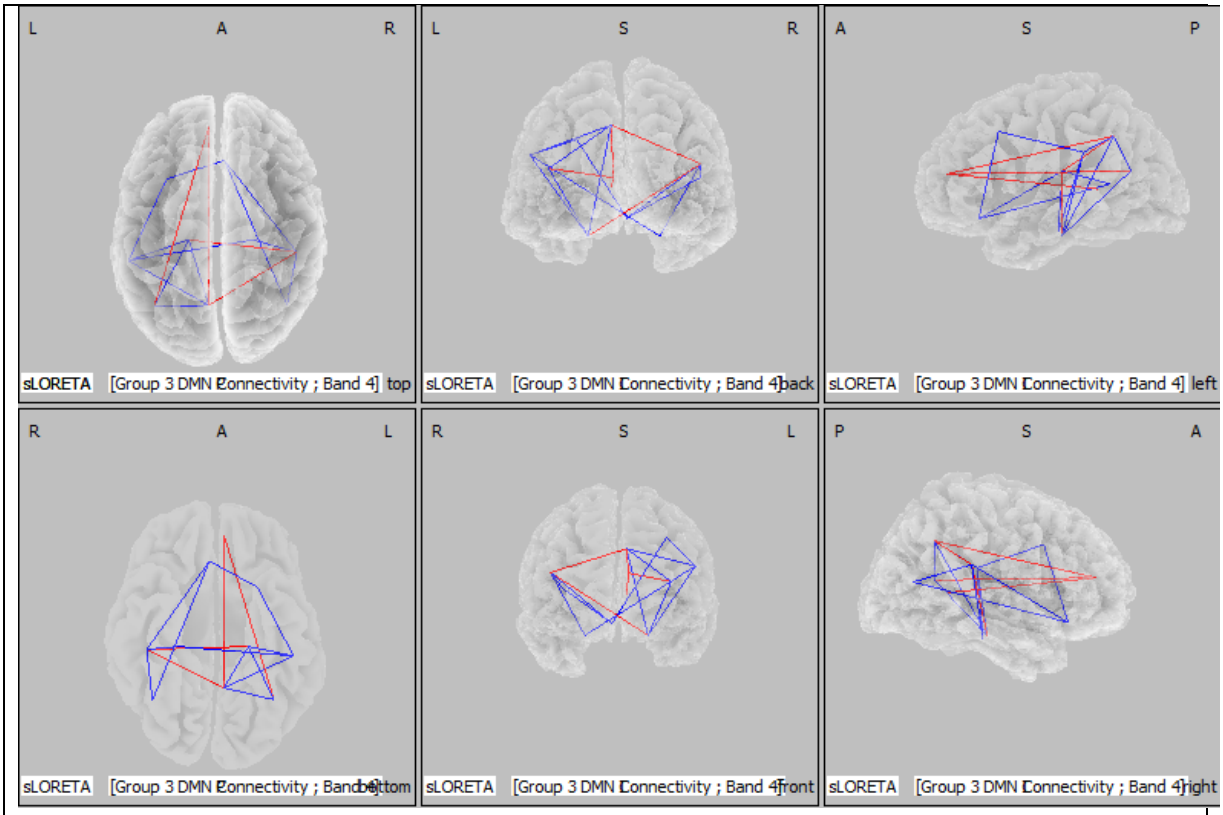
Delta band



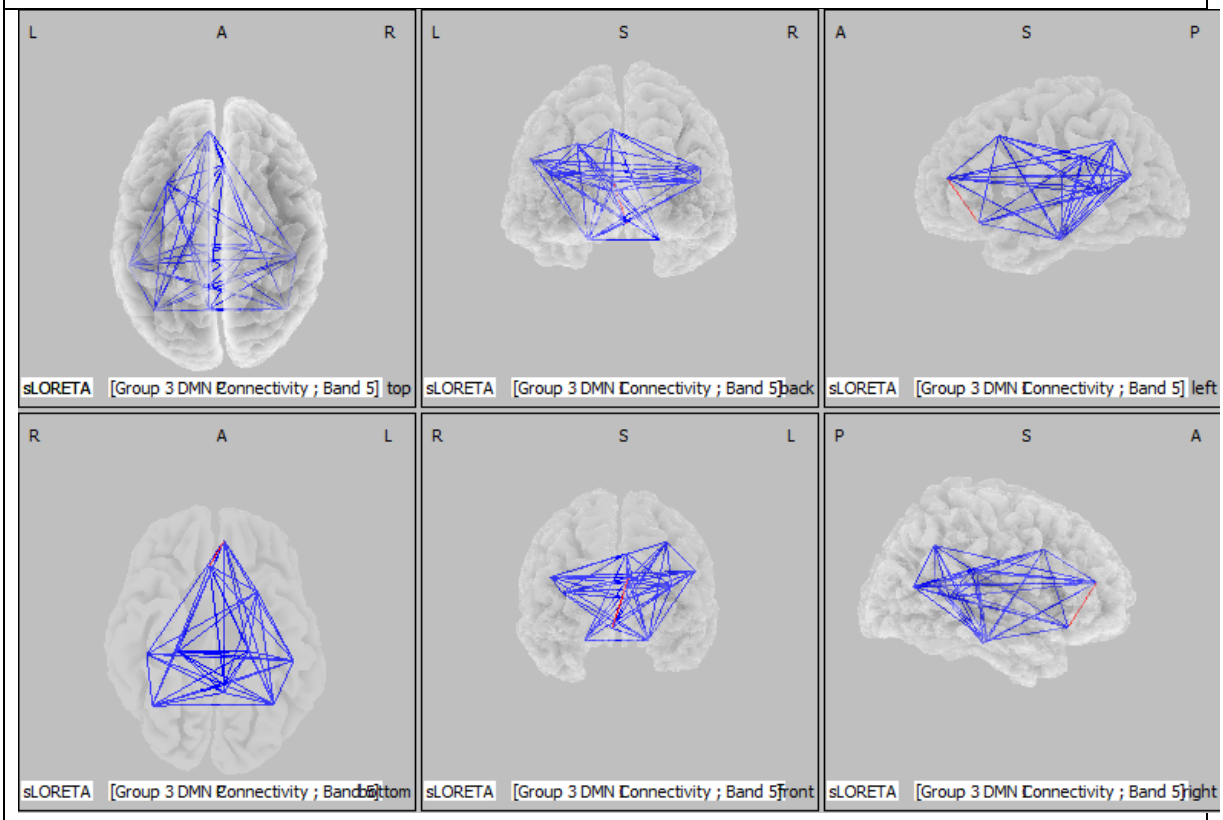
Theta band



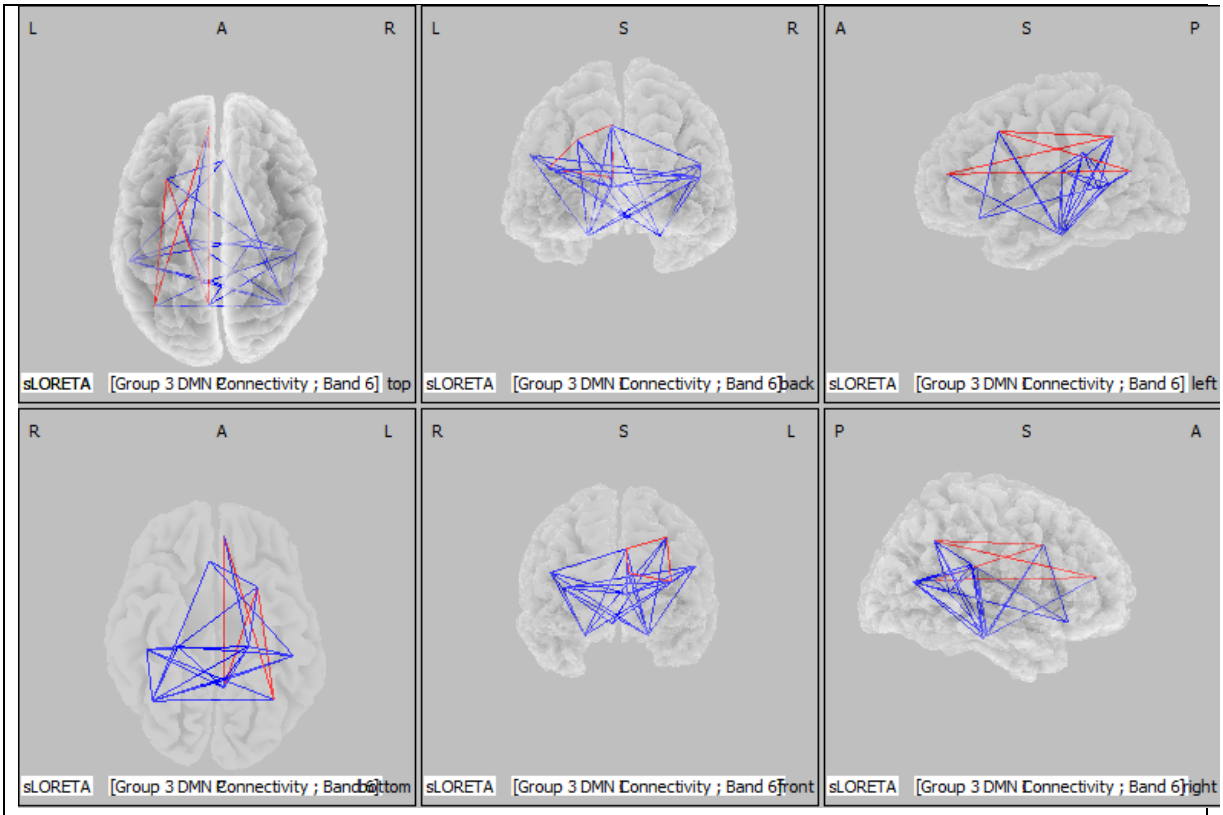
Alpha 1 band



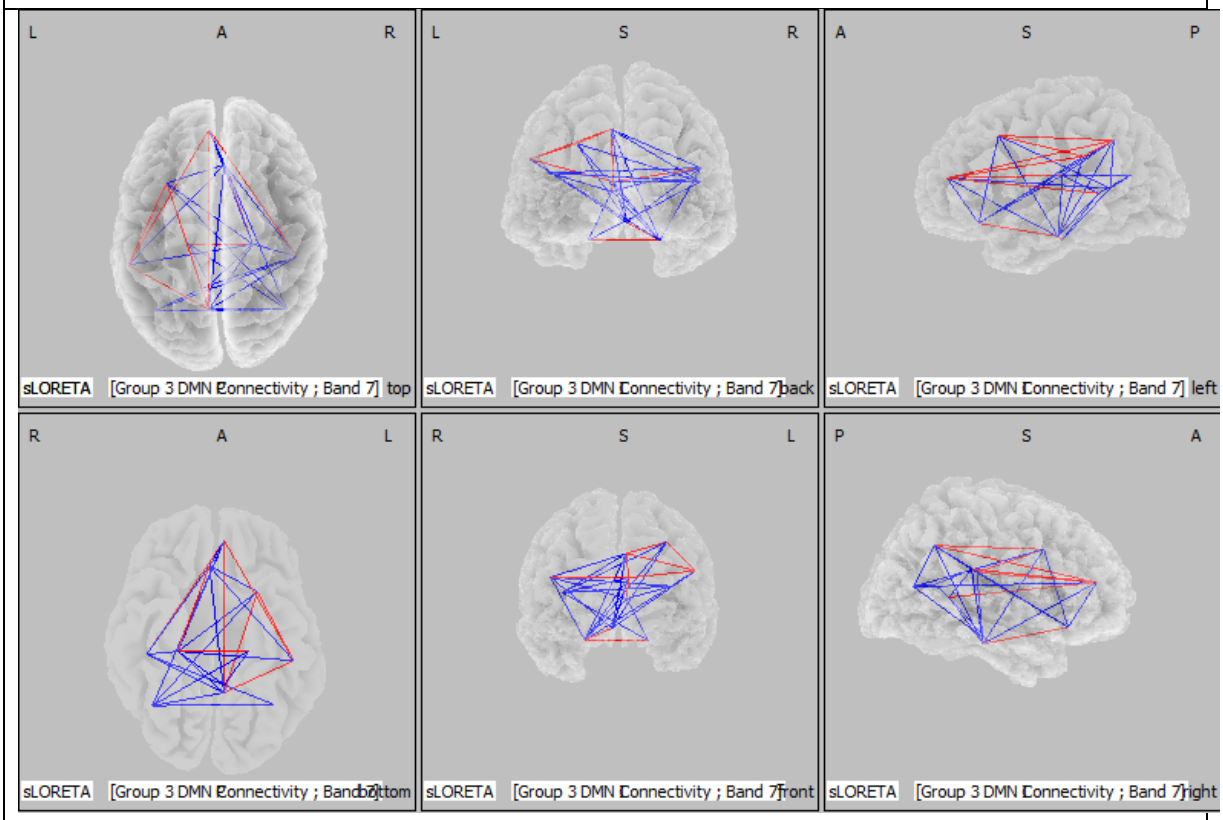
Alpha 2 band



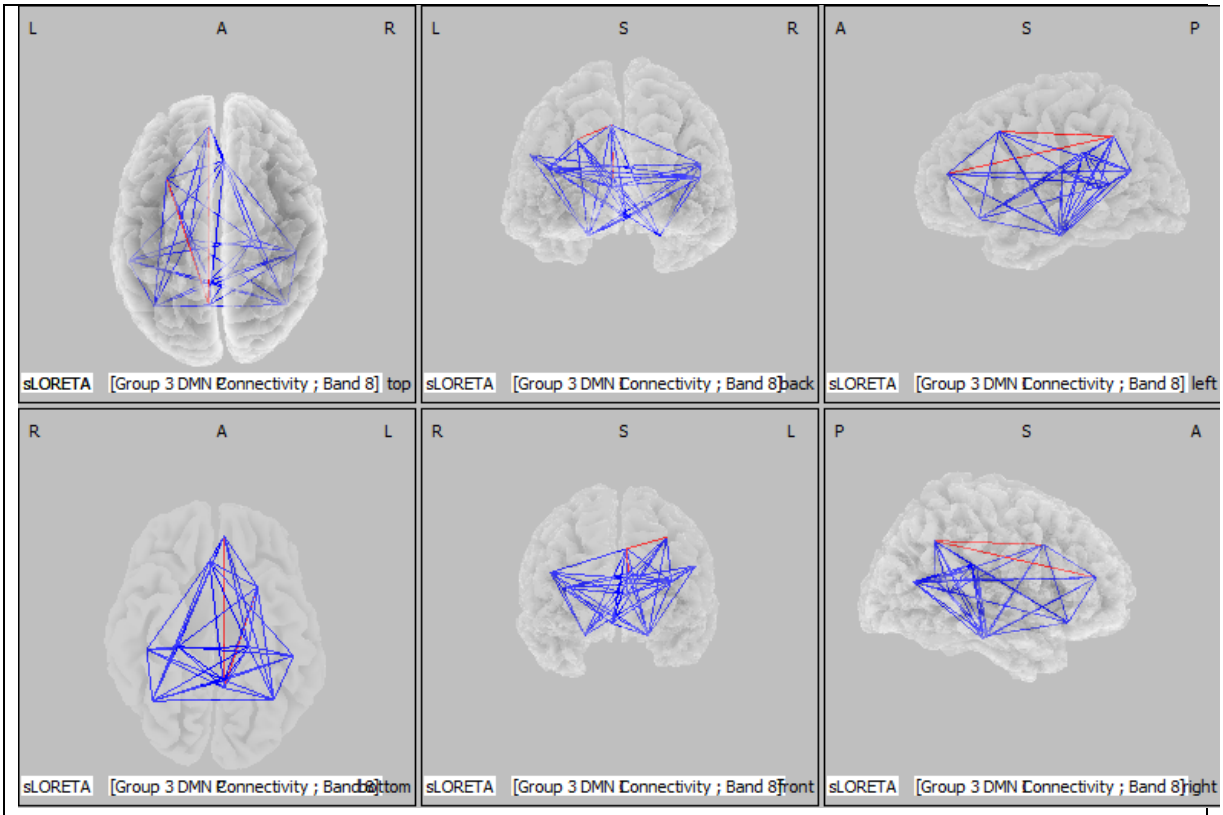
Beta 1 band



Beta 2 band



Beta 3 band



Omega band

Figure C-37: Maps of change in phase lagged synchronisation of the DMN comparing 6 week follow up resting state recording to the baseline resting state recording in the placebo feedback group

Appendix D

Appendix D1: Coordinates of the Posterior DMN

Table D-1 below shows the co-ordinates used in the restricted connectivity analysis of the default mode network.

Table D-1: MNI coordinates of the posterior DMN nodes

X co-ordinate	Y co-ordinate	Z co-ordinate	Anatomical name
-5	-50	10	Posterior Cingulate
52	-28	24	Right Inferior Parietal Lobule
-56	-36	28	Left Inferior Parietal Lobule
-22	-26	-21	Left parahippocampal gyrus
25	-26	18	Right parahippocampal gyrus

Appendix D2: Variables included in the correlation analysis for the assessment of validity

Tables D-2 shows the variables included in the third level of correlation described, including six memory variables with 24 EEG variables

Table D-2: Variables correlated for assessment of validity

Memory outcomes	**EEG outcomes**
Difference between the immediate follow up and the pre-training Immediate memory index	In training correlation coefficient for theta band PCC current density and session number
Difference between the 6 week follow up and the pre-training Immediate memory index	In training correlation coefficient for alpha 1 band PCC current density and session number
Difference between the 6 week follow up and the immediate follow up Immediate memory index	In training correlation coefficient for alpha 2 band PCC current density and session number
Difference between the immediate follow up and the pre-training Delayed memory index	In training correlation coefficient for beta band PCC current density and session number
Difference between the 6 week follow up and the pre-training Delayed memory index	In training correlation coefficient for theta band PCC-MTL phase-lagged synchronisation and session number
Difference between the 6 week follow up and the immediate follow up Delayed memory index	In training correlation coefficient for alpha 1 band PCC-MTL phase-lagged synchronisation and session number
EEG Outcomes	In training correlation coefficient for alpha 2 band PCC-MTL phase-lagged synchronisation and session number
Difference between the 6 week follow up phase-lagged synchronisation between the PCC and MTL and the average of pre-training, 8th session and 12th session resting state in the theta band	

Difference between the 6 week follow up phase-lagged synchronisation between the PCC and MTL and the average of pre-training, 8th session and 12th session resting state in the alpha 1 band	In training correlation coefficient for beta band PCC-MTL phase-lagged synchronisation and session number
Difference between the 6 week follow up phase-lagged synchronisation between the PCC and MTL and the average of pre-training, 8th session and 12th session resting state in the alpha 2 band	Resting state correlation coefficient for theta band PCC current density and session number
Difference between the 6 week follow up phase-lagged synchronisation between the PCC and MTL and the average of pre-training, 8th session and 12th session resting state in the beta 1 band	Resting state correlation coefficient for alpha 1 band PCC current density and session number
Average within session change in the theta current density in the PCC	Resting state correlation coefficient for alpha 2 band PCC current density and session number
Average within session change in the alpha 1 current density in the PCC	Resting state correlation coefficient for beta band PCC current density and session number
Average within session change in the alpha 2 current density in the PCC	Resting state correlation coefficient for theta band PCC-MTL phase-lagged synchronisation and session number
Average within session change in the beta 1 current density in the PCC	Resting state correlation coefficient for alpha 1 band PCC-MTL phase-lagged synchronisation and session number

Average within session change in the theta phase-lagged synchronisation between the PCC and MTL	Resting state correlation coefficient for alpha 2 band PCC-MTL phase-lagged synchronisation and session number
Average within session change in the alpha 1 phase-lagged synchronisation between the PCC and MTL	Resting state correlation coefficient for beta band PCC-MTL phase-lagged synchronisation and session number
Average within session change in the alpha 2 phase-lagged synchronisation between the PCC and MTL	
Average within session change in the beta 2 phase-lagged synchronisation between the PCC and MTL	

Appendix D3: Correlation of Baseline EEG variables with Baseline RBANS Scores

Table D-3 below shows the Pearson correlation and the significance of changes in baseline EEG variables to the baseline cognitive scores. This includes all 'normal brain' controls (n=70) and all participants (n=54).

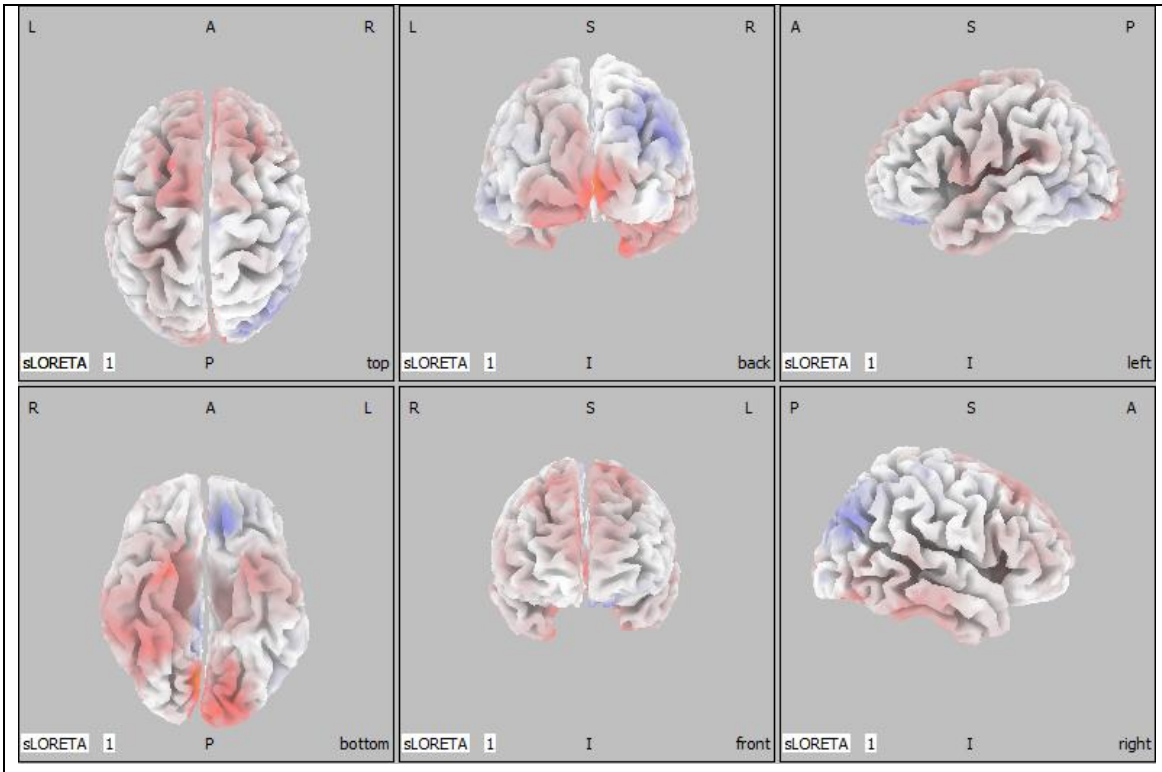
Table D-3: Shows the Pearson Correlation of EEG variables and Cognitive Indices.

		PCC MTL connectivity Density Theta	PCC MTL connectivity Density Alpha 1	PCC MTL connectivity Density Alpha 2	PCC MTL connectivity Density Beta 1	PCC Activity Theta	PCC Activity Alpha 1	PCC Activity Alpha 2	PCC Activity Beta 1
Immediate Memory Index	Pearson Correlation	-.184*	-.118	-.161	-.016	-.110	-.058	-.034	-.054
	Sig. (2-tailed)	.041	.191	.075	.863	.223	.521	.710	.549
	N	124	124	124	124	124	124	124	124
Delayed Memory Index	Pearson Correlation	-.263**	-.047	-.021	-.074	-.151	-.052	-.080	-.049
	Sig. (2-tailed)	.003	.604	.819	.414	.093	.568	.378	.589

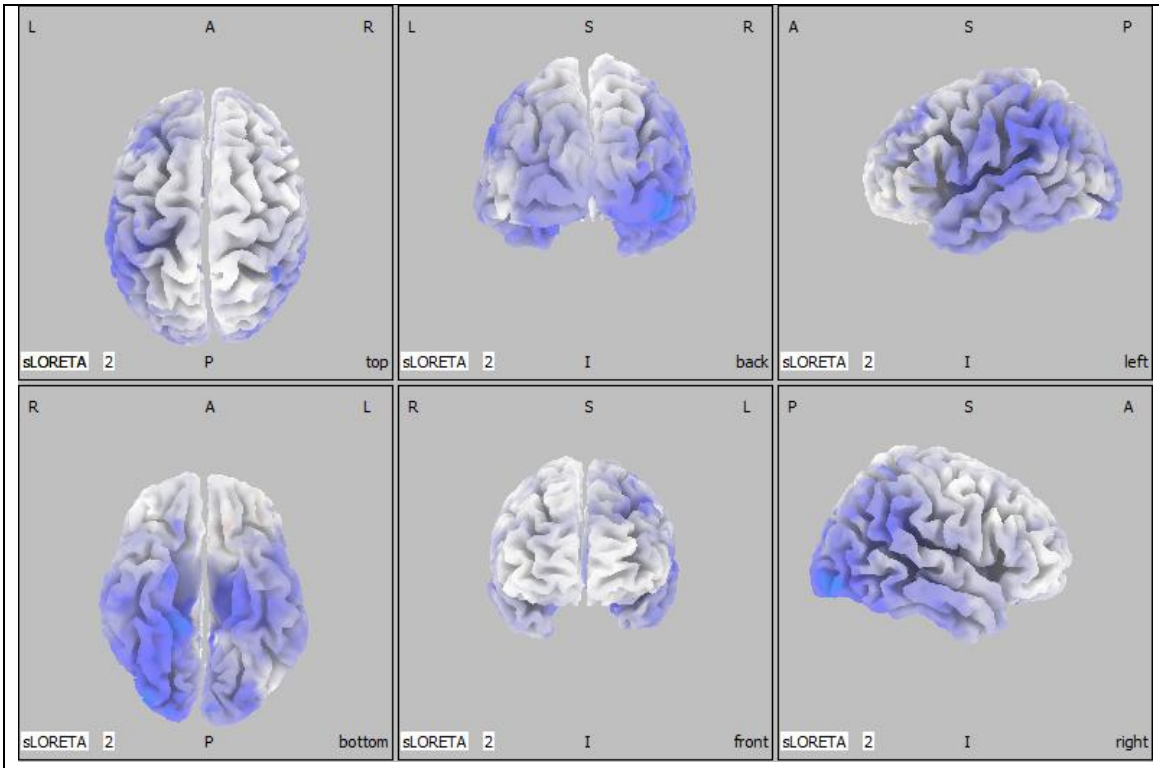
** indicates p<0.05, **indicates p<0.01*

Appendix D4: PCC Seed-Based Connectivity Comparing Participants and 'Normal Brain' Controls

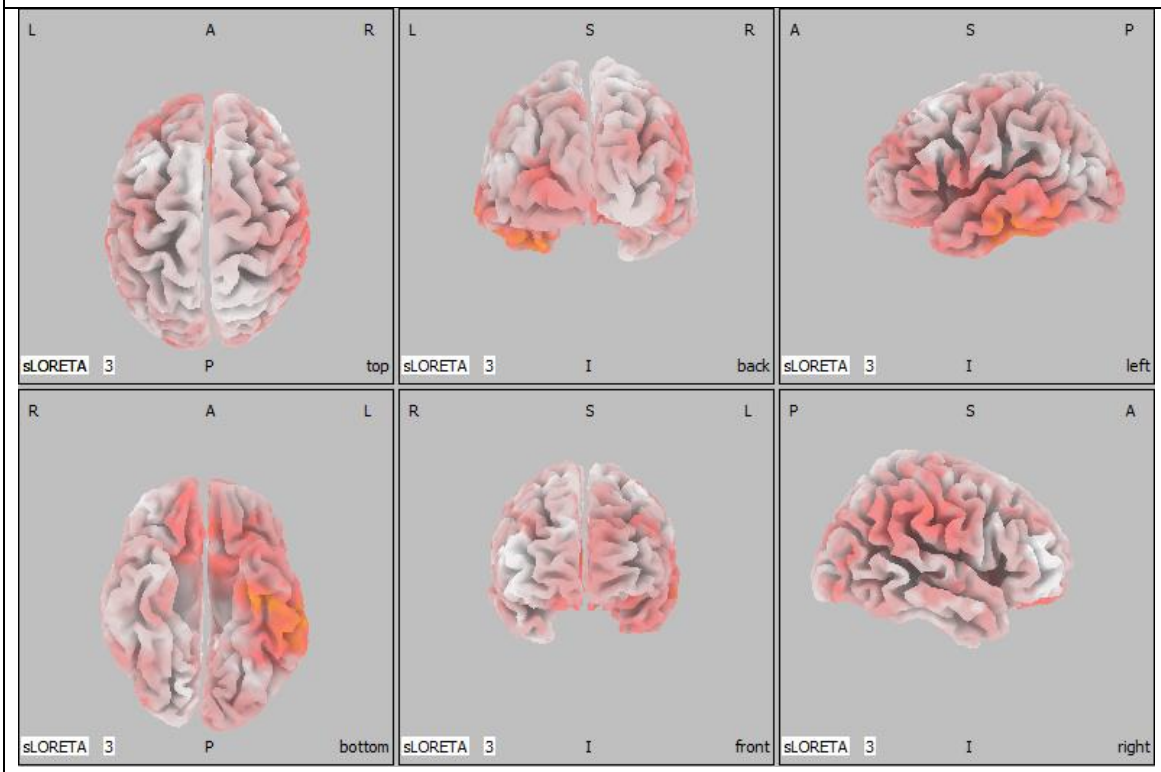
Figure D-1 shows the connectivity of the PCC to the other parts of the brain, comparing the participants in the trial to the matched normal brain controls. Areas of blue represent decreased connectivity between that part and the PCC, and areas of red represent increased connectivity between that part and the PCC in the participants compared to the controls (p=0.12)



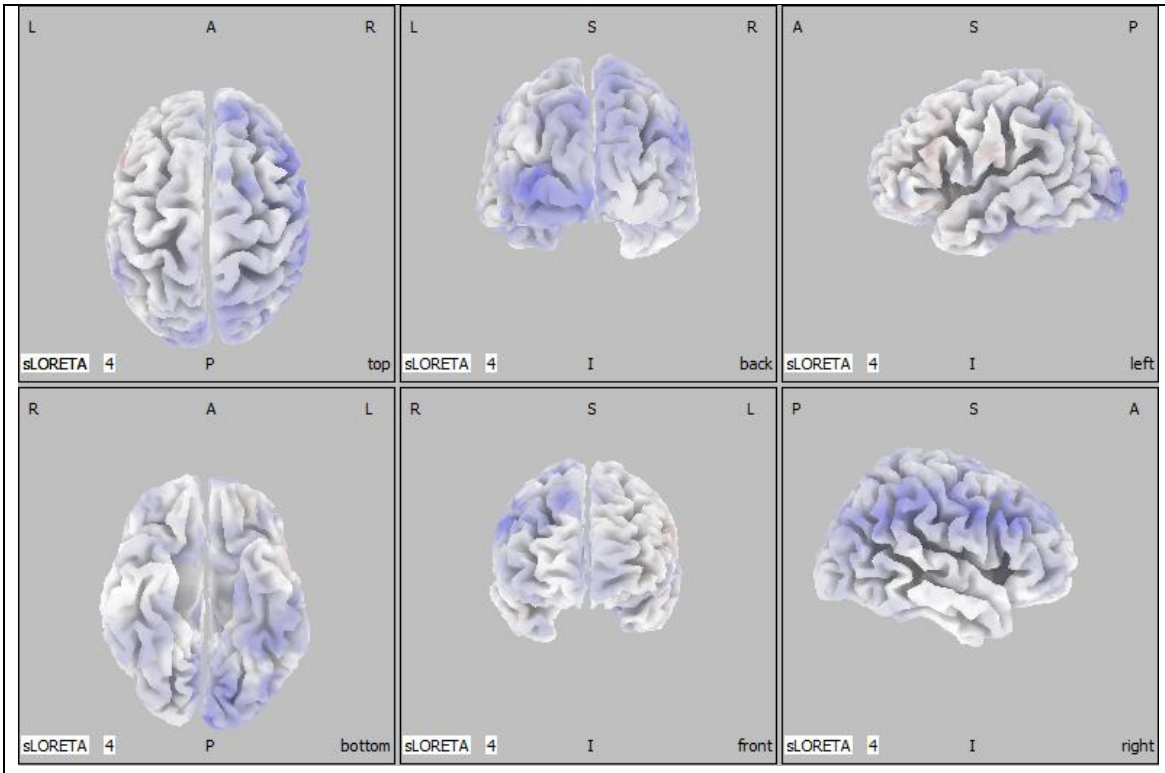
Delta Band



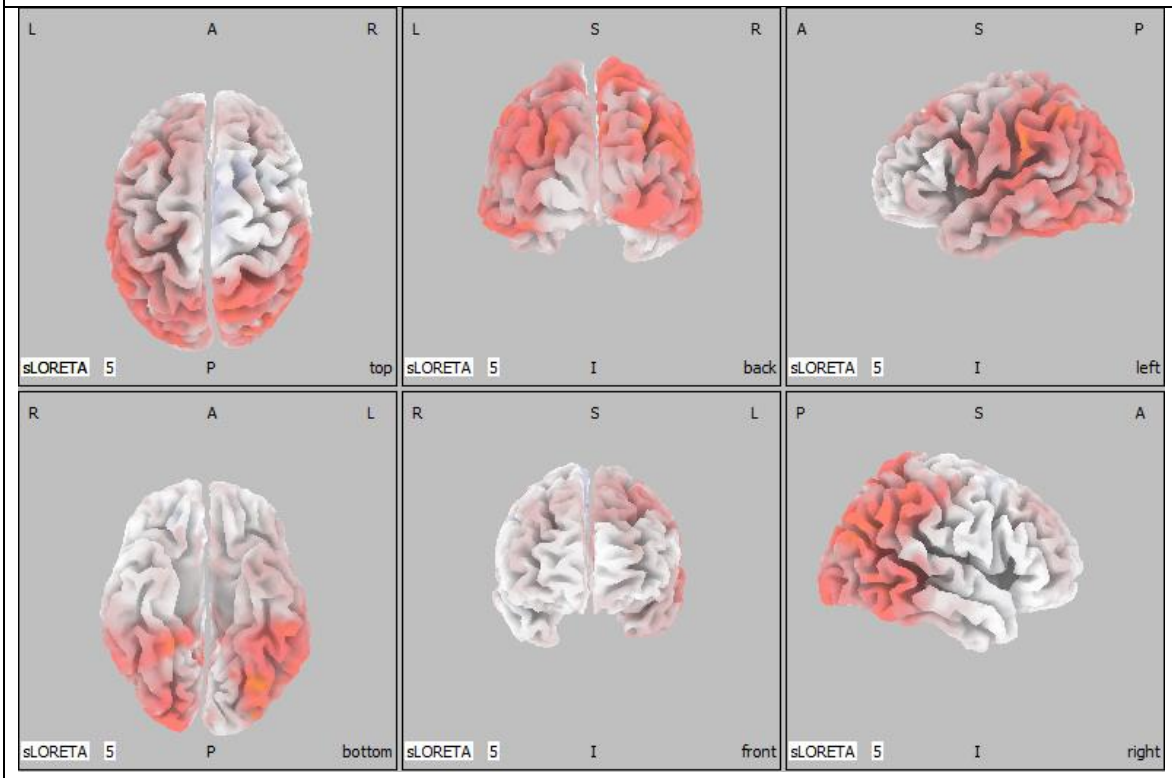
Theta Band



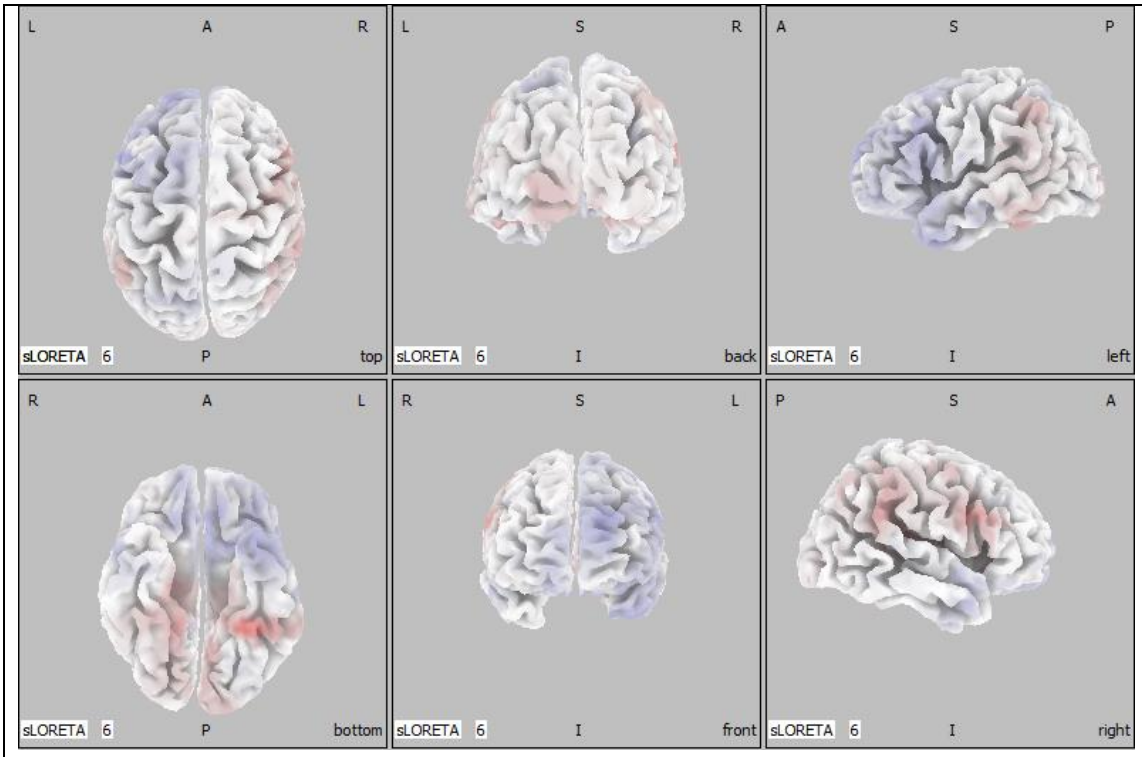
Alpha 1 Band



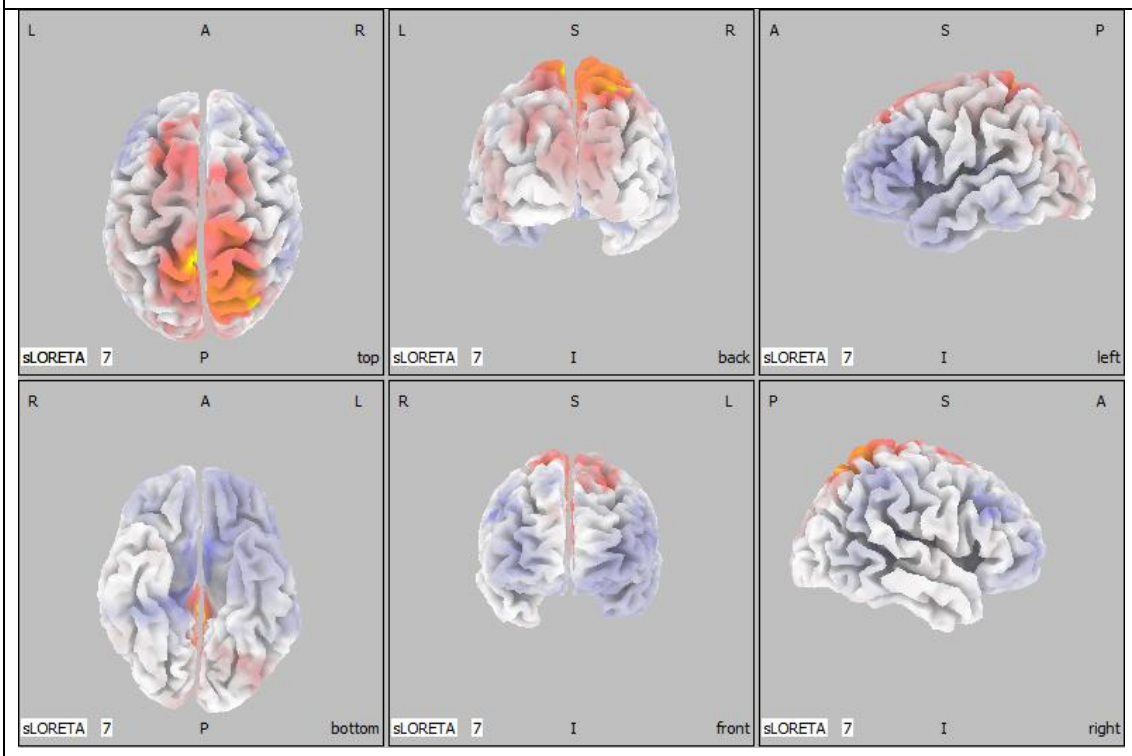
Alpha 2 Band



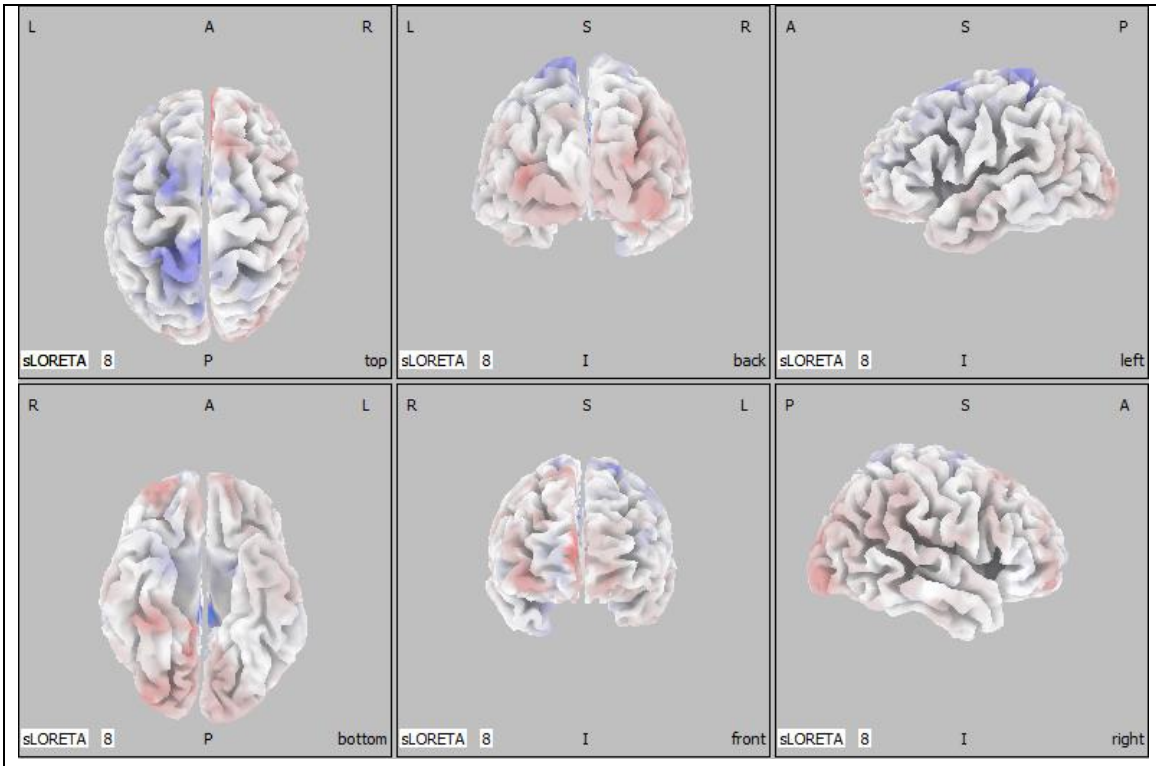
Beta 1 Band



Beta 2 Band



Beta 3 Band

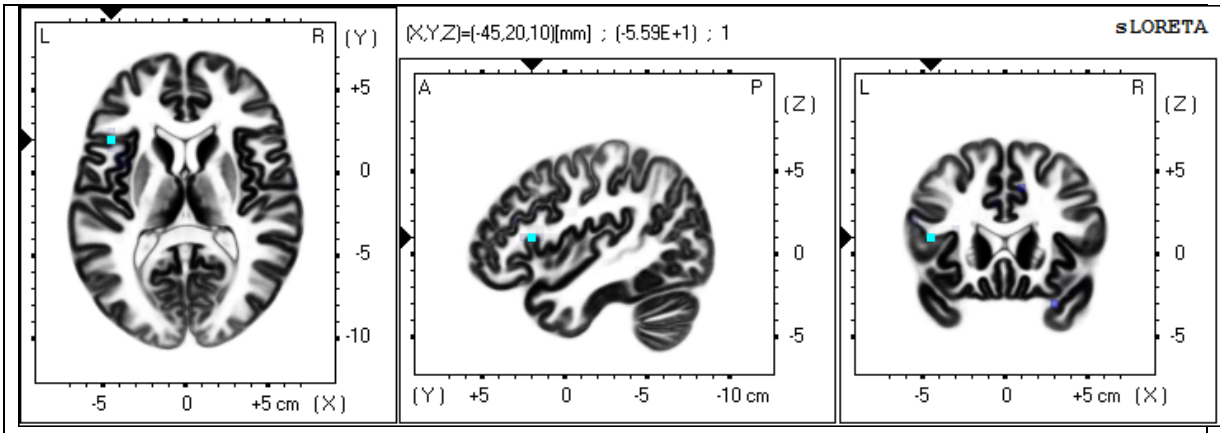


Omega Band

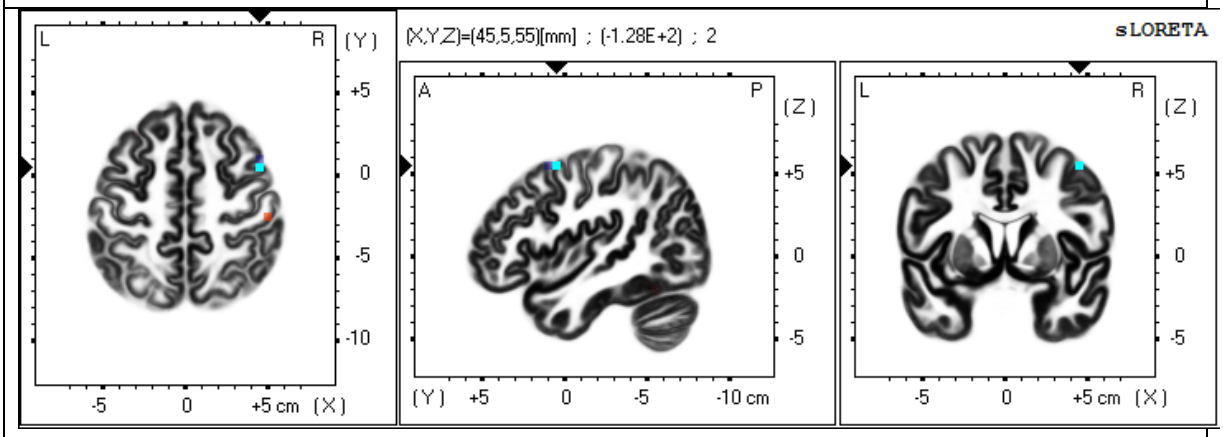
Figure D-1: Maps of PCC seed-based connectivity differences at baseline between match participants and 'normal brain' controls

Appendix D5: Changes in PCC Seed-Based Connectivity Between Baseline and Immediate Follow Up

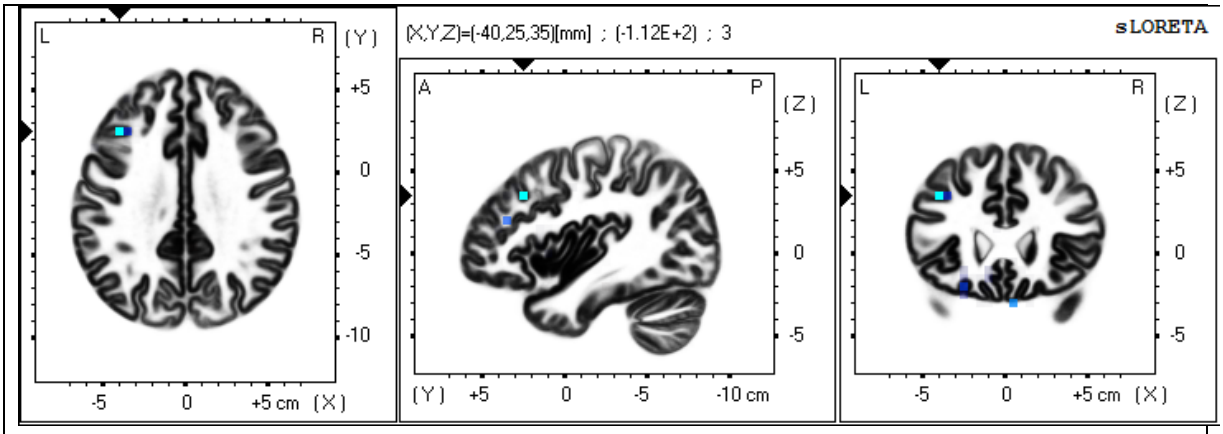
Figure D-2 below shows the changes in connectivity between the baseline and immediate follow up resting state recordings of the PCC to the voxels highlighted below in the narrowband feedback group, assessed by the seed based method. These changes are non-significant (p=0.74)



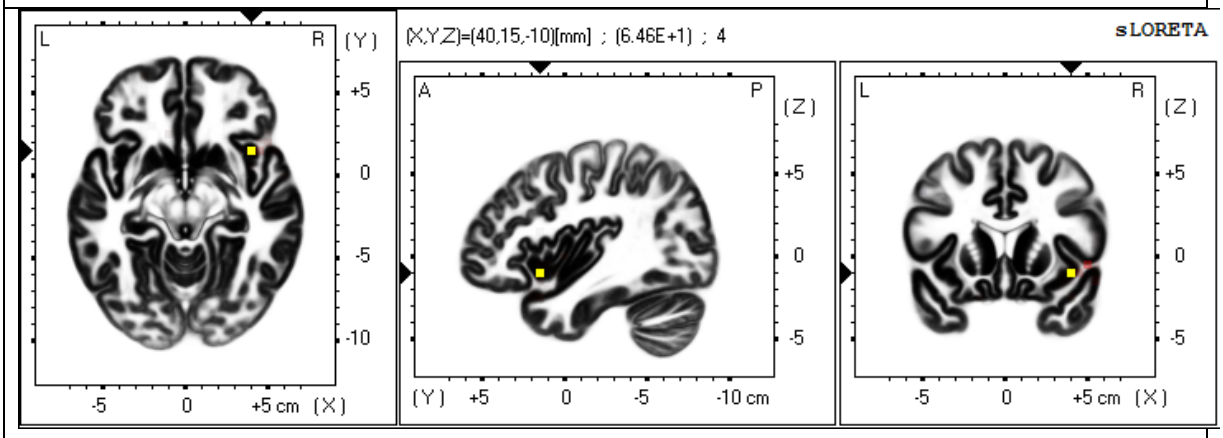
Delta band



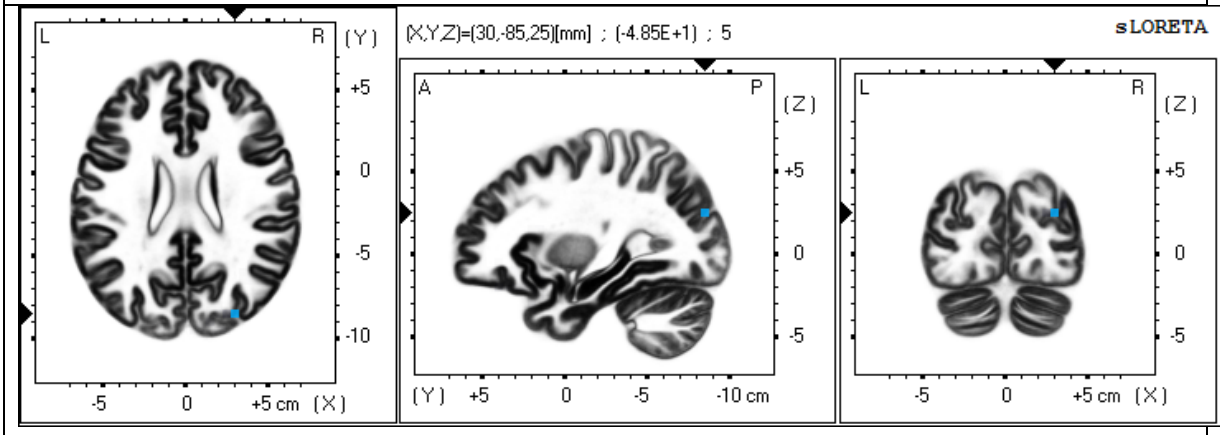
Theta band



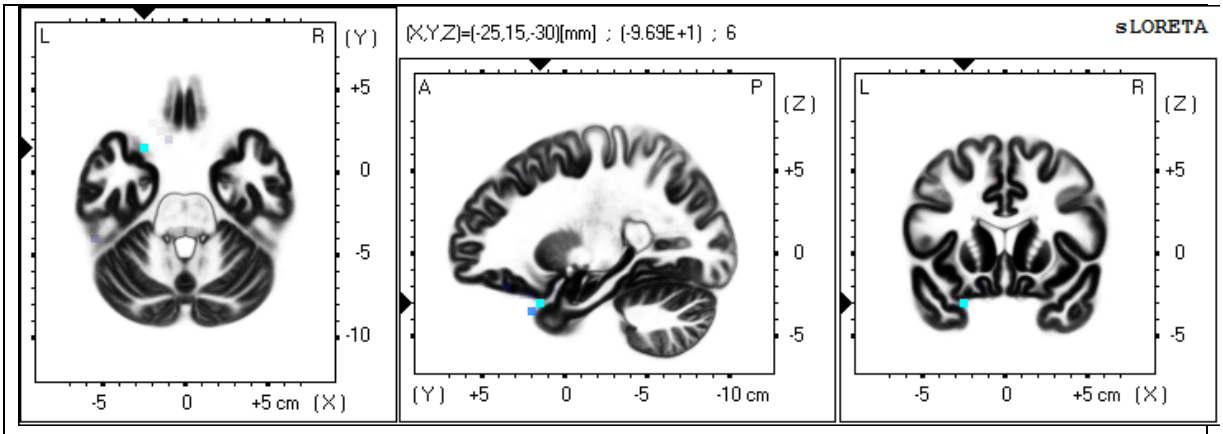
Alpha 1 band



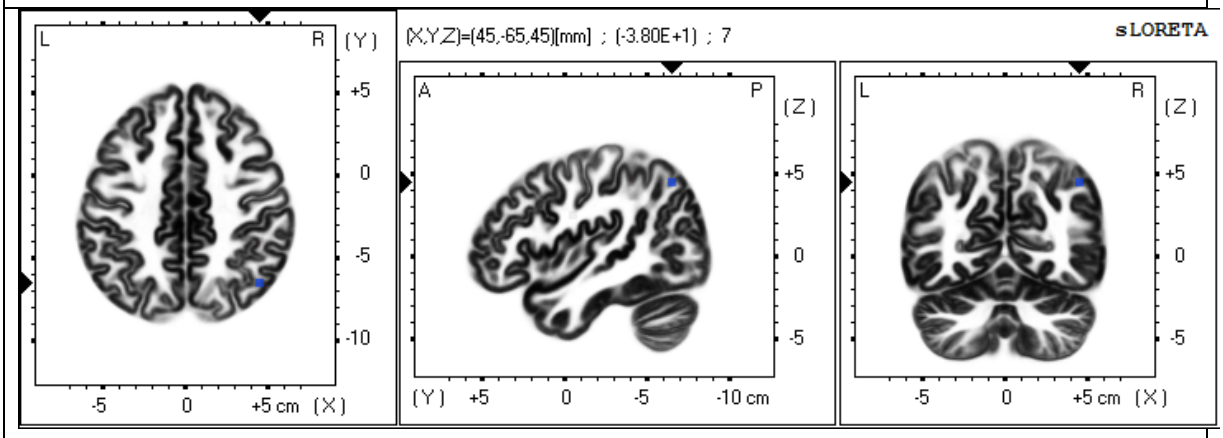
Alpha 2 band



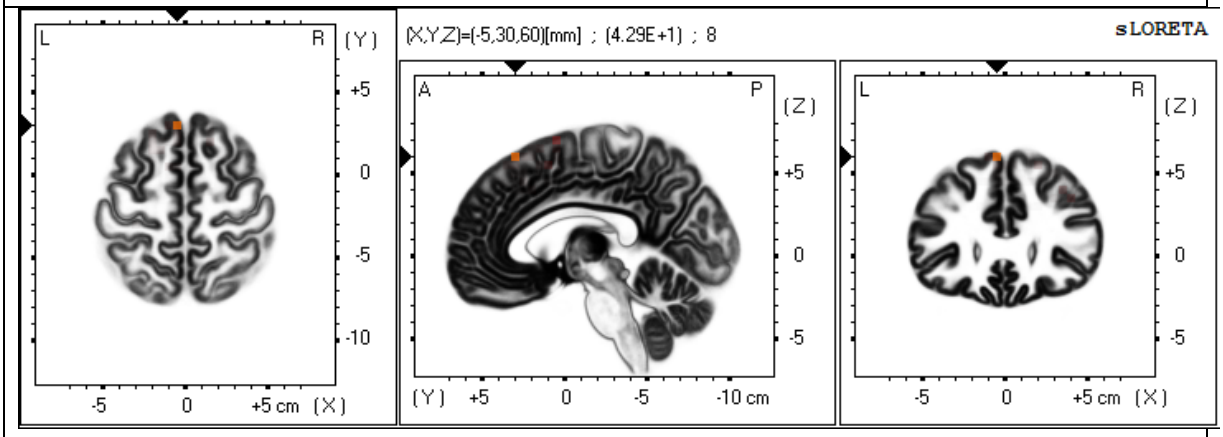
Beta 1 band



Beta 2 band



Beta 3 band



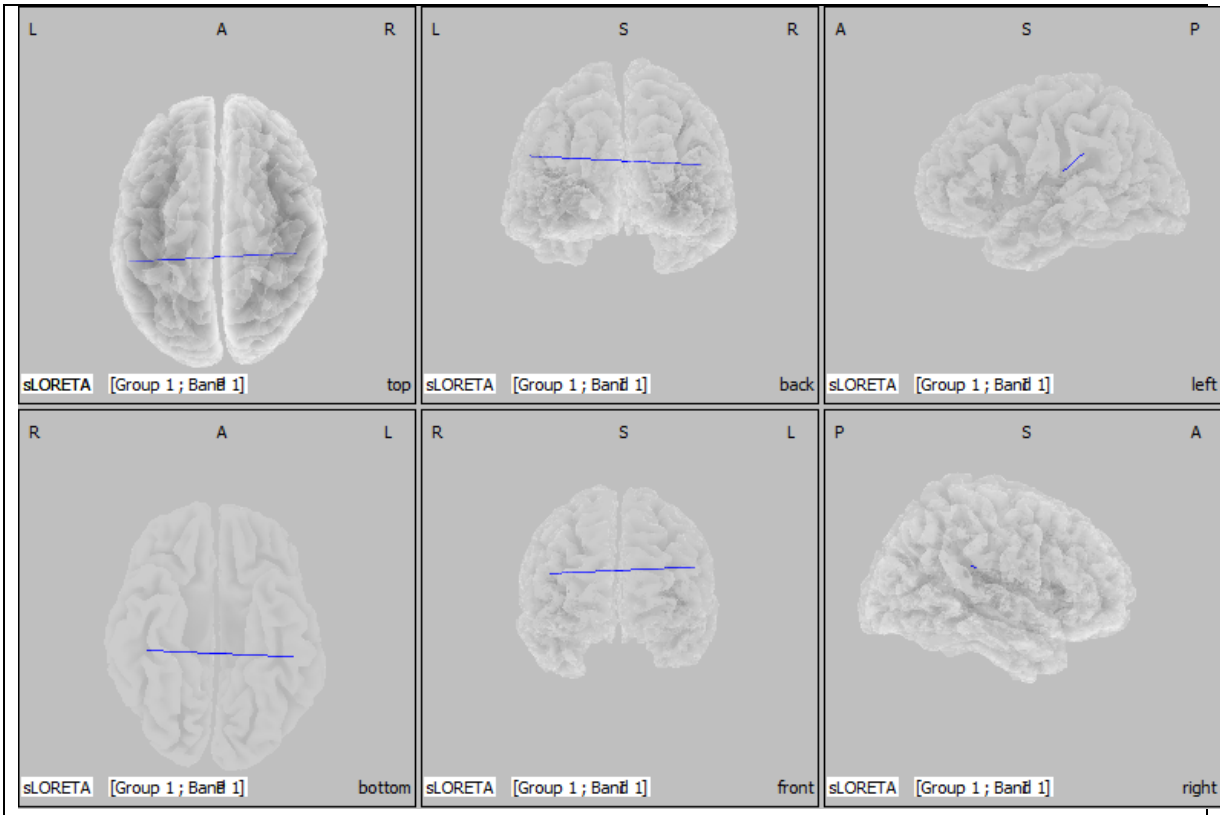
Omega band

Figure D-2: PCC seed-based connectivity changes between baseline and immediate follow up resting state recordings in the narrowband feedback group

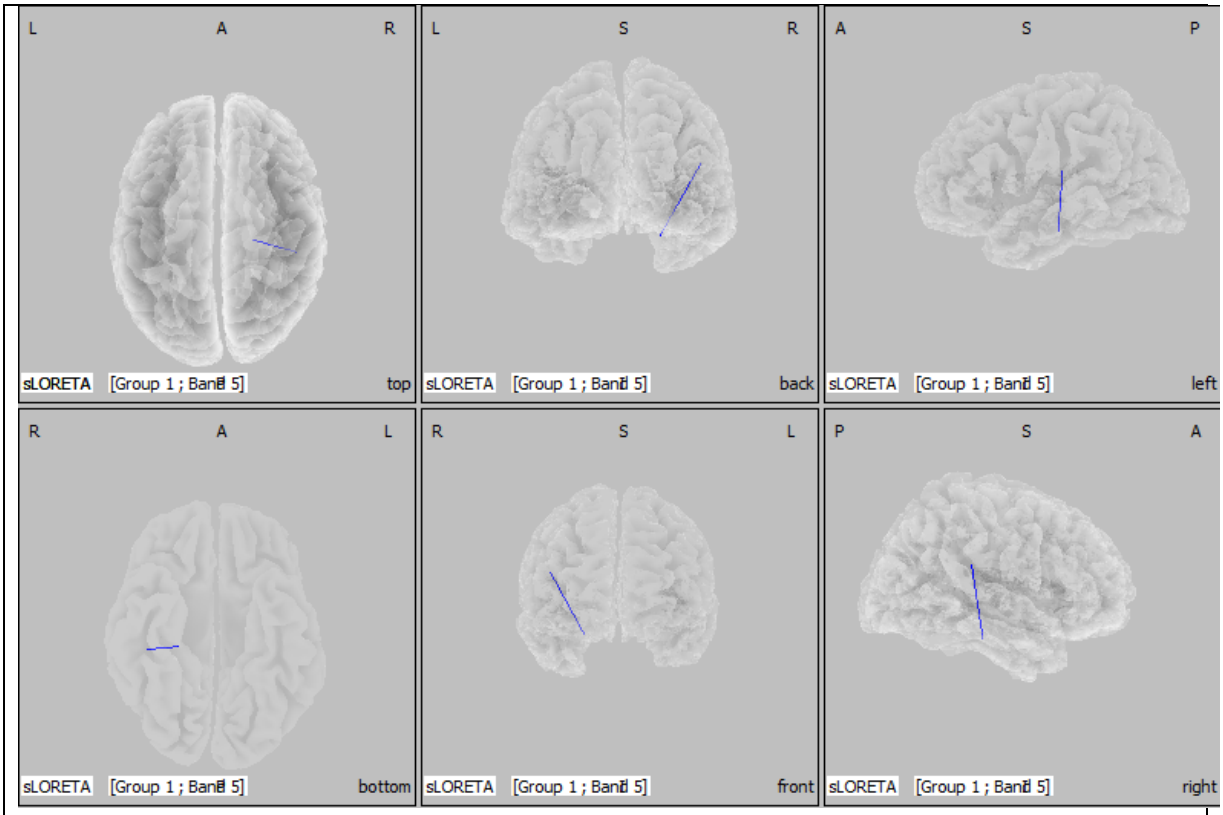
Appendix D6: Changes in the Phase Lagged Synchronisation of the Posterior DMN from Baseline to Follow Up

Broadband Feedback Group

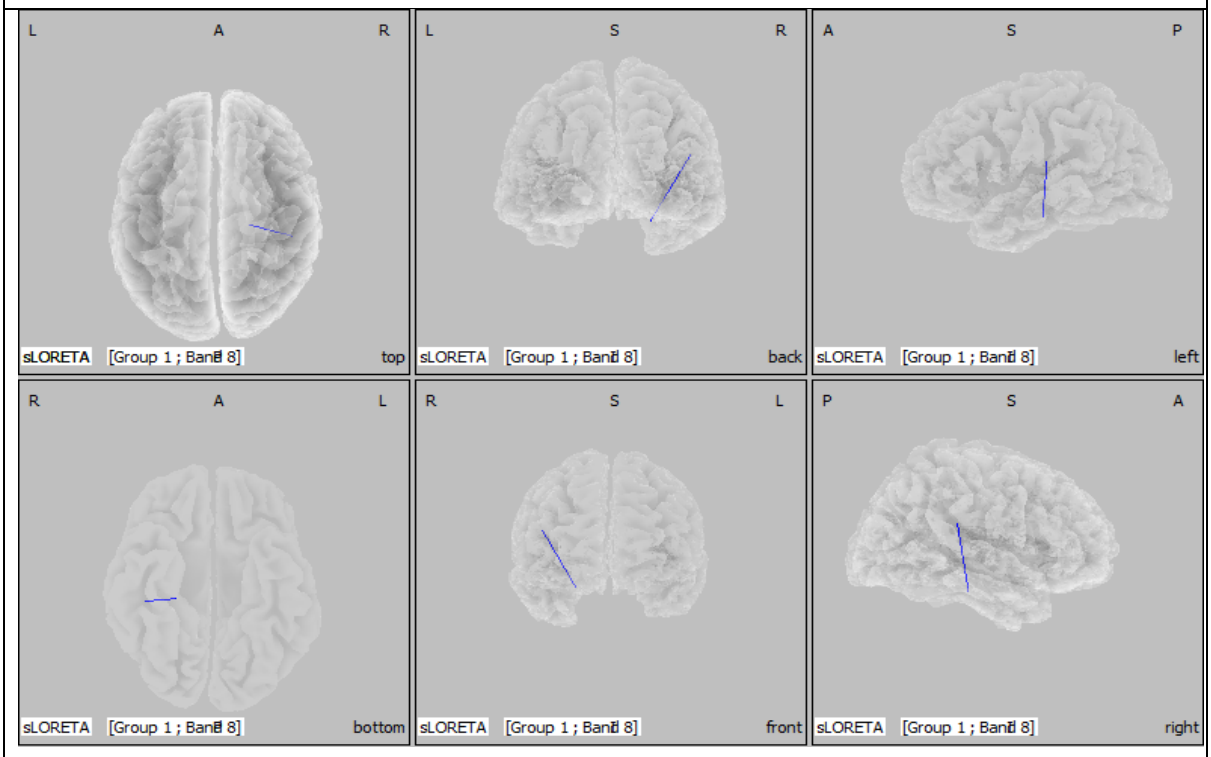
Figure D-3 below shows the changed in the posterior default mode network at the immediate follow up time point compared to baseline (p=0.071) in the broadband feedback group. Red indicates higher connectivity at follow up and blue indicates lower connectivity at follow up.



Delta band



Beta 1 band

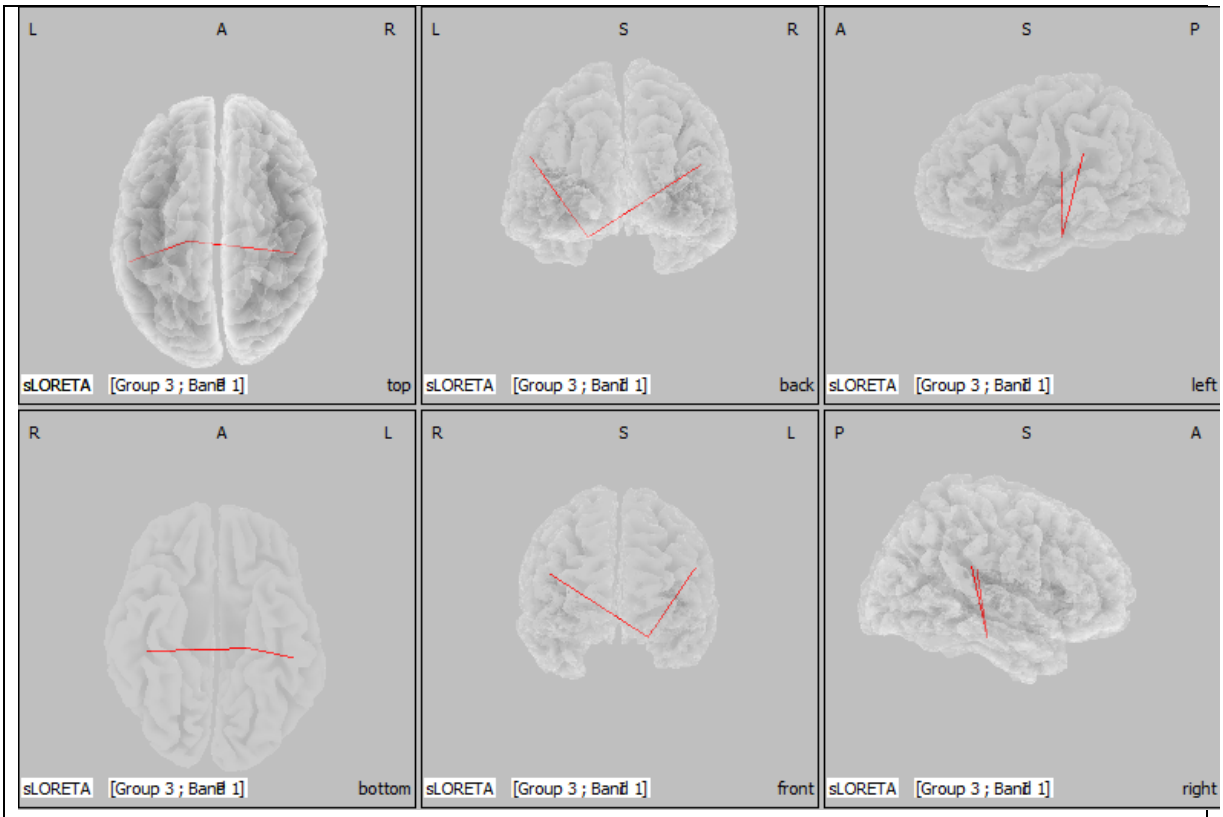


Omega band

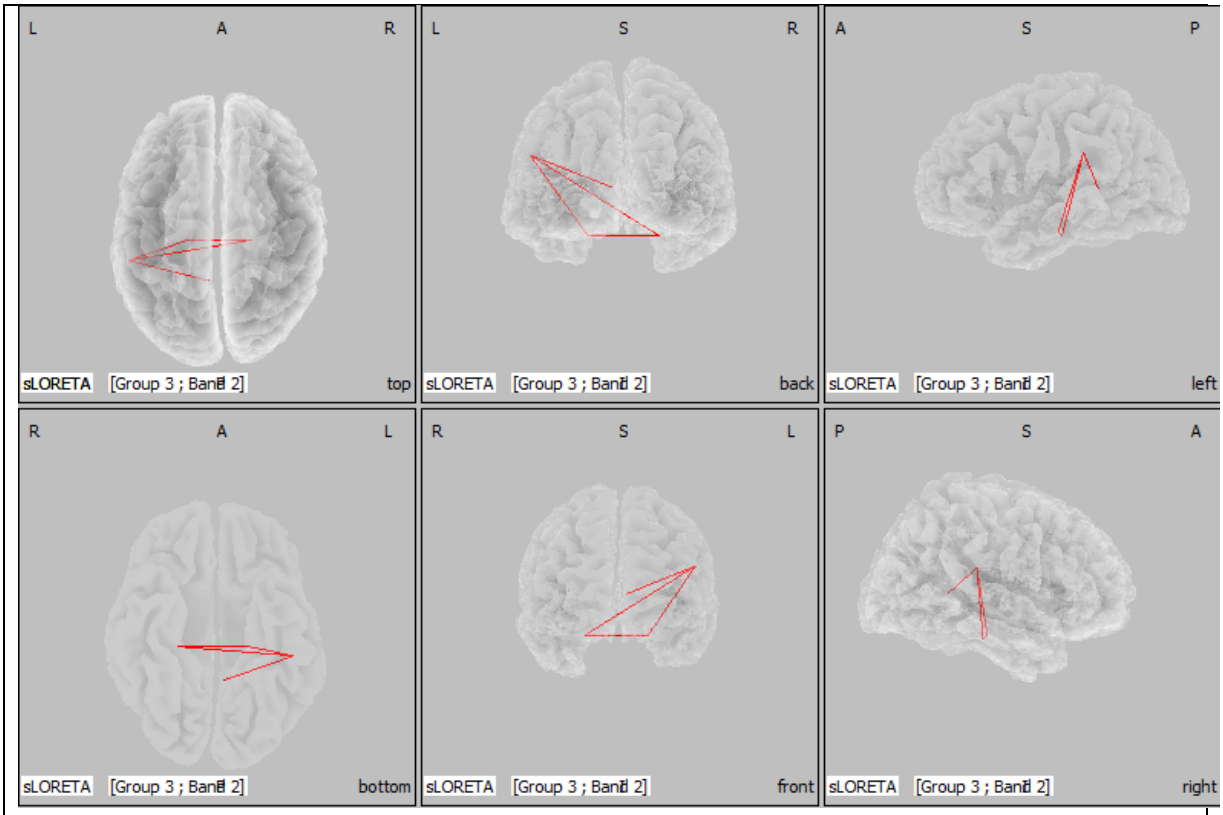
Figure D-3: Maps of phase lagged synchronisation changes in the posterior DMN comparing baseline to immediate follow up resting state recordings in the broadband feedback group

Placebo Feedback Group

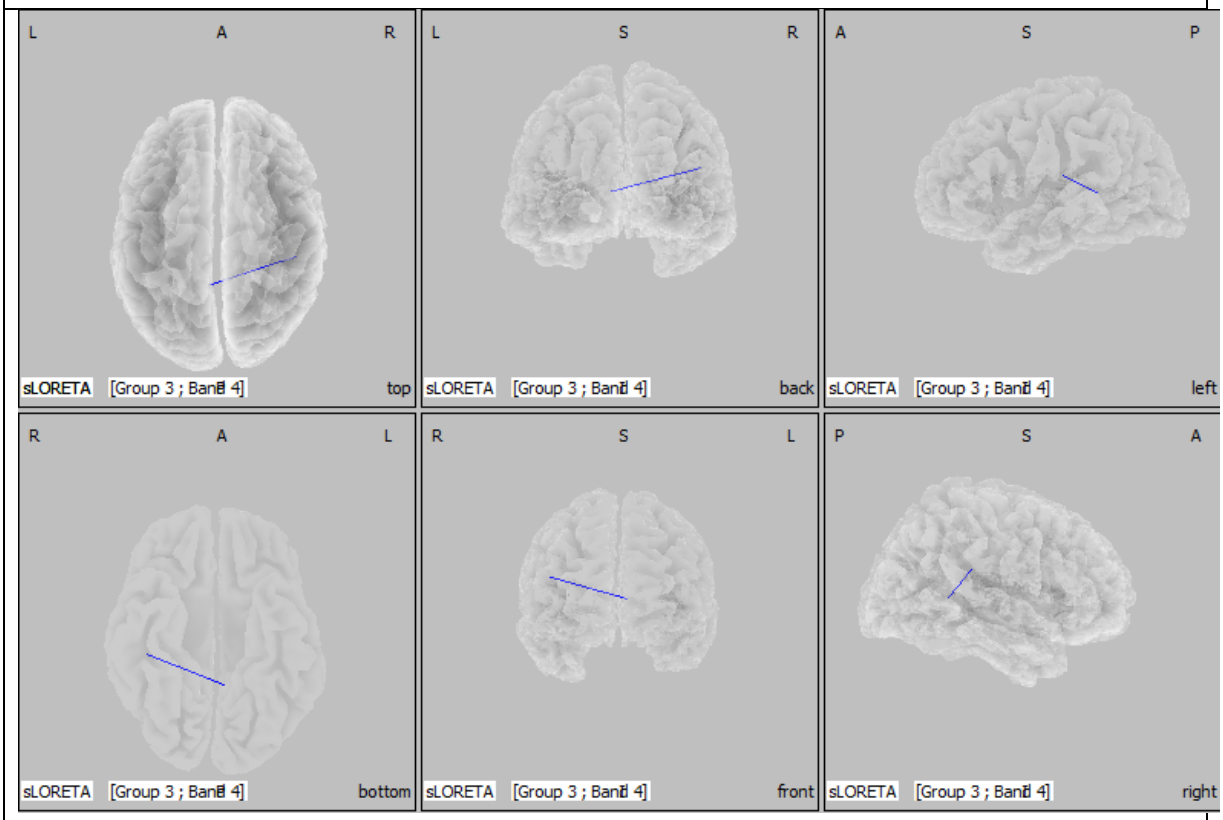
Figure D-4 below shows the changed in the posterior default mode network at the immediate follow up time point compared to baseline (p=0.471) in the placebo feedback group



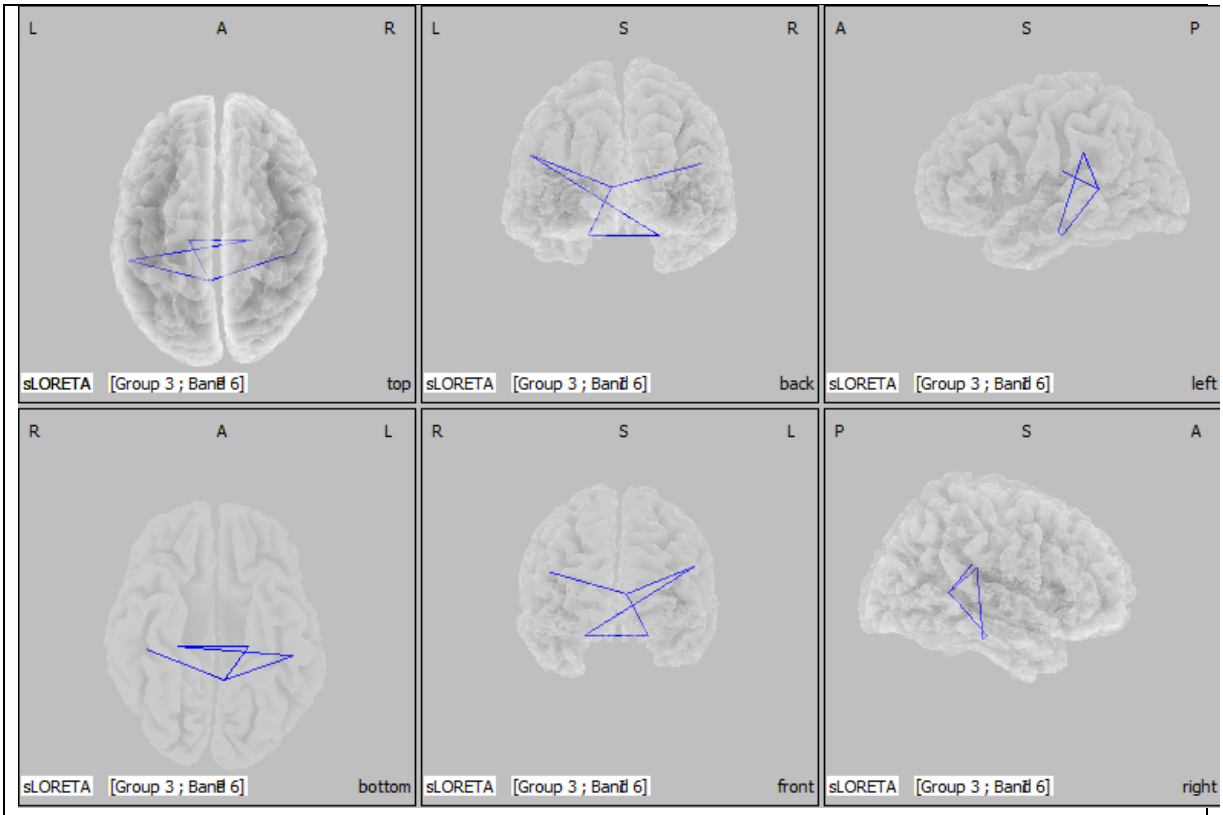
Delta band



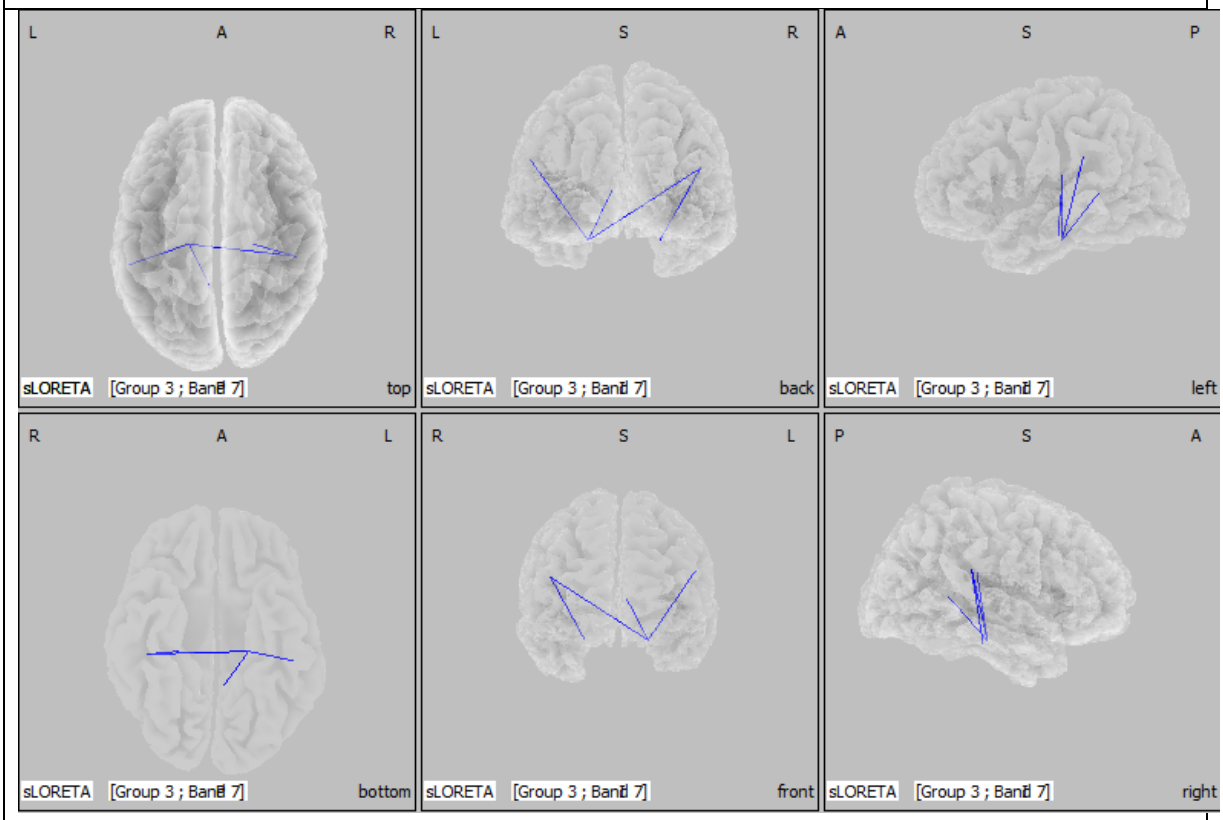
Theta band



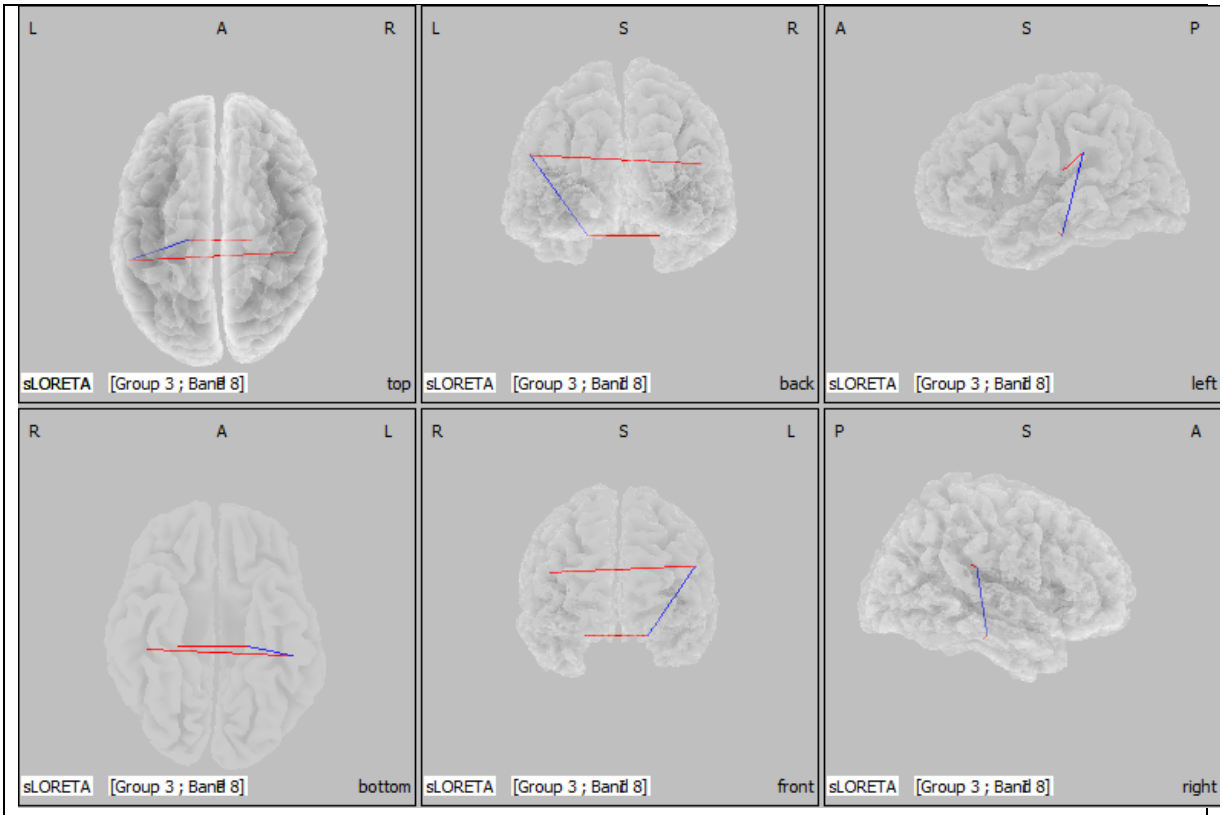
Alpha 2 band



Beta 2 band



Beta 3 band



Omega band

Figure D-4: Maps of phase lagged synchronisation changes in the posterior DMN comparing baseline to immediate follow up resting state recordings in the placebo feedback group