Vestibular Contributions to Human Memory

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Declaration

The research presented in this thesis was conducted at the School of Psychology, University of Kent, whilst the author was a full-time postgraduate student. The author received a University of Kent 50th Anniversary Graduate Teaching Assistantship Award to support this research. The theoretical and empirical work presented is original work completed by the author under the supervision of Dr David Wilkinson and the experiments were conducted with limited assistance from others. The author has not been awarded a degree by this, or any other University for the work included in this thesis. The data reported in Chapters 2, 3, 4 and 5 has been presented at the following conferences:

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Abstract

The vestibular system is an ancient structure which supports the detection and control of self-motion. The pervasiveness of this sensory system is evidenced by the diversity of its anatomical projections and the profound impact it has on a range of higher level functions, particularly spatial memory. The aim of this thesis was to better characterise the association between the vestibular system and human memory; while many studies have explored this association from a biological perspective few have done so from a psychological one. In Chapter 1, evidence was drawn from 101 neuro-otology patients to show that vestibular dysfunction can exert a direct negative effect on memory and allied cognitive processes, independently of age and comorbid psychiatric and fatigue symptoms. In Chapters 3 and 4, the separability of these cognitive, psychiatric and fatigue symptoms was further demonstrated in eight traumatic brain injury patients who, following a programme of daily vestibular stimulation, showed cognitive improvement and electrophysiological modulation in the absence of psychiatric or fatigue-related changes. Finally in Chapter 5, a set of normative experiments indicated that, beyond any generic arousal effect (unspecific to any particular cognitive process), visual memory can utilise temporally coincident vestibular activation to help individuate one memory from another. Together these findings help clarify the range of and manner in which vestibular signals interact with visual short-term memory and allied cognitive processes. The findings also have clinical implications for the diagnosis and management of vestibular, neuropsychiatric and amnesic conditions.

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I would also like to express my gratitude to the patients who took part in this research, as well as their families for making their participation possible. Their determination to overcome the hurdles thrown at them by their disorders served as constant a reminder for the purpose that I want my research to serve.

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Chapter 1
General Introduction

The Vestibular System

When thinking about how sensory systems affect our thinking and decision making, one might be drawn towards the famous characterisation of the five senses made by Aristotle (vision, audition, touch, smell and taste). Indeed much popular imagination and perceptual research has been driven by this characterisation. However, at least within the scientific committee, there is now consensus that a vestibular sense also affects our cognition and is worthy of further study (Grabherr, Macauda & Lenggenhager, 2015).

Deep within the inner ear and enclosed within dense temporal bone lies the vestibular system, a small but complex structure that provides sensory information about the acceleration and movement of the head in space (Highstein, 2004). The vestibular system is arguably one of the most ancient sensory systems, first appearing around 500 million years ago within species such as sea squirts who needed to be able to sense what was up and down in the ocean (Smith, Darlington & Zhen, 2010). The system quickly evolved to form an effective structure that was then adopted and preserved to a striking degree across different vertebrae phylogeny (Straka, Zwergal & Cullen, 2016). Vestibular signals have subsequently become invaluable to vertebrates by enabling the detection and execution of self-movement within any environment (Highstein, 2004). The signals even appear to be important for human embryos; the ear is among the first sensory organs to form and develop (complete by the eighth week), from which it has been inferred that vestibular inputs allow the foetus to orient itself and thus prevent births in the breech positon (Eliot, 1999).

Within everyday life, vestibular receptors continually monitor the motion of the head (which houses other vital sensory organs) to help keep it balanced and orientated towards an object of interest. The signals are also critical for several autonomic reflexes which enable

gaze (oculomotor) and postural (muscular) stability (Fuchs, 1992). Although, vestibular afferents are constantly active (even when we are stationary), the sensory experience produced by the vestibular system typically goes unnoticed unless the vestibular system receives an unusual stimulus (e.g. a jerky boat trip) or is damaged (Fuchs, 1992). A noticeable vestibular sensation such as vertigo (illusory sensation of spinning or swaying), visual disturbance and/ or unsteadiness is then generated and the vital role of the vestibular system becomes apparent (Goldberg, 2012).

In addition to the extremely troublesome symptoms of dizziness and imbalance, vestibular disturbances are frequently accompanied by far reaching disabling consequences including cognitive, psychiatric and autonomic impairments (Goldberg, 2012). Such pervasive effects are not present following other sensory disorders (e.g. visual, olfactory), and may reflect the diverse network of vestibular projections which extend to multiple cortical and subcortical regions that are associated with higher-level functions, including the brain stem, thalamus, basal ganglia, hippocampus, cerebellum, and cerebral cortex (Highstein, 2004). This distributed network also means that vestibular processing is far more multimodal than any other sensory modality. Vestibular information is continuously being integrated with other sensory inputs (i.e. visual, joints, skin, and muscles) throughout the central nervous system as opposed to being processed in a single core vestibular region that uniquely responds to vestibular inputs (akin to the other primary sensory cortices; Angelaki & Cullen, 2008).

Taken together, the information above highlights the unique and perhaps special role of the vestibular system in everyday functioning. Although the vestibular sense has often been overlooked within psychological enquiry, vestibular contributions to motor, cognitive, affective and perceptual functions are increasingly being reported, suggesting further study of this elegant system is likely to be valuable (Grabherr et al., 2015).

Overview

Building upon this growing appreciation for the vestibular system, this thesis aimed to explore the role of the vestibular system in cognition, particularly visuospatial memory. Four empirical chapters investigate under what conditions and how visuospaital memory processing is affected by vestibular signals. By doing so, this thesis aspires to advance current understanding of the functional relevance of vestibular signals to memory processing and provide novel therapeutic insights for vestibular and memory disorders. In short, the findings unveil novel aspects of cognitive functioning affected by vestibular dysfunction which are not simply due to mood or fatigue-related disturbances (i). Despite the strong modulatory effects of vestibular dysfunction on cognition, artificial vestibular stimulation via thermal currents did not consistently improve cognitive impairment in individuals with traumatic brain injury (TBI) (ii). Lastly, visual memory appears to use vestibular signals to help individuate one spatial location from another (iii).

This chapter will begin by highlighting the basic anatomy and physiology of the vestibular system to contextualise the elegance and relevance of vestibular signals, before providing an overview of existing evidence showing that memorial aspects of cognition are amongst the most affected by vestibular signals. Vestibular contributions to other cognitive processes and psychiatric symptoms which could impact memory function will also be reviewed. The chapter will conclude by introducing the specific aims of the thesis and the experiments that are to follow.

Anatomy

The main components of the peripheral vestibular system are illustrated in Figure 1.1. All of these precious structures are embedded within the petrous portion of the dense temporal bone for protection (Baloh & Honrubia, 2010). The vestibular system has a bony labyrinth and a membranous labyrinth (Khan & Chang, 2013). The bony labyrinth comprises

the cochlea, vestibule and semicircular canals which enclose the membranous labyrinth, a smaller structure which contains the utricle, saccule and the lateral, superior and posterior semicircular ducts. Both membranes are filled with fluid: perilymph (similar to cerebrospinal fluid) through both the bony labyrinth, and endolymph (high in potassium and low in sodium) through the membranous labyrinth (Tascioglu, 2005).

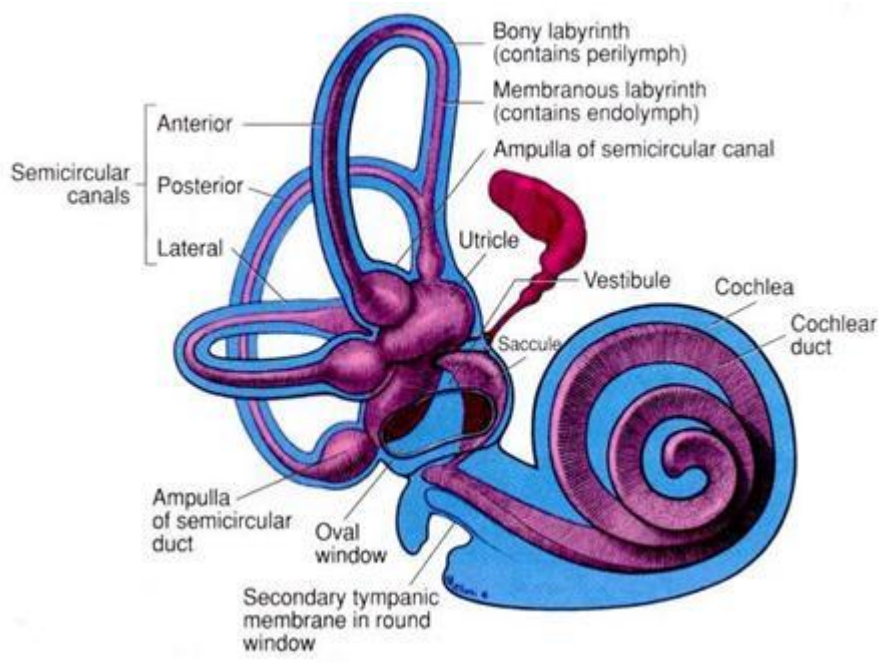
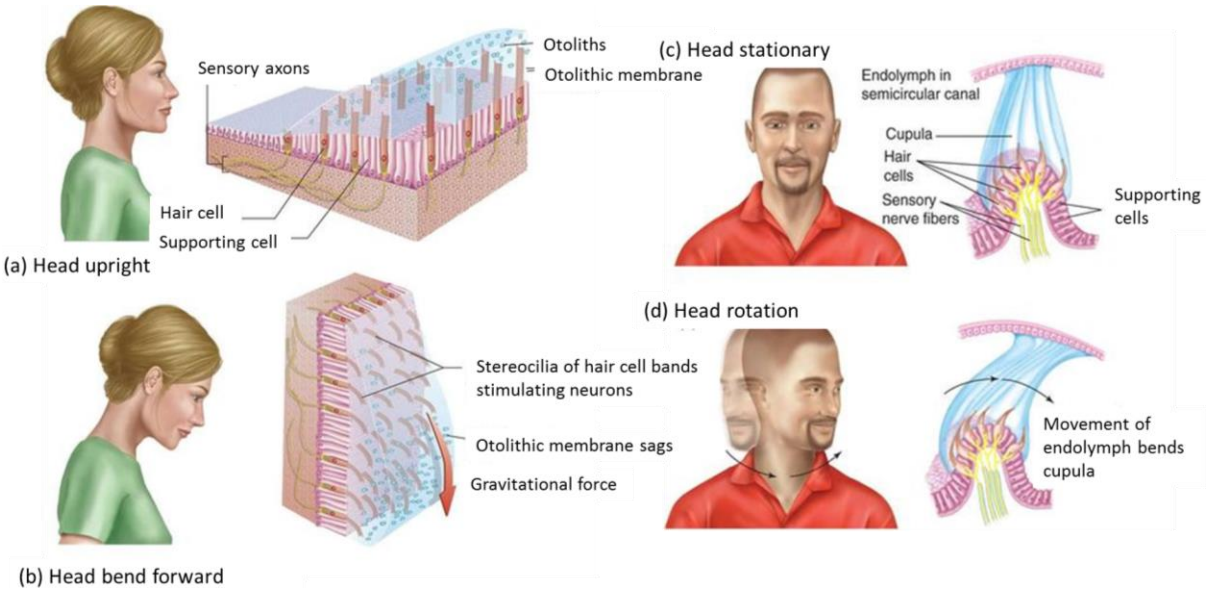


Figure 1.1. Schematic representation of the main components of the peripheral vestibular system. Reprinted from *Vestibular System and Illusions*. Retrieved July 28, 2016, from http://www.skybrary.aero/images/Vest_Fig2.jpg

There are five distinct peripheral end organs related to vestibular function which combine together to perceive the variety of physical motions that we experience. These include the two otolith organs (utricle, and saccule) and the three (lateral, anterior and posterior) semicircular canals. While the otolith organs sense linear accelerations (moving forward or to the side), the semicircular canals sense rotational movements (turning motion) (Angelaki & Cullen, 2008). Signals from the peripheral vestibular system are transduced into behaviourally relevant receptor potentials by vestibular hair cells that are comprised of rows of stereocilia and a single kinocilium immersed in a gelatinous mass (cupula). When the head undergoes an acceleration, hair cells within the utricle and saccule are bent and transmit

sensory impulses to primary processing centres in the brainstem through the vestibular nerve (Figures 1.2 A & B). Similarly when the head is rotated, movement of the endolymph fluid causes changes in the shape of the cupula which bends the stereocilia and increases/ decreases the firing rate of the hair cells depending on the direction of movement (Figures 1.2 C & D). Information from the peripheral organs is subsequently combined with other sensory inputs that converge on vestibular nuclear sites to provide a central estimate of the relative position of the body within space (Highstein, 2004). In turn, these estimates can then be used for the reflexive control of stance and gait, as well as compensatory eye rotations which keep retinal images stable during head movement (vestibulo-ocular reflex- VOR; Tascioglu, 2005).



Figures 1.2A-D. Schematic representation of the vestibular hair cells in response to gravitational linear acceleration (A and B) and rotational head movements (C and D). Reprinted from *Sense Organs*. Retrieved September 16, 2016, from http://humanphysiology2011.wikispaces.com/10.+sense+organs.

Vestibulo-Cortical Maps

The extent to which these vestibular signals are projected to multiple cortical and subcortical areas demonstrates how the vestibular system has become intimately integrated into our central nervous system and likely contributes to a range of reflexive and higher-level operations (Gurvich, Maller, Lithgown, Haghgooie & Kulkarni, 2013). Several key cortical regions have been revealed to be active during selective artificial stimulation of the vestibular

system (where visual and proprioceptive inputs are minimised, further information provided in later sections) which offer a partial neuroanatomical basis for the involvement of vestibular signals in a variety of cognitive processes. These regions include the parietal cortex, the temporo-parieto-insular and retroinsular cortex, cingulate cortex, frontal cortex, plus multiple subcortical structures (including the thalamus, basal ganglia, and cerebellum; see Hitier, Besnard & Smith, 2014 for a review).

Importantly, these projections also suggest that vestibular areas are widely distributed rather than housed in a single core primary vestibular cortex. The parietoinsular vestibular cortex (PIVC) has been described as a potential candidate for a primary vestibular cortex (especially in non-human primates) since it connects with several other regions involved in vestibular processing, and electrical stimulation of the posterior insula can elicit vestibular sensations (Hitier et al., 2014; Lopez & Blanke, 2011; Mazzola et al., 2014). However, as the PIVC also receives other sensory inputs (e.g. proprioceptive inputs are acquired during body movements when the head is stationary) and vestibular signals converge with other sensory modalities throughout the central nervous system, the PIVC is unlikely to represent a well-defined primary cortex that is topographically organised in a comparable manner to the other sensory modalities (Lopez & Blanke, 2011).

Following a variety of research efforts (neurochemical, neuroimaging, brain stimulation, lesion studies) our knowledge of these vestibular cortical projection areas has continued to grow, highlighting the probable role of vestibular inputs beyond balance effects (see Gurvich et al., 2013; Hitier et al., 2014; Hüfner et al., 2007; Shinder & Taube, 2010 for reviews). Most vestibular signals are projected across the cortex in three relays: (1) from the vestibular nuclei to the brain stem nuclei (raphe nuclei and locus coeruleus) then (2) to subcortical structures or cortical regions related to movement and vision (i.e. the cerebellum and occipital lobe); finally (3) there are several other direct (e.g. parabrachialnucleus- PBN)

and indirect (e.g. hippocampus, prefrontal cortex) vestibular projections (mainly via the thalamus) to cortical regions that are implicated in cognitive processing, autonomic function and psychiatric wellbeing (Lopez, 2013). This evidence moves some way towards explaining the role of vestibular signals in higher-level functions but falls short of a complete explanation. Despite recent advances, deeper theoretical questions about how vestibular function influences cognition, or what functional role vestibular inputs have in cognition, remain unanswered (Hanes & McCollum, 2006).

Nevertheless, this neuroanatomical perspective has played an important role in evidencing vestibular contributions to cognition. Amongst the strongest anatomical evidence for vestibular-cognitive interactions are vestibular projections to cortical regions that are important for memory. The next section will therefore focus on these pathways.

Vestibular-memory pathways. Vestibular pathways which transmit (indirectly) to the hippocampus, an area which has long been associated with memory processing, have been especially important in providing an anatomical substrate for vestibular contributions to cognition (Hanes & McCollum, 2006), especially spatial memory (ability to recall previously encountered locations and to learn the configuration of environments). Four primary pathways have been hypothesised to show how vestibular signals might be passed to the hippocampus (see Hitier et al., 2014 for a potential fifth pathway). Figure 1.3 provides an illustration of these pathways which include the vestibulo-thalamo-cortical pathway (A), theta pathway (B), head direction pathway (C), and vestibulo-cerebello-cortical pathway (D) (Hüfner et al., 2007). Pathway A has been proposed to transmit spatial and self-motion information via the parietal, entorhinal and perirhinal cortices to the hippocampus. Pathway B passes through the pontine reticular formation, supramammillary nucleus and medial septum to the hippocampus and has been suggested to support memory processing. Pathway C is associated with head orientation and occurs via the dorsal tegmental nucleus which transmits

to the lateral mammillary nucleus and anterodorsal thalamic nucleus before reaching the hippocampus. Finally, information relevant to spatial learning is thought to be provided by pathway D which occurs via the cerebellum, and the ventral lateral nucleus of the thalamus (Hitier et al., 2014; Hüfner et al., 2007; Smith et al., 2005).

Although some aspects of these pathways remain hypothetical and will require further experimental investigation (Hitier et al. 2014), these models provide a progressive anatomical account of how vestibular signals might contribute to cognitive functioning, particularly those processes related to spatial memory, orientation and perception (Shinder & Taube, 2010).

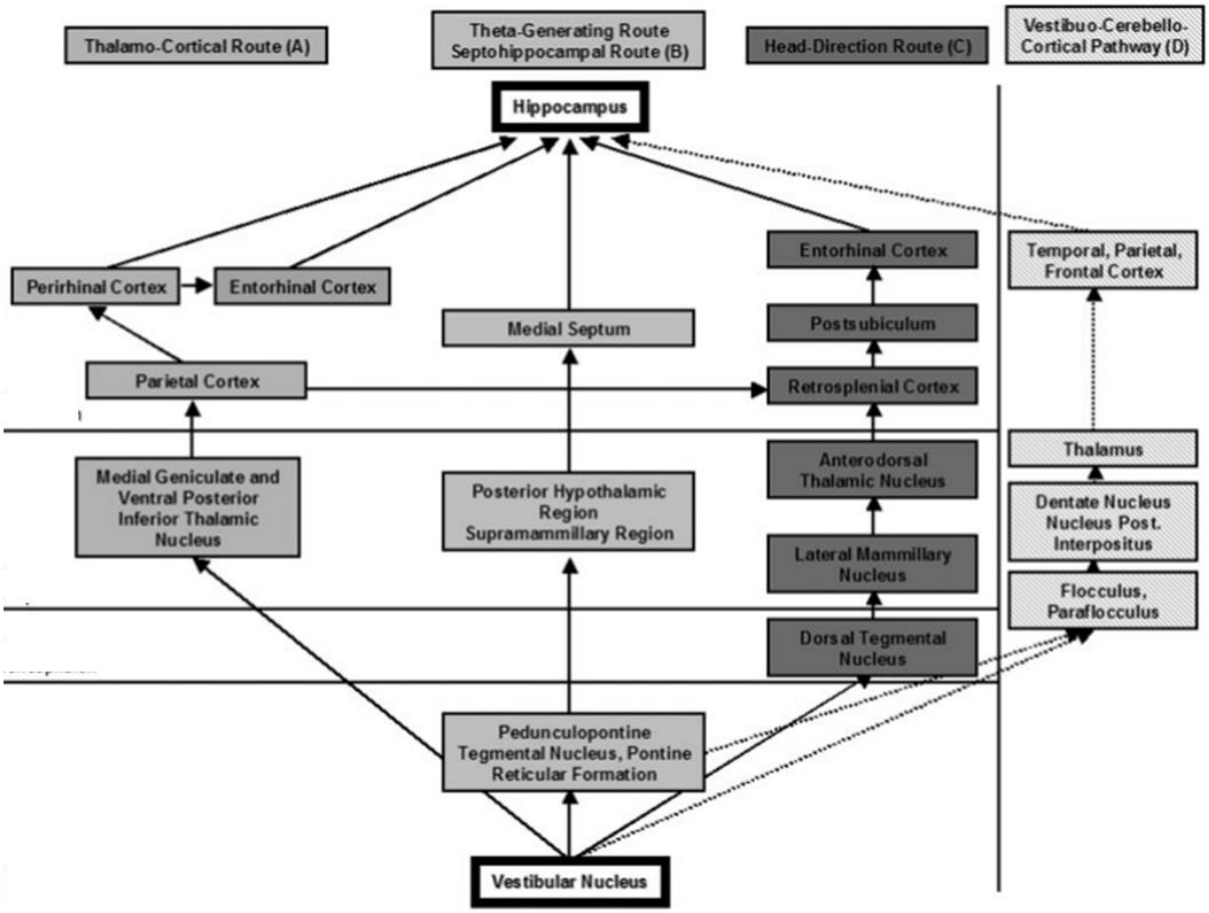


Figure 1.3. Neuroanatomical model of vestibular-hippocampal pathways reprinted from Hüfner et al., 2007.

Interestingly, several of the neural networks that are activated by vestibular signals (including the pathways above) also overlap with multiple regions that are implicated in memory processing (Glikmann-Johnston, Saling, Reutens & Stout, 2015; Squire, 2009).

Table 1.1 provides a summary of the core anatomical regions engaged during memory functioning and the sub-components with which they have mainly been associated. Note that various aspects of memory, particularly spatial memory and navigation, are largely mediated by temporal areas of the brain (especially the hippocampus) that comprise the vestibular cortical network (Glikmann-Johnston et al., 2015). Although, these neuroanatomical models cannot prove that vestibular signals make a distinct contribution to memory or determine how the signals might be used, the overlap between these networks does indicate that vestibular processing is likely to be relevant to memory function.

Smith et al. (2010) offered one explanation for how this cortical overlap might relate to memory processing. The authors suggested that vestibular signals may have become incorporated within memory representations as an evolutionary response, since movement is vital for survival and the vestibular system is specifically designed to detect changes in self-motion (i.e. is the head is upright, is it moving, what speed/ direction am I travelling?; Wilkinson, Morris, Milberg & Sakel, 2013). However, it could be argued that because vestibular inputs are so widely distributed across the cortex and converge with other sensory inputs and motor signals, they are unlikely to make an isolated contribution to memory (Angelaki & Cullen, 2008; Hitier et al., 2014). Nevertheless, perhaps they could still make a unique contribution to memory by providing baseline information about self-motion which then acts as a reference for other sensory inputs and enables accurate and synchronised motor and cognitive actions, including memory (Smith et al., 2010).

Table 1.1

Neuroanatomical Overlap between Key Memory Centres and Vestibular Pathways (based on a review by Squire, 2009).

Structure	Sub-Components of Memory	Pathway
Frontal Cortex	Working.	Vestibulo-thalamo-cortical. The anterior cingulate cortex is thought to bridge vestibular areas (e.g. insula) with prefrontal regions (Preuss, Hasler & Mast, 2014).
Parietal Cortex	Episodic, long-term, spatial representation.	Vestibulo-thalamo-cortical and potentially vestibulo-cerebello-cortical (via the ventral lateral nucleus of the thalamus; Hitier et al., 2014).
Hippocampus	Declarative, autobiographical, spatial, navigation, path integration.	See Figure 1.3.
Amygdala	Retention of emotional experiences, emotional learning.	Dopaminergic mesolimbic: limbic regions (e.g. raphe nuclei/ PBN) have reciprocal connections with vestibular nuclei and amygdala (Gurvich et al., 2013).
Entorhinal Cortex	Spatial representation, acts as an interface between hippocampus (encoding new memories) and neocortex (remote memory).	Vestibulo-thalamo-cortical and Head-direction route (see Figure 1.3).
Thalamus	Internal representations of reality, declarative memory (retrieval).	Multiple thalamic nuclei receive vestibular inputs which are then relayed to the cortex (i.e. the ventroposterior complex, the ventroanterior–ventrolateral complex, the intralaminar nuclei and the posterior nuclear group; Lopez & Blanke, 2011).
Cingulate Cortex	Early acquisition of memory (anterior) and episodic retrieval (posterior).	Vestibulo-thalamo-cortical, connected with the insular cortex (Gurvich et al., 2013).
Cerebellum	Procedural and conditioned learning.	Vestibular projections to the cerebellum are numerous but include the relay of otolith signals from the vestibular nuclei to the medullary reticular formation, inferior olive, and lateral reticular nucleus to cerebellar nuclei (Büttner-Ennevra, 1999).
Basal Ganglia	Procedural, conditioned learning, decision making. Working – acts as an inhibitory gate keeper (Baier et al., 2010).	Pathway proposed between the vestibular nucleus and striatum, going through the thalamic nucleus (Hitier et al., 2014).

Note. Working= temporary storage and manipulation of information; Episodic= encoding and

retrieving daily personal experiences; Declarative= conscious recollection of facts and events; Procedural= unconsciously remembering how to perform different tasks/ skills.

The next section will summarise an emerging body of clinical investigations which have actually measured the association between the vestibular system and memory by examining the cognitive processing of individuals (and animals) who either have a dysfunctional vestibular system or have received artificial stimulation of the vestibular nerves. In short, they appear to evidence a connection between vestibular inputs and visuospatial memory, but lack clarity regarding the functional mechanisms which underlie these interactions and the diversity of the higher-level functions that are impacted.

Vestibular Dysfunction and Memory

Numerous animal experiments dating back to the 1960s (Beritoff, 1965) have demonstrated that disturbance to one or both vestibular labyrinths can result in animals being unable to orient themselves or learn new spatial locations on memory tasks which involve foraging or navigating to a learnt route (see Smith et al. 2010; Smith & Zheng, 2013 for reviews). Data from human patients also appear to echo these findings, one of the first reports comes from Grimm, Hemenway, Lebray and Black (1989) who showed that patients with perilymph fistula syndrome (tear/ defect in the bony membranes between the mid and inner ear) had suffered memory loss according to several objective tasks (paired associate learning, auditory recall), while their performance on others remained normal (IQ, digit span, visual reproduction). However, it should be noted that perilymph fistula syndrome also induces auditory dysfunction which could add to any cognitive deficit. Nevertheless, a more recent epidemiological study into the impact of vestibular loss on age-related cognitive decline (which controlled for auditory and visual impairments) also showed that reduced vestibular function was significantly associated with worsened cognitive performance on tests of visuospatial function (including visual memory) but not executive function or verbal memory (Bigelow et al., 2015b).

Perhaps the most direct tests of memory performance have come from Schautzer, Hamilton, Kalla, Strupp and Brandt (2003) and Brandt et al. (2005) who used a virtual Morris Water Maze task (maze tasks are the gold standard for testing spatial memory in rodents). In these studies patients with bilateral vestibular neurectomies (conducted five to ten years prior to the study) and healthy controls were trained to navigate to a target platform, later this target platform was removed and participants had to return to this point from memory. While healthy controls could navigate directly to the target from several starting points (using fixed spatial cues in the maze environment), patients struggled to remember the route, taking longer to arrive at the target and spending less time overall in the location where the target platform would have been located. This group difference was present only when the target platform was no longer visible, indicating a specific impairment to spatial memory which was dissociated from the patients' intact perceptual, motor and cognitive capacities (including non-spatial memory) on other standardised tests (Wiener-Vacher, Hamilton & Wiener, 2013).

Following on from these studies, Kremmydal et al. (2016) recently demonstrated that patients with partial rather than complete bilateral vestibular loss also show delayed spatial learning on the virtual Morris Water Maze task relative to controls. Additionally, Guidetti, Monzani, Trebbi and Rovatti (2008) attempted to provide a more ecologically valid test of spatial memory by comparing the performance of 50 well-compensated (without vertigo) unilateral labyrinthine-defective patients with 50 healthy controls on a task which required navigating three different routes in a physical rather than virtual environment. Patients were slower to walk along memorised routes during an eyes-closed condition where visual inputs were unavailable (placing more reliance on vestibular signals) relative to the controls. The study also revealed impaired visuospatial short-term memory abilities amongst the patients using the Corsi block test (participants must remember and repeat an increasingly difficult sequence that is tapped on a number of blocks; Kessels, van Zandvoort, Postma, Kappelle, &

De Haan, 2000). Once again these findings highlight the importance of vestibular signals in cognitive processing, particularly those concerning spatial short-term memory. However, since the navigation task required movement, these results may also reflect the contribution of vestibular reflexes to motor actions (Cohen, 2000; Péruch et al., 1999).

Taken together, these findings suggest that when the vestibular system is disturbed, at least some memory functions are impaired. Since most of the patients were tested years after the initial loss and had retained some hearing function, confounding auditory and reflex deficits were unlikely to explain the findings. Normal vestibular function could therefore be necessary for some memory processes, particularly those relating to visuospatial information (Bigelow & Agrawal, 2015; Smith et al., 2010).

Recall that the hippocampus has long been a focus in the study of how spatial information is represented and stored, and thus neuroanatomical as well behavioural changes might be expected to occur in response to vestibular dysfunction (Smith, 2016). In line with this idea, the patients recruited by Schautzer et al. (2003) and Brandt et al. (2005) had significantly decreased (16.9%) hippocampal volumes relative to a control sample. Kremmydal et al. (2016) also demonstrated significant atrophy of the mid-hippocampus and the posterior parahippocampus in patients with bilateral but not unilaterally reduced vestibular function. A number of researchers have shown a similar trend, with the greatest structural changes occurring amongst those patients with bilateral loss and more subtle changes following unilateral/ partial vestibular loss, where sufficient information may still be passed from the remaining healthy labyrinth to compensate for the deficit (Brandt, Zwergal & Glasauer, 2017; Helmchen, Ye, Sprenger & Münte, 2014; Hüfner et al., 2007; Seo, Kim & Kim, 2016; zu Eulenburg, Stoeter & Dieterich, 2010). A parallel stream of research has also revealed that the hippocampus responds to vestibular input in healthy individuals who undergo unusual spatial memory experiences. For example, Hüfner et al. (2010) reported

alterations including smaller anterior volumes and larger posterior volumes of the hippocampus within professional dancers and slackliners. Collectively these findings demonstrate that alterations to vestibular inputs can influence hippocampal morphology. However, this effect is likely to be complex and may vary across vestibular syndromes and according to the recency of the condition/ spatial experience (Smith, 2016).

Further insights into the influence of vestibular signals on memory relate to the cognitive maps which are formed within the hippocampus and parahippocampal area (i.e. entorhinal, perirhinal and postrhinal cortices; Hitier et al., 2014). Place cells (activated when a particular place is entered), border cells (core to an environmental boundary), head direction cells (fire when the head is orientated in a certain direction) and grid cells (provide a triangular array of the environment to signal one's changing position within space) all combine to form an internal representation of the environment (Moser, Kropff & Moser, 2008; O'Keefe & Conway, 1978). These maps represent relevant spatial features of an event and thus may form an early step in spatial memory formation and shape later navigational planning (Hitier et al., 2014; Squire 2009).

Importantly, vestibular loss has been shown to disrupt the selective firing of hippocampal place cells within rats, both temporarily after intratympanic injections of tetrodotoxin (Stackman, Clark & Tauge, 2002) and permanently following surgical bilateral vestibular damage (Russell et al., 2003). Moreover hippocampal theta rhythm, a large amplitude electroencephalogram (EEG) oscillation associated with combining and coordinating the firing of hippocampal place cells during movement and navigation was also disrupted following bilateral vestibular damage in animals (Buzsáki, 2005; Neo et al., 2012; Smith et al., 2013). Additionally, Taube and colleagues demonstrated that the firing of head direction cells in the postsubiculum and the anterior thalamus could be degraded following vestibular damage in rodents (Stackman and Taube, 1997; Stackman et al., 2002; Yoder and

Taube, 2009). More recently, Jacob, Poucet, Liberge, Save and Sargolini, (2014) temporarily abolished theta oscillations in the medial entorhinal cortex (using intratympanic injections) and found that this resulted in a disorganisation of grid cell firing. Taken together, these animal studies highlight the major influence that the vestibular system has over the firing properties of cells whose activity strongly supports spatial encoding and navigation (Jacob et al., 2014).

Artificial Vestibular Stimulation and Memory

If the self-motion information produced by the vestibular system is required for the development of normal spatial memory, then one important question is whether altering or boosting the signals carried by the vestibular system can influence human memory (Smith et al., 2010)? Space exploration provides a unique testing environment for the temporary alteration of vestibular inputs since the contribution of the otolithic sensation of gravity is largely absent (Bigelow & Agrawal, 2015). Although the cognitive-effects of micro-gravity have been variable, some impairments relating to visuospatial functions which draw on memory processes (e.g. pointing to memorised locations with your eyes closed) have been noted (see Bigelow & Agrawal, 2015; Grabherr & Mast, 2010 and Oman, 2016 for reviews). Importantly, these findings support the studies of vestibular dysfunction described above but also extend them by demonstrating temporarily reduced memory performance (e.g. larger errors in pointing) amongst healthy individuals during a transition period which parallels that of patients who have recently underdone vestibular lesioning, but without some of the potentially confounding disturbances (e.g. hearing loss, ongoing vertigo). Nevertheless, other non-vestibular factors such as stress and sleep deprivation could have contributed to the cognitive impairments observed within this highly trained population (Grabherr & Mast, 2010).

Experimental techniques are also available to enable researchers to study the effects of increased or unusual (artificial) vestibular stimulation in a more controlled manner. Table 1.2 provides a breakdown of the most frequently used methods of stimulation in cognitive psychology. Although these techniques were originally intended to aid clinical diagnosis, they are now frequently applied in research contexts due to their safe, inexpensive, non-invasive and simple application (Fitzpatrick & Day, 2004; Palla & Lenggenhager, 2014; Utz, Dimova, Oppenländer, & Kerkhoff, 2010).

Table 1.2
Methods of Vestibular Stimulation Used in Cognitive Research (based on reviews by Lopez, Blanke & Mast, 2012 and Palla & Lenggenhager, 2014).

Technique	Mechanism of Action	Predominantly Activated Vestibular Organ
Caloric Vestibular Stimulation Irrigates the external ear canal with warm or cold water/ air.	Thermal energy induces endolymphatic flow within the semicircular canals, thus increasing the firing rate of afferents mainly within the horizontal semicircular canals.	Horizontal semicircular canals (also a weaker response in vertical canals).
Galvanic Vestibular Stimulation Weak electrical currents are applied, often by placing an anode and cathode over the opposite mastoid processes.	Increases the firing rate of vestibular afferents ipsilateral to the cathode and decreases those on the side of the anode (interpreted as an unplanned head movement in space).	Afferents of the otoliths and semicircular canals.
Motion Stimulator Rotatory chairs and linear motion simulators are programmed to approximate natural movement.	Rotational: The head is positioned at different angles relative to the chair rotation axis (i.e. tilting, lateral displacement) to activate different vestibular organs. Linear: Enables testing of the 6-degrees-of-freedom in which a body is able to move (yaw, pitch, roll, surge, heave, sway).	Rotational: horizontal semicircular canals. Linear: otoliths and horizontal semicircular canals.
Auditory Stimulation Presentation of clicks or short-tone bursts through headphones.	Sounds induce the flow of inner ear fluid through movements of the stapes.	Otolith organs (mainly from the saccular receptors).

A small literature exists on the effects of vestibular stimulation on memory. When supra-threshold, the electrical currents elicited by galvanic vestibular stimulation (GVS) can

be used to induce behaviours analogous to mild vestibular deficits. In line with this idea, Dilda, MacDougall, Curthoys and Moore (2012) showed that supra-threshold stimulation significantly interfered with healthy participants' performance on a visuospatial short term memory (match-to-sample) task compared to sub-threshold GVS (no distracting reflexes) and placebo conditions. However, it remains unclear whether the supra-sensory GVS worsened memory indirectly via visual disturbances (i.e. oscillopsia where objects in the visual field appear to oscillate, or nystagmus where the eyes make rapid and uncontrollable movements), or more directly potentially by diverting cognitive resources away from the task and towards reconciling the mismatching inputs from the vestibular, visual and proprioceptive systems (Bigelow & Agrawal, 2015).

Of more therapeutic relevance, is the finding that visual memory can also be enhanced by vestibular stimulation. Bächtold et al. (2001) improved healthy participants' performance using water-based caloric vestibular stimulation (CVS). When the currents are constantly warm, CVS can be used to activate the ipsilateral hemisphere, while cold currents activate the contralateral hemisphere (Miller & Ngo, 2007). A first experiment showed that unilateral (cold water) left ear stimulation increased spatial memory for the locations that objects were presented at and a second demonstrated enhanced verbal memory for visually presented words after right ear stimulation. Bächtold et al. concluded (in a post-hoc manner) that CVS had improved visual memory by facilitating cerebral blood flow to the contralateral brain structures required for these spatial and verbal cognitive processes.

Although these findings are promising, it should be noted that water-based CVS can also induce side-effects of nausea and visual disturbance (nystagmus) which can distort the impact of vestibular inputs on cognition. To avoid these limitations, Wilkinson, Nicholls, Pattenden, Kilduff and Milberg (2008) applied small sub-sensory GVS currents to participants whilst they learnt the names of several faces. Participants who had received

anodal and cathodal stochastic (noise-enhanced) GVS applied to the left and right vestibular nerves respectively, later recalled details about the faces more quickly than those who had received the opposite configuration or non-noisy or sham stimulation. More recently, Ghaheri, Ghahraman, Jarollahi and Jalaie (2014) tested the performance of 60 women on the Corsi Block test (Kessels et al., 2000) before and after stimulation. Those who received sub-sensory GVS again showed a significant improvement across multiple performance measures (span, total score, learning score), relative to those who received sham stimulation.

Taken together these findings suggest that memory processes can be affected by increased/ unusual vestibular activity, sometimes with a beneficial effect. However, the fact that these techniques stimulate distinct aspects of the vestibular system and have been differentially applied (e.g. stimulation configuration, intensity, during different phases of the memory task), means further exploration is still required before conclusions can be made about the demonstrability and mechanism of effect (Bigelow & Agrawal, 2015).

Allied Vestibular-Cognitive Effects

Although existing literature (particularly biological) has tended to focus on vestibular influences on memory, evidence has shown that other cognitive processes may also be impacted or reduced by altered vestibular inputs. These findings are important to consider since they provide further demonstrations of the impact that vestibular signals can exert on cognitive function beyond the reflexive tasks with which they are typically associated. Moreover, given that memory performance is partly determined by other cognitive processes (e.g. attentional, perceptual, executive function, motivational capacities), these results will also offer some insight into how vestibular inputs might influence memory performance. This section provides an overview of the strongest evidence and discusses the inferences that can be gained from these studies.

Visuospatial abilities. In line with the spatial memory studies described above,

other cognitive tasks which rely on visuospatial abilities including mental imagery have also been associated with vestibular loss. These tasks tend to involve participants viewing similar sets of stimuli which have been rotated to varying degrees and mentally translating them to determine whether or not they are the same image (Bigelow & Agrawal, 2015; Smith & Zheng, 2013). Rotations involving human figures, two/ three-dimensional objects and familiar and unfamiliar environments have all been shown to be altered by vestibular hypofunction (Bigelow et al., 2015b; Grabherr, Cuffel, Guyot & Mast, 2011; Péruch et al., 2011; Wallwork, Butler & Moseley, 2013). Mental rotation abilities, particularly those relating to human figures (egocentric – own bodily reference frame), have also been facilitated by vestibular stimulation in healthy participants (Falconer & Mast, 2012; van Elk & Blanke, 2014). Vestibular signals may thus be particularly useful in building internal spatial representations when our own body becomes the object of spatial cognition (Lenggenhager & Lopez, 2015).

A few studies have indicated that the visuospatial deficits associated with vestibular dysfunction may also impact numerical cognition (Smith, 2012). The earliest such report demonstrated that patients with vertigo exhibited a consistent error of displacing decades on a task which required counting backwards by two (Risey & Briner, 1990). Later, Yardley et al. (2002) revealed impaired mental arithmetic performance amongst patients with vestibular dysfunction whilst they continuously monitored their orientation. Following evidence which suggests that numerical representation is tightly linked to the processing of spatial information (i.e. smaller numbers tend to be associated with the left side of space and larger numbers with the right), Hartmann, Grabherr and Mast (2012) later used vestibular stimulation (whole-body rotations) to encourage the generation of smaller (with leftward and downward movements) and larger numbers (with rightward and downward movements).

These studies provide initial evidence that vestibular contributions to visuospatial abilities are likely to extend to other less obvious aspects of cognition which are represented spatially.

Further insights can also be gained from hemispatial neglect, a syndrome characterised by a visuospatial deficit of failing to acknowledge stimuli arising spatially contralateral to the side of a cortical lesion (Hanes & McCollum, 2006). Cognitive deficits relating to awareness of extrapersonal space (example measures include target cancellation, figure copying and line bisection) have been temporarily remediated using CVS (Cappa, Sterzi, Vallar & Bisiach, 1987) and GVS (Wilkinson, Zubko, DeGutis, Milberg & Potter, 2010; Utz, Keller, Kardinal & Kerkhoff, 2011). Moreover, Rode and Perin (1994) showed transient relief from neglect relating to mental representations of space using CVS. The authors asked participants to mentally evoke a map of France and to name towns on the left and right side of the vertical axis; representational neglect was evidenced by the worsened recall for the left relative to the right side. When CVS was delivered to the neglected side recall for items on the left side was then facilitated. This effect was thought to have occurred because CVS had produced an ipsilesional stimulus to counteract the contralesional bias underlying the participants' internal representations. Importantly, these studies show that vestibular stimulation can elicit beneficial effects in neurological conditions where mental representations of space are disturbed by inducing lateralised attentional shifts (via asymmetric modulation of the vestibular nerves) (Hanes & McCollum, 2006; Karnath & Dieterich, 2006; Wilkinson et al., 2014). Further research is now required to determine whether these improvements might extend to other cognitive processes or neurological conditions involving spatial representations.

Taken together, these findings suggest that the vestibular system is likely to make a significant and specialised contribution to how the mind organises and represents two-and three dimensional space. Thus when vestibular inputs are altered by dysfunction or

stimulation, cognitive processes such as spatial memory and navigation which rely on these mental representations to determine the position of the self or an external object in three-dimensional space might also be affected (Bigelow & Agrawal, 2015). One interpretation of these effects relates to the cortical networks that are activated by the vestibular system, since several of the brain regions which respond to vestibular input are also implicated in visuospatial processing (e.g. hippocampus, insula, superior temporal gyrus, inferior parietal lobule, temporo-parietal junction, ventral intraparietal cortex and posterior parietal cortex) (Bigelow & Agrawal, 2015; Blanke et al., 2005; Lopez et al., 2012; Smith, 2012). Thus when the vestibular system is disturbed, a cascade of neural changes are likely to occur (throughout the vestibular cortical network) resulting in a range of impairments to visuospatial aspects of cognition such as navigation, mental imagery and memory (Smith et al., 2010).

Attentional capacity. Another line of vestibular research has investigated cognitive function using dual-task paradigms where participants are asked to engage in a postural exercise (e.g. minimise body sway while standing) at the same time as a cognitive task (Hanes & McCollum, 2006). Performance is then compared to a baseline level of function where each task was completed individually (Bigelow & Agrawal, 2015). Studies with healthy individuals have shown that cognitive functioning declines with increasing postural demands (see Bigelow & Agrawal, 2015; Smith & Zheng, 2013 for reviews), suggesting balance maintenance is a complex process (rather than a simple reflex) that draws on cognitive resources which when depleted may have a knock-on effect on processes such as memory (Redfern et al., 2002). These interference effects were especially prominent within elderly participants, who are generally more vulnerable to vestibular dysfunction as well as cognitive deterioration (Furman, Müller, Redfern & Jennings, 2003; Redfern et al., 2002). Moreover, patients with a range of vestibular disorders have exhibited impaired performance across several cognitive tasks (including basic tests of processing speed). Importantly, these

interference effects even occurred when the cognitive tasks were completed under minimal postural demands (i.e. when seated); therefore reducing concerns that these cognitive impairments were driven by anxiety-related fears of falling within the more challenging postural conditions, as opposed to the lack of available attentional resources (see Bigelow & Agrawal, 2015; Hanes & McCollum, 2006; Smith & Zheng, 2013 for reviews).

These dual-task effects provide tentative evidence of functional connectivity between the vestibular and attentional systems by showing that balance maintenance and various cognitive domains do not operate in isolation, particularly in individuals with vestibular dysfunction (Hanes & McCollum, 2006). However, the mechanisms underlying these findings remain unclear. Yardley et al. (2001) aimed to address this by exploring whether the reported dual-task effects were due to general capacity limitations (i.e. postural instability reduces the availability of spare attentional resources and this interference induces widespread cognitive impairment), or competition for specific spatial processing resources (i.e. disturbing the spatial reference through vestibular disorder or a postural challenge has a more direct effect on specific spatial cognitive tasks) (Hanes & McCollum, 2006). In line with previous research, reaction times (RT) were greater as the postural demands increased across tasks with low (simple RT) and high (choice RT) mental load and on both spatial and non-spatial tasks, an effect that was greater in vestibular patients than controls. These results would suggest that postural performance is not particularly affected by the content of the co-occurring mental activity (spatial versus non-spatial), but relates to general capacity limitations caused by the increased attentional demands of the balancing tasks (although see Maylor, Allison & Wing, 2001 for a contrasting report). If correct, then the aforementioned reports of vestibular contributions to memory processing may reflect a widespread gain (vestibular stimulation)/ general depletion of attentional resources (vestibular dysfunction)

which extends to multiple cognitive functions (e.g. attention, information processing), as opposed to only being restricted to visuospatial memory functions.

Connections with Psychiatric Disorders

In addition to the vestibular-cognitive connections described above, clinical reports also highlight a well-established association between vestibular dysfunction and psychiatric symptoms including anxiety, panic and depression (see Balaban & Thayer, 2001; Gurvich et al., 2013; Jacob & Furman, 2001 for reviews). Patients with vestibular dysfunction are more likely to suffer from anxiety and depressive disorders (Lahman et al., 2014) and individuals with psychiatric conditions can often complain of feeling dizzy and unsteady (Eagger, Luxon, Davies, Coelho & Ron, 1992). More generally, the presence of vestibular damage has been shown to significantly reduce quality of life and present substantial economic burdens related to unproductivity (Sun, Ward, Semenov, Carey & Della Santina, 2014). This bi-directional association must be taken into account when considering vestibular contributions to memory, since psychiatric symptoms occurring without vestibular dysfunction can also induce cognitive impairments (e.g. attention and working memory deficits in schizophrenia or excessive attention to threatening stimuli in panic disorder; Millan et al., 2012), meaning any cognitive deficits could potentially be psychological and/ or vestibular in origin (Hanes & McCollum, 2006; Smith & Zheng, 2013; Smith, 2016).

By virtue of its shared neural pathways, vestibular signals can contribute to a variety of autonomic and higher level functions (Gurvich et al., 2013). Consequently, impairments to the vestibular system are likely to cause a multitude of changes in cognition, mood and wellbeing which are often difficult to disentangle from one another (Smith, 2012). In fact, the PBN provides a direct link between the vestibular system and limbic networks (including the amygdala, locus coeruleus, hypothalamus and prefrontal cortex) that are involved in emotional processing and implicated in psychiatric illness (Gurvich et al., 2013). Vestibular-

hippocampal interactions could also induce psychiatric symptoms since this region is implicated in both spatial and emotional processing (Smith & Zheng, 2013). In line with this idea, Bremner et al. (2000) previously demonstrated reduced hippocampal volumes amongst individuals with depression, and Tillfors, Furmark, Marteinsdottir and Fredrikson (2002) showed that patients with social phobias had increased cerebral blood flow to the anterior and middle hippocampal regions during periods of stress and anxiety. These studies raise the possibility that the reduced hippocampal volumes and associated cognitive effects mentioned previously (Brandt et al., 2005; Kremmyda et al., 2016; Schautzer et al., 2003) could have had a psychiatric or a vestibular cause.

Despite a number of recent epidemiological investigations into the association between vestibular dysfunction and concomitant psychiatric and cognitive impairments (Bigelow, Semenov, du Lac, Hoffman & Agrawal., 2015; Harun, Bigelow & Agrawal, 2016), current research is still unable to definitively determine whether vestibular-cognitive interactions (including memory processes) occur as a direct response to damaged vestibular signals, or via indirect mechanisms such as psychiatric distress (Bigelow & Agrawal, 2015). Continued research is therefore needed to build upon the theoretical underpinnings of vestibular contributions to cognition and in turn improve clinical practices for vestibular patients (Bigelow et al., 2015a; Smith, 2016).

Chapter Summary

The preceding discussion presented clinical and experimental evidence demonstrating the relevance of vestibular inputs beyond postural and oculomotor control to a variety of higher-level functions, especially memory. The ascending vestibular pathways project diffusely to areas involved in spatial memory and navigation such as the hippocampus, entorhinal cortex and the thalamus (Hitier et al., 2014). Moreover, when the vestibular system is disturbed spatial memory impairments and structural changes to the hippocampus have

been observed, suggesting that the self-motion and postural information provided by the vestibular system is somehow relevant for visuospatial memory. Additionally, a small number of studies with healthy adults have shown that conditions of microgravity (where otolith inputs are absent) can induce memory-related errors (Oman, 2006; Watt, 1997), whereas artificially stimulating the vestibular system with thermal or electric currents could facilitate memory (Bächtold et al., 2001; Wilkinson, 2008).

Although our knowledge of vestibular-memory interactions has continued to develop, psychological accounts of why or how vestibular signals are incorporated within memory representations remain very limited (Hanes & McCollum, 2006). That is, we know that the two systems are connected and interact but the type and nature of this interaction remains unexplained at the psychological level. A growing body of evidence has continued to report upon the far-reaching effects of artificially altered or damaged vestibular signals on cognition, particularly visuospatial processes where there might be a need to internally reference external space. What is more, balance maintenance appears to be a complex higher-level process which draws upon cognitive resources and thus can impede attention and concentration. Importantly, these vestibular-cognitive effects do not necessarily appear to be generalised, with some cognitive processes remaining unaffected by the presence or absence of vestibular signals (Hanes & McCollum, 2006). Despite some methodological limitations, these studies offer relevant insights into the nature of vestibular interactions with memory. Both the spatial information produced by the vestibular system and the attentional demands of maintaining balance appear to be important, but further investigation is still required to better characterise the connection between the vestibular and memory systems and to understand the theoretical underpinnings of vestibular contributions to memory processing. The bi-directional association between vestibular dysfunction and psychiatric symptoms (as well as more general wellbeing) has previously complicated these mechanistic inferences,

since psychiatric morbidity is also associated with cognitive deterioration (see Smith & Zheng, 2013 for a review).

Current Research Questions

This thesis aims to build upon the current understanding of vestibular contributions to memory. The extent to which vestibular dysfunction impacts memory is still unclear and the mechanisms underlying these effects are also poorly understood. Theoretically, there are at least two ways in which one can explore vestibular contributions to memory: by looking at the profile of memory impairment (alongside other relevant symptoms) in patients with vestibular dysfunction (i), and by testing whether modulating the vestibular system via artificial vestibular stimulation can change memory performance (ii). The former gives an indication of which memory (and other co-morbid) processes might be reliant on vestibular signals, while the latter tells us whether the presence of unusual or increased vestibular inputs could potentially modify specific aspects of memory processing (Smith et al., 2010). This thesis incorporated both approaches and the next section will introduce the four experimental chapters and the paradigms they each applied.

Chapter 2 examines the effects of vestibular dysfunction on memory and other relevant cognitive functions. Particular focus is placed on visuospatial memory but more general aspects of cognition and wellbeing were also considered to better understand the reach of the system and contextualise any memory-related effects. The chapter also explored whether vestibular-cognitive effects occur due to vestibular dysfunction or as an indirect consequence of psychiatric/ fatigue symptoms, with the aim of moving closer towards a psychological model of how and why vestibular signals influence memory. A group of neuro-otology outpatients with varying levels of dysfunction performed a comprehensive neuropsychological battery (alongside balance function testing) from which the prevalence of impairment was calculated. Structural equation modeling (SEM) was then used to estimate

whether cognitive deficits were likely to be directly related to vestibular damage or to arise as a secondary consequence of psychiatric/ fatigue symptoms. These analyses helped to determine whether vestibular signals themselves are necessary for memory function, or they express themselves more indirectly via psychiatric disturbance.

Once Chapter 2 had identified relevant cognitive, psychiatric and fatigue symptoms which were reliant on vestibular input, Chapters 3 and 4 then investigate whether these symptoms can be remediated using CVS in a neurological sample with memory deficits and unmet therapeutic needs. The rationale for this study was based on recent evidence that CVS can modulate multiple brain regions and neurotransmitters simultaneously, often resulting in beneficial alterations to cognitive, psychiatric and autonomic processes across both healthy and clinical populations (Bottini & Gandola, 2015). Behavioural (Chapter 3) and electrophysiological (Chapter 4) measures were implemented to further investigate which specific aspects of cognition (mainly visual memory) and wellbeing were affected by vestibular signals within a novel patient group (TBI). As in Chapter 2, the results also explored whether any memory-related changes were dependent on concurrent alterations in psychiatric/ fatigue symptomology albeit using a different experimental approach.

Finally, Chapter 5 presents a series of experiments designed to explore one putative psychological mechanism by which visual memory might make use of vestibular signals. More specifically, by applying GVS to a sample of healthy individuals under varying conditions this chapter attempts to determine whether memory function can be modulated, and if so is the effect being driven by the specific self-motion signal content being incorporated within individual memory representations (to mark one visual event from another), or a more generalised enhancement in arousal which leads to non-specific cognitive gains (Wilkinson et al., 2008). These experiments are significant since further knowledge of

the functional role of vestibular inputs will aid theoretical understanding and help to harness the potentially therapeutic effects of vestibular stimulation.

In summary, the current thesis presents three strands of research that investigate whether specific visual memory processes are affected by the vestibular system and the manner in which this happens. The paradigms and research methods utilised will be introduced in more detail in the relevant upcoming chapters.

Chapter 2
Neuropsychiatric Outcomes in Individuals with Vestibular Dysfunction.

Chapter 1 reviewed a number of studies evidencing an association between the vestibular and cognitive systems whereby cognitive processing, particularly visuospatial memory, was affected by alterations in vestibular inputs (vestibular-cognitive effects). This chapter aims to build upon existing knowledge by examining what happens to specific visual memory processes when the vestibular system becomes dysfunctional. Other cognitive functions (attention and information processing) and aspects of wellbeing (psychiatric, fatigue disturbances) known to affect memory were also monitored to characterise any relevant effects. Prevalence estimates were produced to highlight which neuropsychiatric outcomes are likely to be affected by vestibular dysfunction. Structural equation modeling (SEM) techniques were also employed to investigate the mechanisms behind any potential vestibular-cognitive effects by testing whether cognitive deficits occur as a direct consequence of vestibular dysfunction, or via secondary co-morbid symptoms.

The following sections will first highlight the importance and pervasiveness of the vestibular system by describing the disabling neuro-otological symptoms associated with several common vestibular disorders. The relevance of vestibular inputs to cognition will then be evidenced using studies which link vestibular dysfunction to cognitive impairment, particularly spatial memory disturbances. The mechanisms underlying these effects will then be considered and evidence supporting potential direct (i.e. vestibular dysfunction causes cognitive impairment) and indirect (i.e. vestibular dysfunction affects cognitive functioning indirectly via comorbid symptoms) pathways will be reviewed, before the experimental approach is presented.

Vestibular Dysfunction

To understand the impact of vestibular dysfunction on cognition, one must first consider what vestibular dysfunction actually entails in terms of the neuro-otological symptoms patients present with and the pathophysiology of common vestibular syndromes. This is because the severity of symptoms and extensive neurological changes experienced by these patients can offer important insights into why and how cognitive losses might arise following vestibular dysfunction.

When the vestibular system is damaged or disturbed the most immediate symptoms are unsteadiness and vertigo. These terms describe an unpleasant disturbance of spatial orientation and/ or the illusory perception of movement of the body and/ or the surroundings (Brandt & Strupp, 2005). Vestibular symptoms are among the most frequent complaints in medical settings (Brandt, Zwergal & Strupp, 2009; Saber et al., 2013). In a survey of over 30,000 adults, around 17% suffered from dizziness and vertigo, this rose to 39% in elderly individuals (aged ≥80) (see Brandt & Strupp, 2005). Balance problems remain an important health concern since they increase with age and are associated with a greater falls risk (often leading to physical injury and mortality; Semenov, Bigelow, Xue, du Lac & Agrawal, 2016). Moreover, because the effects of vestibular dysfunction are so pervasive, these problems often lead to general functional decline (encompassing cognition and wellbeing) and pose a significant burden to society (Oghalai, Manolidis, Barth, Stewart & Jenkins, 2000).

There are many different types of vestibular malady covering multiple sensory experiences with various aetiologies and pathogenesis. One distinction routinely made by clinicians is whether the dysfunction concerns the central or peripheral vestibular component (or both) (Furman & Whitney, 2000). Recall that the peripheral system consists of two bilateral labyrinths that work in partnership with one another. Each contains three semi-

circular canals which detect rotational head movement as well as the otolith organs (utricle and saccule) which perceive verticality (Thompson & Amedee, 2009). When stimulated, vestibular information leaves each labyrinth and is projected to the central vestibular component (Smith, 1997). The central system is formed of the vestibular nuclear complex and works to maintain our sense of balance by integrating inputs from the peripheral vestibular system with information from other sensory modalities including vision and somatosensation (Furman & Whitney, 2000).

Overall, patients with central vestibular damage tend to have worse outcomes than those with peripheral disorders (Konrad et al., 1992). There are several explanations as to why this might be, firstly the central vestibular system houses the vestibulo-cerebellum which can adapt to damage and respond to sensorimotor demands from the visual and somatosensory centres (Helmchen et al., 2009). When these central structures are damaged this central recalibration cannot take place meaning vestibular compensation is impeded (Furman, Balaban & Pollack, 1997; Baier, Muller, Rhode, & Dieterich, 2015). More generally, central disorders are not diagnosed as easily as peripheral disorders (since they are often accompanied by other neurologic symptoms), and thus these patients must often wait longer to receive a relevant referral and reach treatment (Furman, Marcus & Balaban, 2013). Additionally, when central vestibular disturbance occurs following a TBI or stroke, it is highly likely that other brain structures will have also sustained damage thus impacting general brain function (Shepard, Telian, Smith-Wheelock & Raj, 1993).

Table 2.1
Common Syndromes of Vestibular Dysfunction (based on a review by Thompson & Amedee, 2009).

Syndrome	**Presentation and Pathophysiology**
Benign paroxysmal positional vertigo (BPPV)	Calcium carbonate crystals become dislodged leading to brief spells of vertigo triggered by head movements.
Phobic postural vertigo	Situationally triggered panic attacks, frequently including vertigo with unsteadiness (Brandt, 1991).
Central vestibular lesions	Primarily involves damage to the vestibular nuclear complex and cerebellum (e.g. via brain stem strokes, head trauma, cerebellar degeneration) resulting in ataxia and disequilibrium.
Vestibular migraine (VM)	Episodic disequilibrium (e.g. vertigo, unsteadiness, visual disturbance) accompanied by migraine-related symptoms (e.g. headache, photophobia, phonophobia). Pathophysiology remains incomplete but spreading cortical depression, neurochemical modulation and the reciprocal connections between central vestibular and trigeminal nuclei are likely to be implicated (Furman et al., 2013; Neuhauser & Lempert, 2009).
Menière's disease (MD)	Malabsorption of fluid in the endolymph sac leads to intermittent attacks of vertigo alongside fluctuating tinnitus and hearing loss.
Bilateral vestibulopathy	Impaired or lost function of both peripheral labyrinths or of the eight nerves. Key symptoms are oscillopsia and unsteadiness.
Psychogenic vertigo	Recurring or persistent symptoms of dizziness that are inconsistent with organic vestibular disease and are likely to have a psychological origin.
Vestibular paroxysmia	Neurovascular cross-compression of the eight cranial nerve causing short recurring attacks of vertigo.

Seventy five percent of all patients presenting with balance problems in a neurological dizziness unit will fall into one of eight common syndromes of central and/ or peripheral damage shown in Table 2.1 (Brandt & Strupp, 2005). Damage to the peripheral structures routinely leaves patients with nausea, vertigo and a sense of falling. The most frequent disorders include benign paroxysmal positional vertigo (BPPV), vestibular neuritis and Meniere's disease (MD) (Brandt & Steddin, 1993). Conversely, central damage arising from lesions to the neuronal connections between the vestibular nuclei and cortical structures (e.g.

the brainstem, cerebellum, and thalamus), often results in disequilibrium and ataxia. Central disorders most commonly take the form of vestibular migraine (VM) (although peripheral causes may also be implicated; Dieterich & Brandt, 1999), but can also result from a head trauma, ischemic disease and degenerative disorders that affect the cerebellum (Furman & Whitney, 2000; Thompson & Amedee, 2009). Following the introduction of diagnostic criteria for VM (International Classification of Headache Disorders 2nd edition; Olesen & Steiner, 2004), recent evidence suggests that VM is the most prevalent vestibular disorder (Cherchi & Hain, 2011) with approximately 3.2% of the general population estimated to have the condition (Lempert & Nehauser, 2009). Moreover, given that VM is considered to be under-recognised, this statistic is likely to underestimate the true prevalence (Swaminathan & Smith, 2015).

Neuropsychiatric Symptoms

Although the most immediately striking effects of vestibular dysfunction are oscillopsia and ataxia, damage to the system often results in a complex constellation of symptoms including cognitive impairment (Smith & Zheng, 2013). Clinicians have long reported an anecdotal connection between vestibular dysfunction and cognitive deterioration (Hanes & McCollum, 2006), and patients frequently complain of problems with attending to and remembering information (see patient forums such as, www.mvertigo.org for examples). An increasing number of publications have therefore explored these vestibular-cognitive effects. One of the first showed that out of 102 patients with perilymph fistula syndrome (vestibular disease caused by mild head trauma), 85% self-reported memory loss and 80% reported confusion (Grimm et al., 1989). Black, Pesznecker and Stallings (2004) later found that 22 out of 33 patients with permanent gentamicin-induced vestibulotoxicity self-reported memory problems. More recently, Bigelow et al. (2015a) revealed an eightfold increased odds of self-reporting “serious difficulty concentrating or remembering” in individuals with

vestibular vertigo, and Bisdorff, Jacobs, d'Incau and Schuller (2015) demonstrated that vestibular patients perceived themselves as having significantly more memory impairments than controls across most domains of forgetfulness.

Although these self-reported outcomes can only provide indirect inferences, some experiments have been able to provide more objective evidence of vestibular contributions to cognition (Hanes & McCollum, 2006). Chapter 1 provided a more detailed review of these studies but to recap, patients with a variety of vestibular syndromes have shown cognitive deficiencies across several domains including: ordering information (Risey & Briner, 1990); dual processing (e.g. learning new information while retaining previous items in memory; Grimm et al., 1989); simple RTs (Redfern, Talkowski, Jennings & Furman, 2004); spatial memory (Brandt et al., 2005; Kremmyda et al., 2016; Schautzer et al., 2003; Previc, Krueger, Ross, Roman, & Siegel, 2014); navigation (Guidetti et al., 2008; Péruch et al., 1999); and mental imagery (Candidi et al., 2013; Grabherr et al., 2011).

Importantly, cognitive deficiencies were not present across all cognitive tests or vestibular maladies. While some cognitive functions did not appear to differentiate patients and controls, others showed a reliable deficit which was pertinent within particular vestibular syndromes (Hanes & McCollum, 2006). These findings suggest that specific cognitive processes and patient groups may be more vulnerable to vestibular dysfunction. For example, reduced cognitive performance in activities related to spatial memory and navigation were more commonly reported, with vestibular projections to cortical networks involved in memory and visuospatial cognition (e.g. the insula, hippocampus and temporo-parietal junction) thought to contribute to the effects (Hitier et al., 2014; Smith & Zheng, 2013). Distinctions have also been made between simpler tasks requiring less attentional resources (e.g. immediate recall and comprehension) and those tasks with additional cognitive demands (e.g. counting backwards, organising multiple sources of information) which appear to show

more impairment (Grimm et al., 1989; Redfern et al., 2004; Risey & Briner, 1990). If balance maintenance requires attention, then the increased competition for attentional resources following vestibular dysfunction could explain why simpler tasks were managed, while complex cognitive operations (for which attentional resources are lacking) were more often impaired (Bigelow & Agrawal, 2015; Bisdorff et al., 2015). Thus, while studies do indicate a vestibular-cognitive effect, current understanding about which specific cognitive processes are compromised by vestibular dysfunction remains incomplete.

Although the impact of vestibular dysfunction on cognition remains unclear, there is some consensus that the effects of vestibular inputs on memory processes are likely to be among the most pervasive (Gurvich et al., 2013). This study therefore investigated the cognitive functioning of vestibular-deficient individuals across a broad battery of objective standardised tests which are capable of delimiting more specific cognitive impairments, particularly relating to visuospatial memory. These investigations should help to elucidate the reach of vestibular impairments to different higher level processes, as well as the specificity of vestibular signals to particular cognitive functions (e.g. spatial memory) (Bigelow et al., 2015b; Hanes & McCollum, 2006). Surprisingly, there has been little effort to do so, with the focus either being placed on a single cognitive process, self-reported outcomes, or small samples of patients with specific vestibular syndromes which may not generalise to vestibular patients at large.

Another important question which remains unanswered is by what mechanism vestibular dysfunction relates to cognitive impairments, especially those associated with memory? The literature suggests two theoretical pathways (see Figure 2.1). Vestibular dysfunction either exerts a direct effect on cognitive functioning such that cognitive operations are directly reliant on the content of vestibular signals, or an indirect effect through comorbid symptoms/ changes which accompany vestibular dysfunction. Researchers

need to decide between the alternatives if a psychological model of vestibular-cognitive effects is to be generated.

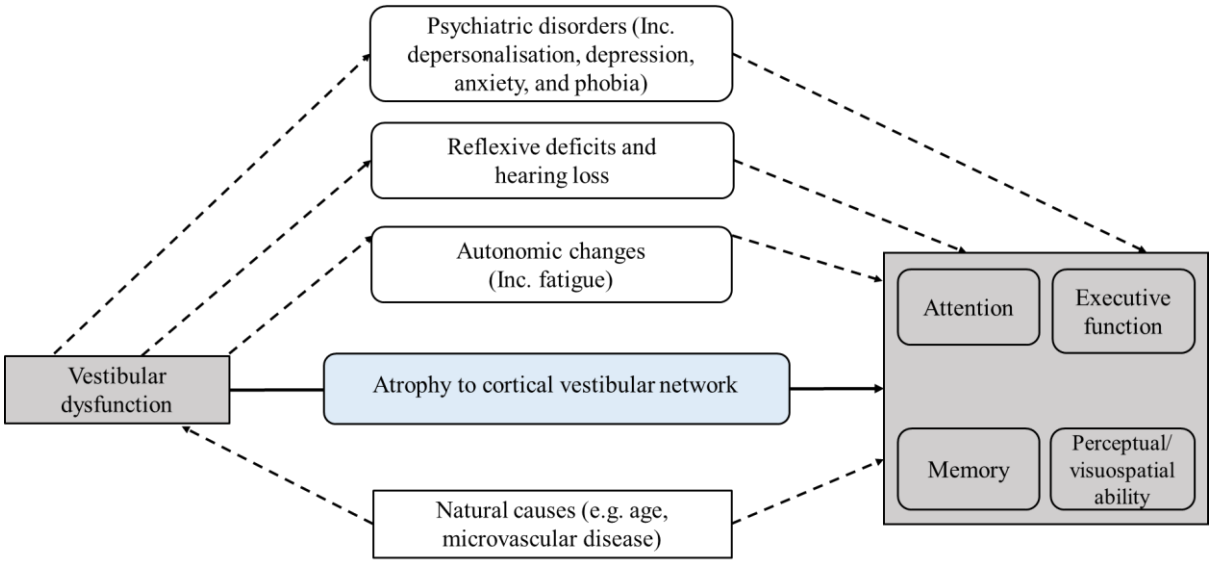


Figure 2.1. Illustration of potential direct (blocked lines) and indirect (dashed lines) pathways for the mechanism of impairment in those cognitive functions which have been most commonly studied following vestibular dysfunction (adapted from Bigelow & Agrawal, 2015).

Direct Vestibular-Cognitive Pathway

The basis of the direct link is evidenced by neural pathways which pass vestibular signals from the brain stem nuclei and thalamus to areas of the cortex that are associated with various cognitive processes. Multiple regions of the human cerebral cortex are responsive to vestibular stimulation (primarily via the thalamus) including the sylvian fissure, insula, retroinsular cortex, fronto-parietal operculum, superior temporal gyrus, and cingulate cortex (Lopez et al., 2012). These areas are involved in at least some cognitive operations and thus provide an anatomical substrate for a direct contribution of vestibular inputs to cognition (Bigelow & Agrawal, 2015).

Key to the direct vestibular-cognitive pathway, are those neural pathways that connect with the hippocampus (see Figure 1.3, Chapter 1), which has been shown to adapt in response to vestibular signals. More specifically, when partial or complete vestibular loss is sustained,

human hippocampal volumes are reduced relative to matched control samples (unilateral loss, zu Eulenburg et al., 2010; residual bilateral loss, Kremmyda et al., 2016; bilateral loss, Brandt et al., 2005 and Schautzer et al., 2003). The hippocampus also undergoes changes within healthy individuals who regularly partake in unusual spatial experiences (e.g. dancers, slackliners, and taxi-drivers), where the self-motion information contained within vestibular signals is likely to be relevant for referencing their position within the environment (Hüfner et al., 2010; Nigmatullina, Hellyer, Nachev, Sharp & Seemungal, 2013; Woolett & Maguire, 2011). Through the use of animal studies, researchers have also been able to evidence an association between vestibular damage and disturbances to the firing rates of hippocampal place cells (Russell et al., 2003; Stackman et al., 2002) and hippocampal theta rhythm (reduced power and corrupted waveform; Russell et al., 2006), both of which help to produce a neural representation of physical space, that is, a cognitive map (Buzsáki & Moser, 2013; O'Keefe & Nadel, 1978). Taken together these findings indicate that the self-motion information contained within vestibular signals modulates hippocampal function. This is significant since the hippocampus is known to play a prominent role in several cognitive processes, particularly memory and navigation (Maguire & Mullally, 2013). Damage to vestibular cortical networks (including the hippocampus) could thus provide a direct pathway for the cognitive impairments, most notably memory, that have been observed in patients with vestibular dysfunction (Bigelow & Agrawal, 2015).

Importantly, because vestibular information is projected to multiple areas of the cerebral cortex, these hippocampal alterations are likely to be part of a complex cascade of neural changes throughout the neocortex and limbic system (Smith et al., 2010). For example, Liu et al. (2003) showed that peripheral vestibular lesions reduced the activity of neurochemical receptors associated with memory and learning within the entorhinal and perirhinal cortices. Models have theorised that the projection of vestibular inputs to grid cells

within the entorhinal cortex may then be used to set the dimensions of place cells in the hippocampus (McNaughton, Battaglia, Jensen, Moser & Moser 2006). Hanes and McCollum (2006) suggest that because of the way that the human brain is likely to compute cognitive operations, these diverse vestibular projections could impact multiple cognitive functions. That is, if the human brain carries out cognitive processes within a relational framework that resembles extra-personal physical space, then many cognitive operations are likely to be directly dependent on the spatial information provided by vestibular inputs for optimal performance.

As mentioned previously (and continued below), the direct pathway is challenged by the links that have been demonstrated between vestibular dysfunction and psychiatric disturbances (Smith et al., 2010). While it remains unethical to directly manipulate the influence of psychiatric comorbidities on vestibular contributions to cognition in humans, there is some evidence from animals to disentangle these indirect effects (Gresty & Golding, 2009; Smith & Zheng, 2013). Across several studies, rats with bilateral vestibular damage who showed increased anxiety (indicated by the avoidance of brightly-lit areas) on the black and white box test (assesses exploration of light and dark areas) were given anxiolytic drugs to reduce their anxiety-like behaviours. While the drug appeared to reduce their anxiety, it had no effect on their performance on a separate spatial maze task (Machado et al., 2012; Zheng, Cheung & Smith, 2012). At least in animals, vestibular contributions to spatial memory seem to be independent of anxiety, indicating a direct vestibular-cognitive pathway. However, the section below indicates that these associations are likely to be more complicated within humans.

Indirect Vestibular-Cognitive Pathway

Psychiatric and fatigue/ sleep symptoms. As can be seen in Figure 2.1, several other symptoms can coincide with vestibular dysfunction which could influence cognitive

processes like memory indirectly (Bigelow & Agrawal, 2015). Multiple reports have already established high but variable rates (30-68.25%) of comorbid psychiatric symptoms amongst patients with vestibular dysfunction (see Table 2.2). Anxiety, panic and phobic disorders appear to be particularly prevalent relative to the general population (Gurvich et al., 2013). Moreover, there is evidence to suggest these psychiatric symptoms exert a substantial influence over interactions between the vestibular and cognitive systems. For example, Bisdorff, et al. (2015) found that anxiety and low general health perceptions were better predictors of subjective memory complaints than the perceived intensity of vertigo symptoms. Bigelow et al. (2015a) also showed that combined depression, anxiety and panic symptoms accounted for a third of the effect of vestibular vertigo on self-rated difficulties remembering or concentrating. However, it should be noted that these studies assessed self-reported cognitive function and thus provide an incomplete account of the connection between the vestibular and cognitive systems (Bisdorff et al., 2015).

Nonetheless, these results suggest that psychiatric disturbances should be taken into account when considering the cognitive complaints of individuals with vestibular dysfunction. Especially since those patients with mixed organic vestibular and psychological symptoms were more likely to have the highest levels of handicap, a lower quality of life and be unresponsive to standard vestibular treatments (Yardley & Redfern, 2001). Given the detrimental impact that these symptoms can have on well-being (and potentially cognition) and the associated costs for healthcare systems, it is important to identify and treat these comorbidities appropriately (Lahmann et al., 2014).

Table 2.2
Reported Prevalence of Psychiatric and Somatic Symptoms in Patients with Vestibular Dysfunction.

Citation	Prevalence Rate	Most Common Symptoms
Eagger et al., 1992.	50% of 54 interviewed patients with peripheral vestibular disorders.	Panic disorder with or without agoraphobia and major depression.
Eckhardt-Henn, Breuer, Thomalske, Hoffmann & Hopf, 2003.	68.3% of 189 patients with organic and/ or psychogenic dizziness.	Anxiety, phobic and somatic disorders.
Eckhardt-Henn et al., 2008.	65.2% of 23 patients with VM; 57.1% of 7 patients with MD; 15% of 20 patients with BPPV; and 22.2% of 18 patients with vestibular neuritis.	Anxiety and phobic disorders.
Gazzola et al., 2009.	55.8% of 120 elderly patients with chronic vestibular dysfunction.	Only geriatric depressive symptoms examined.
Best, Eckhardt-Henn, Tschan & Dieterich, 2009.	Cumulative overall incidence over one year was 67.6% within 68 patients with vestibular vertigo.	Somatoform and anxiety disorders.
Lahmann et al., 2014.	48.8% of 547 interviewed neuro-otology patients.	Anxiety/ phobic, somatoform and affective disorders.
Bigelow et al., 2015a	Self-reported vestibular vertigo resulted in a threefold increased odds of psychiatric morbidity.	Depression and panic disorder.

Note. VM= vestibular migraine; MD= Ménière's disease; BPPV= benign paroxysmal positional vertigo.

Reports of disturbed sleep and fatigue have also continued to emerge on more general measures of wellbeing and psychological health. Yardley, Burgneay, Nazareth and Luxon (1998) revealed that 85.7% of the dizzy patients they assessed reported fatigue symptoms, relative to 33.3% of healthy controls. Mendel, Bergenius and Langius (1999) also found that vestibular patients viewed their sleep health as significantly impaired relative to a control group using an assessment of self-rated functional status. Eagger et al. (1992) also showed that these insomnia and fatigue symptoms could even persist years after other psychiatric symptoms had resolved. More recently, Salhofer et al. (2010) compared the sleep quality of

patients with vestibular and non-vestibular migraine and found those with VM trended towards having poorer sleep. Given that sleep irregularities and lack of sleep are listed amongst the provoking factors of VM attacks (Lempert et al., 2012), and have been found to worsen co-morbid depressive symptoms in patients with chronic vestibular dysfunction (Gazzola et al., 2009), addressing these symptoms is likely to be an important factor in recovery. More generally, clinical levels of fatigue and excessive daytime sleepiness have both been associated with cognitive impairments, particularly on tests which require concentration and short-term memory (Capuron et al., 2006; Neu et al., 2011) and should thus be considered in the interpretation of vestibular contributions to cognition.

Several interpretations have been proposed to explain the emergence of these psychiatric comorbidities and how they might relate to the cognitive impairments observed within vestibular patients. One possibility is that psychiatric symptoms are epiphenomenal and emerge as a reaction to the distress of living with a vestibular condition (Hong et al., 2013; Jacob, Furman, Durrant & Turner, 1996). Similar reactive symptoms are also present in other primary organic conditions such as heart disease or diabetes (Katon, Lin & Kroenke, 2007) and are generally thought to be transient; once the organic (vestibular) disease is resolved, psychiatric and other comorbid symptoms will reduce (Coelho & Balaban, 2015; Eckhardt-Henn et al., 2008). Anxious symptoms of panic and a sense of dread are often considered to be a reactive epiphenomena, such that the unpleasant complaints that accompany vestibular dysfunction (e.g. nausea and visual disturbance) serve as reinforcing stimuli for the conditioned avoidance of situations that evoke discomfort (e.g. supermarkets), the anxiety can also generalise if individuals become hyper-vigilant (Balaban & Thayer, 2001). Attentional Control Theory (ACT) (Eysenck, Derakshan, Santos & Calvo, 2007) suggests that these worrisome thoughts can indirectly impair cognitive functioning by increasing attention towards threat-related stimuli (e.g. supermarket aisles, escalators) and

decreasing the availability of resources for maintaining attentional control (inhibition and shifting) and goal-directed attention, thus impeding upon memory and other related cognitive processes.

Alternatively, psychiatric comorbidities could be considered as brain disorders in the same way as the cognitive processes discussed above (Gurvich et al., 2013). In line with this idea, neurotransmitter changes are implicated in several vestibular syndromes (e.g. VM and MD) and are treated by manipulating chemical properties (Best et al., 2006). Since the affected serotonergic and dopaminergic systems are also implicated in anxiety and depression, these psychiatric comorbidities could reflect the altered functioning of neurotransmitter pathways as opposed to a stimulus-driven secondary reaction (Best et al., 2006). In addition to these neurochemical changes, the vestibular system also has several neuroanatomical links to brain regions involved in generating and maintaining affective states (Balaban, Jacob & Furman, 2011; Gurvich et al., 2013). Multiple comorbid symptoms (including psychiatric, sleep and fatigue disturbances) could therefore arise due to changes to the vestibular cortical network, rather than an exclusive neural link between cognition and vestibular dysfunction. For example, as mentioned previously vestibular loss has been associated with hippocampal atrophy. This could be of relevance here since the hippocampus contributes to emotion processing as well as spatial memory and navigation (Smith & Zheng, 2013).

Balance and psychiatric symptoms also share central neural circuits in some of the most primal areas of the brain which control vestibular processing, autonomic function (including the flight-fight response) and emotional responses. Amongst these is the PBN in the brainstem, which provides a direct link between the vestibular system and emotion processing/ expression, particularly anxiety and fear (Balaban & Thayer, 2001). Other brain stem pathways include the anterior cingulate cortex (ACC) and the insular cortex which

connect the vestibular system with the prefrontal cortex (Preuss et al., 2014). The frontal lobes regulate and integrate incoming sensory and affective information at the highest level, and also exert inhibitory control forces over the vestibular nuclei in the brain stem. Negative stressors triggered through vestibular dysfunction may therefore diminish the availability of shared frontal resources, leading to difficulties in maintaining sensorimotor coordination, as well as impeding upon the self-monitoring of affective states and executive functions (Carmona, Holland & Harrison, 2009; Preuss et al., 2014).

Other explanations suggest that psychiatric symptoms may result from the defective integration of information from multiple senses. More specifically, when the vestibular system is damaged the signals it sends out are distorted, producing a misleading frame of spatial reference which diverges from other senses. This mismatch can give rise to psychiatric symptoms including fears of falling (i.e. space phobia and motorist's disorientation; Baloh & Honrubia, 2010), as well as unreal perceptions of orientation and feelings of detachment from one's mental processes or body (derealisation and depersonalisation; Sang, Jauregui-Renaud, Green, Bronstein & Gresty, 2006). Derealisation and depersonalisation symptoms could therefore influence cognitive processes relating to self-representation and orientation indirectly by providing inaccurate representations of an individual's position in the environment (Gurvich et al., 2013; Jáuregui-Renaud, Sang, Gresty, Green & Bronstein, 2008; Sang et al., 2006).

Reflex deficits and hearing loss. The subtle decrements in oculomotor (VOR) and postural (vestibulo-spinal reflex) control caused by vestibular loss can also distort patients' representations of the external world (Hanes & McCollum, 2006). Impaired vestibular reflexes could indirectly affect cognitive performance if patients are unable to see clearly (e.g. reading while moving, or viewing quick moving stimuli) or move properly (e.g. navigating through the environment; Smith et al., 2010, Smith & Zheng, 2013).

Although patients are unlikely to fully regain normal functioning of their vestibular reflexes, they may compensate for the acute symptoms. Especially if they have undergone vestibular rehabilitation (Hillier & McDonnell, 2011) or have long since recovered from the peripheral vestibular abnormality (e.g. Brandt et al., 2005; Schautzer et al., 2003). Additionally, several studies tested lesioned rats in light and darkness and showed that cognitive deficits were indicative of an impairment to spatial orientation as opposed to an inability to see or move (see Smith et al., 2010 for a review). Taken together, these findings suggest that cognitive impairments do not arise simply as a secondary consequence of impaired vision or mobility.

Another important consideration is whether hearing loss (following vestibular dysfunction) also adds to the cognitive impairment. Auditory stimulation has been shown to affect hippocampal place cell function (Goble, Møller & Thompson, 2009; Sakurai, 1990, 1994), thus it is possible that any cochlear damage sustained alongside vestibular dysfunction may also contribute to these cognitive declines (Smith et al., 2010). However, lesion studies which partially controlled for auditory loss by removing the tympanic membranes (which stops sound being transmitted to the malleus, incus and stapes) have consistently shown that animals with vestibular lesions perform significantly worse than those with lesions to the tympanic membranes (Zheng et al., 2006, 2007, 2009, 2012). This suggests that hearing loss is not the primary cause of cognitive impairment (Smith & Zheng, 2013) and at least some cognitive effects are likely to be driven by vestibular dysfunction. Moreover, studies on healthy populations under conditions of microgravity (Fowler, Comfort & Bock, 2000; Grabherr & Mast, 2010; Gresty & Golding, 2009; Oman, 2006) or during concurrent vestibular stimulation (see Miller & Ngo, 2007; Utz et al., 2010 for reviews) have also evidenced an effect of vestibular inputs on cognition when these reflex and auditory abnormalities are absent.

Natural Causes

Several studies have shown that vestibular function tends to decline over the lifespan, with older adults at greater risk of encountering balance problems (Hansson & Magnusson, 2013). Moreover, older adults are also likely to undergo a decline in their cognitive faculties (Robbins et al., 1994a). An emerging body of evidence has therefore begun to explore the impact of age-related, vestibular declines on cognitive function (Harun, Oh, Bigelow, Studenski & Agrawal, 2016).

Semenov et al. (2016) analysed data from a large health survey and found that vestibular dysfunction mediated 14.3% of the association between age and visuospatial ability. The group (Bigelow et al., 2015b) also revealed significant consistent associations between reduced vestibular function and impaired visuospatial abilities in a large sample of elderly adults. Previc (2013) also highlighted vestibular loss as a potential contributor to the onset of Alzheimer's disease (AD). A hypothesis that was supported by the finding that topographic memory (the ability to locate a place and find your way back to it- one of the earliest signs of AD) is significantly related to vestibular functioning (primarily horizontal canal function) in the elderly (Previc et al., 2014). Taken together, these studies indicate that cognitive impairments (particularly visuospatial skills) may result from the natural deterioration of inputs to key regions within the vestibular cortical network (e.g. the hippocampus, posterior cingulate, and parietal-temporal cortex) due to aging and vestibular loss (Cyran, Boegle, Stephan, Dieterich & Glasauer, 2016; Previc et al., 2014).

The Current Study

To further elucidate upon interactions between the vestibular and cognitive systems this study addressed two outstanding issues. Firstly, the study aimed to more accurately determine the prevalence and nature of memory and other allied cognitive and wellbeing impairments following vestibular dysfunction using a broad battery of standardised

assessments, recall that previous research has implemented smaller batteries that often rely on self-report measures of cognition. Secondly, to try and generate a psychological model, the study explored the mechanisms underlying vestibular-cognitive interactions by examining direct and indirect (i.e. psychiatric, fatigue/ sleep disturbances) vestibular influences on cognitive performance. Patients attending their first neuro-otology appointment were recruited to perform a battery of cognitive, psychiatric and fatigue/ sleep assessments, alongside neurophysiological tests of vestibular function and balance questionnaires to probe the relevant factors discussed above. Responses were analysed to determine the prevalence of different neuropsychiatric symptoms, relative to normative data and published clinical cut-offs. SEM was then used to test whether vestibular inputs influenced cognitive processing directly, or indirectly via psychiatric, fatigue/ sleep, or age-related variables. More specifically, if vestibular signals make an independent contribution to cognitive functioning, then analyses should reveal a significant path between vestibular function and cognitive performance that is independent of any age, psychiatric or fatigue/ sleep mediators. Alternatively, if vestibular signals influence cognitive function indirectly through age, psychiatric or fatigue/ sleep mediators, then only those models with a mediated pathway should reach significance.

To briefly foreshadow the outcomes, psychiatric, fatigue/ sleep and cognitive (particularly sustained attention and working memory) disturbances were all highly prevalent within the sample. SEM further revealed that vestibular dysfunction (assessed using a balance platform) had a significant direct influence on cognitive performance, independent of any age, psychiatric or fatigue/ sleep-related effects.

Method

One hundred and one non-preselected participants (N= 101) were recruited from the Medway Maritime Neuro-otology outpatient service over a twelve month period. Sampling

was opportunistic; patients were offered the chance to participate at their initial neuro-otology appointment. Only those patients who were in an active stage of vestibular disorder (last attack or presentation of symptoms occurred within the past six months) were invited to participate. All assessments took place at the clinic, typically across two sessions. Overall compliance was high with the main reason for refusal being time constraints (i.e. work, travel).

The study was approved by the Cambridge Central NHS Research Ethics Committee (REC) and adhered to standard ethical guidelines.

Exclusion Criteria

Patients were excluded from participating if they had other illnesses which could produce dizziness symptoms without a vestibular component (e.g. light-headedness due to cardiovascular disease), or induce neuropsychiatric symptoms within the same time-frame as the presentation of dizziness symptoms (e.g. Parkinson's disease and cognitive impairment). Additionally those with a historic head injury (with loss of consciousness), or psychiatric illness (for which secondary care was accessed) were also excluded. A broad range of ages were sampled (16- 75), all participants reported noticing a change in their cognitive, psychiatric or general well-being that coincided with the onset of their vestibular condition (aside from any age-related effects). Participants who did not participate in both the psychological and neuro-otologic examinations were withdrawn from the analysis (N= 19; N= 120- 19= 101).

All participants underwent the same assessment procedure which lasted approximately two hours and consisted of two parts, as follows.

Neuro-Otologic Assessment

This was completed by a consultant neuro-otologist who was blind to the participants'

psychological performance. A standardised interview was first delivered to establish the history of the presenting condition as well as any other relevant medical history, clinical neurological and neuro-otological examinations (including positional manoeuvres, stepping tests) then followed. Additional neurophysiological examinations were also used to measure ocular mobility and optokinetic nystagmus (videonystagmography), as an indicator of central vestibular functioning. Asymmetries in lateral semi-circular canal responses associated with peripheral vestibular damage were also assessed using video-Head Impulse Testing (vHIT). Additionally, general unassisted posture was tested using a computerised balance platform where participants had to maintain their balance for 30s under four test conditions which varied the availability of different sensory inputs (vision, proprioception, vestibular) for balance maintenance. The most difficult condition (eyes closed, foam surface) exclusively tests the use of vestibular inputs for balance maintenance. Both the videonystagmography and vHIT were scored categorically according to normed data (abnormal/ normal), whereas the balance platform tracks shifts in a participants' centre of pressure and was thus analysed in terms of velocity of sway (mm per second).

The interpretation of these neurophysiological tests can be limited by the intermittent nature of several vestibular symptoms (e.g. vertigo attacks) which typically resolve over time (usually within minutes to hours) or once compensatory strategies are actioned (Thompson & Amedee, 2009; Yardley, Masson, Verschuur, Haacke & Luxon, 1992). Thus it was also necessary to obtain a general estimate of how participants' symptoms had presented over the previous months in addition to the day of examination. Three well-validated questionnaires were therefore selected and administered to quantify participants' perceptions of their dizziness symptoms (see Table 2.3).

Diagnoses were made by the neuro-otologist according to the patient history, published diagnostic criteria (International Classification of Headache Disorders 2nd edition,

Olesen & Steiner, 2004; International Statistical Classification of Diseases and Related Health Problems 10th Revision- ICD-10, American Academy of Otolaryngology- Head and Neck Foundation, 1995; Committee on Hearing and Equilibrium; 1995), and any relevant neuro-otological examinations/ tests (e.g. Dix-Hallpike manoeuvre).

Table 2.3
Balance Questionnaires

Assessment	Scale	Example Item
Vertigo Symptom Scale- VSS (Yardley et al., 1992). Measures organic and somatic vestibular symptomology.	22 items form two sub-scales (vertigo severity-VS and somatic anxiety- SA). All items are rated on a five point Likert scale (0= never, 4= very often) indicating the frequency of symptoms over the past year.	Unable to stand or walk properly without support. Difficulty breathing, short of breath.
Dizziness Handicap Inventory- DHI (Jacobson & Newman, 1990). Measures functional impairment.	25 items rated on a three point Likert scale (yes, sometimes, no).	Because of your problem have you been embarrassed in front of others? Does your problem significantly restrict your participation in social activities?
Visual Vertigo Analogue Scale- VAS (Longridge et al., 2002). Measures visual disturbance.	Nine items rated on a visual analogue scale representing the dizziness felt in a situation. The scale ranges from 0 (no dizziness) to 10 (most dizziness).	Walking through a supermarket aisle. Going down an escalator.

Psychological Assessment

This began with a short semi-structured interview regarding participants' experiences of their comorbid symptoms and their demographic background. Several questionnaires were administered (see Table 2.4) to quantify the clinical significance of participants' comorbid psychiatric, sleep and fatigue symptoms. All questionnaires have been well-validated and are recognised for use with neurological patient groups, including vestibular dysfunction (e.g. Eagger et al., 1992; Huisinga, Fillipi, Schmid & Stergiou, 2011; Ireland & Walker, 1994; Langguth et al., 2007; Tschan, Wiltink, Adler, Beutel & Michal, 2013). Importantly, the questionnaires were also concise enough for patients to complete within a short space of time.

Table 2.4
Mood, Sleep and Fatigue Questionnaires

Assessment	Scale	Example Item
Beck Depression Inventory II- BDI (Beck, Steer & Brown, 1993).	21 items rated on a four point Likert scale (0, 1, 2, 3). Total scores ≥21 indicate clinically relevant depression.	Pick out the one statement in each group that best describes the way you have been feeling over the past two weeks (Inc. today): Sadness. 0 I do not feel sad 1 I feel sad much of the time 2 I am sad all the time 3 I am so sad or unhappy that I can't stand it
Beck Anxiety Inventory- BAI (Beck & Steer, 1993).	21 items rated on a four point Likert scale (not at all, mildly, moderately, and severely). Total scores ≥16 indicate clinical levels of anxiety.	Over the past week (Inc. today) how much have you been bothered by each symptom: -Heart pounding or racing. -Unable to relax.
Cambridge Depersonalisation Scale- CDS (Sierra & Berrios, 2000).	29 items rated on two Likert scales which sum together to form a total score: Frequency (0= never - 4= all the time). Duration (1= few seconds - 6= more than a week). Total scores ≥70 suggest abnormal levels of depersonalisation.	How often have you had these experiences over the last six months? What was their approximate duration? -What I see looks 'flat' or 'lifeless', as if I were looking at a picture. -Whilst doing something I have the feeling of being a "detached observer" of myself.
Fatigue Severity Scale- FSS (Krupp et al., 1989).	Nine items rated on a seven point Likert scale (1= strongly disagree - 7= strongly agree). Excessive fatigue levels if the average of all sub-scores is ≥4.	During the past week, I have found that: -My motivation is lower when I am fatigued. -Fatigue interferes with my work, family or social life.
Epworth Sleepiness Scale- ESS (Johns, 1991).	Eight items on a four point Likert scale (0= no chance of dozing - 3= high change of dozing). Total scores >10 indicate excessive daytime sleepiness.	How likely are you to doze off or fall asleep in the following situations? -Watching TV -Sitting inactive in a public place
Pittsburg Sleep Quality Index- PSQI (Buysse et al., 1989).	19 items which form seven component scores. A combination of open-ended questions and Likert scaling is used. A global score of ≥5 differentiates poor sleepers.	During the past month: -When have you usually gone to bed? -How often have you had trouble sleeping because you: Cannot get to sleep within 30 minutes. (0= not during past month - 3= three or more times a week).

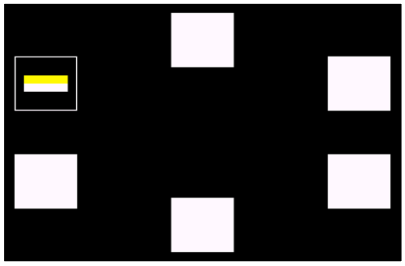
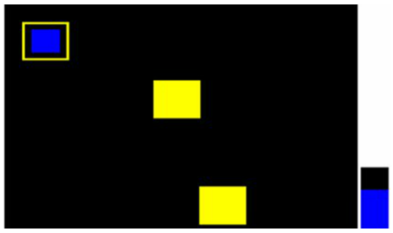
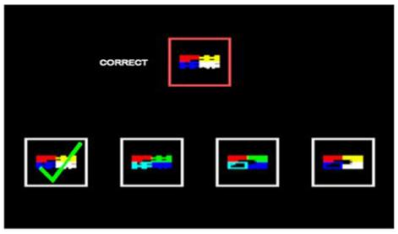
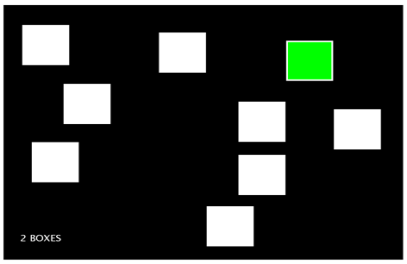
Cognitive morbidity was investigated using a customised battery of six computer-interfaced tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®-eclipse) which has been well validated for studying brain-behaviour

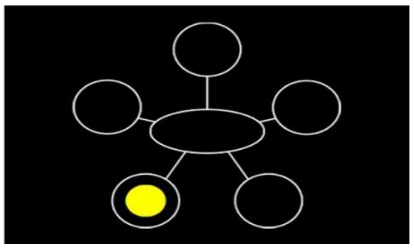
relationships (Robbins et al., 1994b) and can differentiate normal adults from various clinical populations (Saunders & Summers, 2010). Tests were carefully selected to probe a range of cognitive functions including information processing, attention, executive functioning and memory (both with and without a spatial emphasis). Table 2.5 provides a brief breakdown of the tests and their most relevant outcome measures (for more information see CANTAB^{TM} 6 test administration guide, 2013).

Two different test orders were used to administer the CANTAB assessments. Half the sample received the tests in order one (PAL, RVP, SWM, RTI, SSP, DMS), the other in order two (RTI, DMS, SSP, SWM, RVP, PAL). These orders were selected to counterbalance serial position effects while avoiding placing similar tasks next to each other to reduce the demands placed on a particular cognitive function. Rest breaks were given after every two cognitive assessments, one or two questionnaires were usually completed during these breaks.

Table 2.5

Cognitive Assessments from the CANTAB

Test	Task	Example Trial and Key Outcome Measure
Paired Associates Learning (PAL)	Assesses new spatial learning for multiple object-location associations (participant completes multiple attempts until each trial display is learnt). Requires the retention of pattern and spatial information. Participants are shown patterns appearing in boxes, they must remember the location of each pattern. Difficulty increases from one to eight patterns.	 Total number of incorrect placements (adjusted for the number of attempts made).
Spatial Working Memory (SWM)	Requires the retention and manipulation of spatial (but not pattern) details. Executive control is also probed. Using a process of elimination participants need to find "blue tokens" and avoid revisiting boxes which have already been found to contain a token. The search display increases from 3, 4, 6 to 8 boxes.	 The number of errors (returning to previously visited box) and the strategy used (beginning a search at the same box).
Delayed Match to Sample (DMS)	Requires the retention of complex patterns (with minimal reliance on spatial memory). Participants are shown a target pattern which is then covered for a short delay (up to 12s). Participants must identify which of four options matches the target from memory.	 Percentage of correct responses.
Spatial Span (SSP)	Assesses memory capacity for a spatial sequence. No pattern recognition is required. White boxes briefly change colour in a variable sequence. Participants must remember the sequence and touch the boxes in the same order. Sequence length is increased until the participant's capacity is reached (maximum of 9).	 The longest sequence recalled by the participant.

Reaction Time (RTI)	Tests information processing speed for a single simple target. Participants must react and touch a yellow dot as soon as it appears on the screen. The dot can appear in one or five locations.	 Average speed (ms) of target button presses.
Rapid Visual Processing (RVP)	Assesses sustained attention. Requires the detection of several targets within a continuously changing display. Single digits are rapidly presented for four minutes, participants need to continue to detect and respond to multiple target sequences during this period.	 *d'* sensitivity measure calculated from hits and false alarms and response time (ms).

Results

Statistical Approach

Analyses first attempted to characterise the participant sample in terms of their demographics and vestibular diagnoses. The prevalence of psychiatric, fatigue and sleep disturbances as well as specific cognitive impairments were then calculated based on normed data and established cut-offs. An exploratory factor analysis (EFA) was subsequently performed to identify core latent abilities underlying the multiple cognitive tests. Finally, the extracted factors were entered into SEM designed to test hypotheses about whether vestibular function influences cognitive performance directly or indirectly via age, psychiatric and fatigue/ sleep mediators.

Participant Characteristics

In line with previous epidemiology studies, the majority of the sample were middle-aged (*M*= 48 (±14.47), female (77: 24), and suffered from VM (63%) (Lempert & Neuhauser, 2009), further demographics are presented in Table 2.6. The duration of participants'

vestibular symptoms ranged from three months to 23 years (*M*= 3.15 years) before they had attended the specialist clinic. At interview unsteadiness, light headedness, vertigo, visual disturbances and nausea were the most commonly reported symptoms. Many patients had a balance problem that was constantly present (75.2%), intermittent attacks where the symptoms worsened were also prevalent (72%).

Table 2.6
Demographic Characteristics of the Sample

Diagnosis	*N*	%	**Age**		**Gender**		**Constant**	
			M	*SD*	Male	Female	Yes	No
VM	64	63.4	43.85	14.07	13	51	47	17
BPPV	8	7.9	59.45	11.35	1	7	5	3
BVF/ hypofunction	3	3	58.74	5.05	1	2	3	0
VM & BPPV	7	6.9	53.63	8.46	0	7	4	3
VM & peripheral loss	6	5.9	46.45	15.10	3	3	6	0
MD	2	2	54.48	12.16	1	1	1	1
Central (cerebellar dysfunction)	5	5	60.93	7.28	3	2	5	0
Central & peripheral hypofunction	1	1	68.30	-	0	1	1	0
Other	5	5	54.40	14.34	2	3	4	1
Total	101	100	48.18	14.30	24	77	76	25

Note. VM= vestibular migraine; BPPV= benign paroxysmal positional vertigo; BVF= bilateral vestibular failure; MD= Ménière's disease.

Neurophysiological examinations. Performance on the vestibular function tests tended to support the diagnoses made by the consultant. Abnormal scores were obtained for 27% of the sample on the videonystagmography and 25% on the vHIT, relative to normed data (age, gender matched) made available by GN Otometrics©. The fact that most participants showed normal ocular mobility and optokinetic nystagmus on the videonystagmography reduced concerns about cognitive impairments occurring as an indirect

consequence of VOR deficits. Moreover, the vHIT scores suggested that the majority of the sample were suffering from a central rather than peripheral-related dysfunction.

Although these figures may appear low, it should be noted that the majority of the sample were diagnosed with VM for which there is no diagnostic marker that presents during neuro-physiological examinations (Cherchi & Hain, 2011). Additionally, any participants who attended the clinic on a "good day" when they were not amidst an attack of symptoms may have performed normally whilst holding a diagnosis of a vestibular dysfunction. In light of these prevalence rates, further analysis of the neurophysiological data was restricted to the balance platform, a continuous measure of postural abnormalities, which is sensitive to ongoing chronic balance problems (Agrawal, Carey, Della Santina, Schubert & Minor, 2009; Lipp & Longridge, 1994).

Prevalence of Neuropsychiatric Comorbidity

Prevalence rates were established by comparing each participant's average/ total test score to established clinical cut-offs and age-matched normed data.

Figure 2.2 shows the prevalence of each psychiatric and fatigue symptom compared with established clinical cut-offs. Over half of the sample (59.8%) presented with clinically significant anxiety scores on the BAI at their initial clinic appointment. Depression symptoms on the BDI were less prevalent but still common, with over a third of the sample (36.64%) falling above the clinical cut-off. Clinical levels of depersonalisation disorder were infrequent (12.87%). Importantly, the majority of patients (61%) had not experienced psychiatric symptoms or sought contact with a health professional regarding these psychiatric symptoms prior to the onset of their vestibular disorder, indicating that the presence of vestibular dysfunction can worsen pre-existing psychiatric symptoms as well as trigger the onset of these symptoms.

The incidence of fatigue within this sample was high with over 70% of the sample reporting symptoms which met the FSS clinical cut-off, and 43.56% reporting significant levels of daytime sleepiness on the ESS. Disrupted sleep was also highly prevalent with over three quarters of the sample (78.35%) falling above the abnormal cut-off on the PSQI (see Figure 2.2).

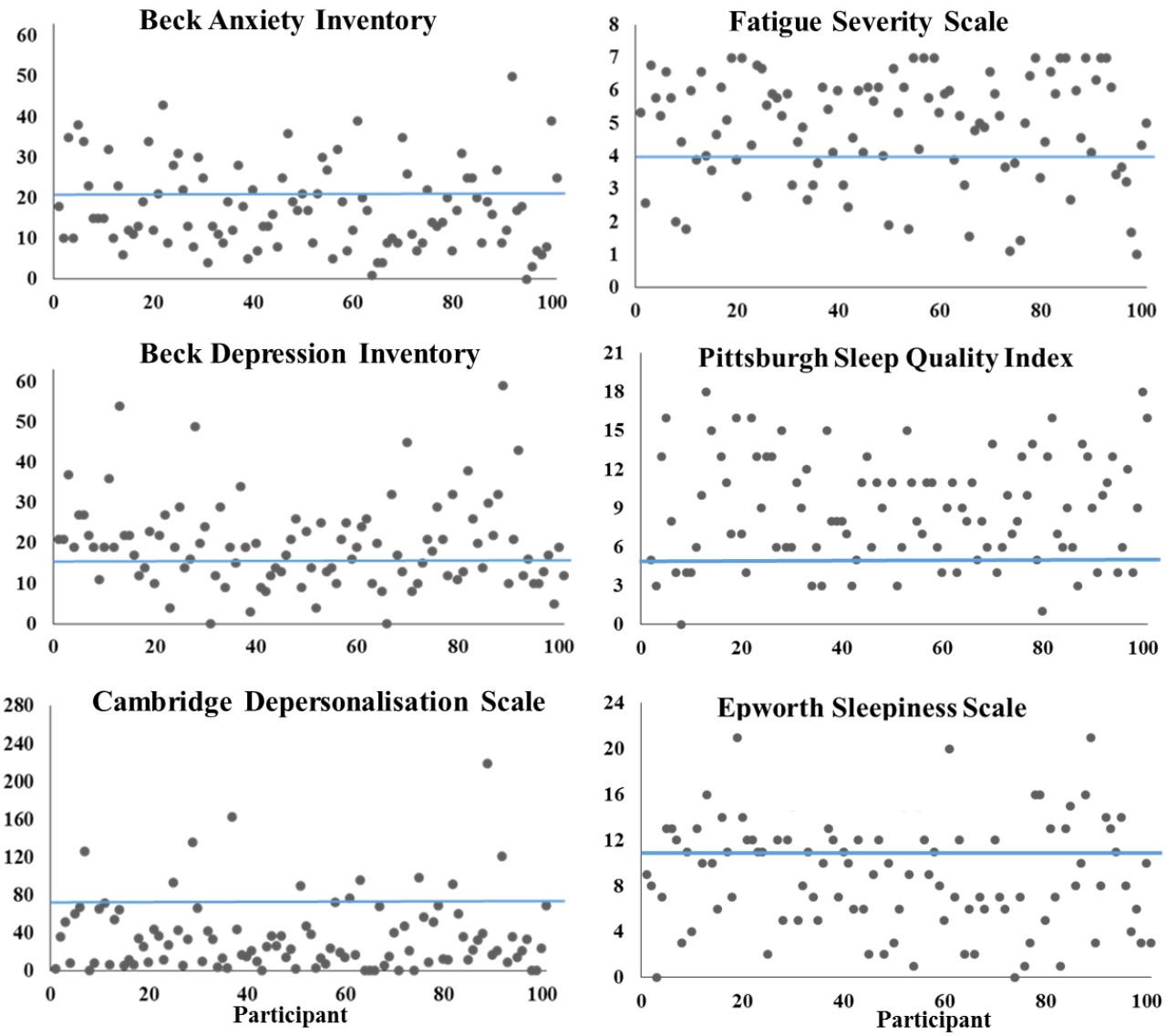


Figure 2.2. Relative incidence (%) of psychiatric and fatigue/ sleep morbidities across the 101 participants as compared with established clinical cut-offs (indicated by the blue lines). *Note.* The maximum scores that can be achieved on the BAI and BDI are 63 and an average score is used for the FSS.

Each CANTAB assessment has several outcome measures, the most informative and widely published measures are presented in Figure 2.3 alongside the percentage of

participants that fell outside of normative performance limits (i.e. the participant obtained a negative *z* score indicating lower performance than the normative mean) according to a database provided by CANTAB®. Where possible, participants' performance was matched with the normative sample in terms of age and gender. In those instances where matched data was unavailable (particularly limited for RTI and RVP), participants' scores were compared with the normative sample as a whole. Short-term memory capacity (SSP) and sustained attention (*d'* RVP) were particularly impaired relative to the normative sample, indicating that these functions may be especially vulnerable following vestibular dysfunction.

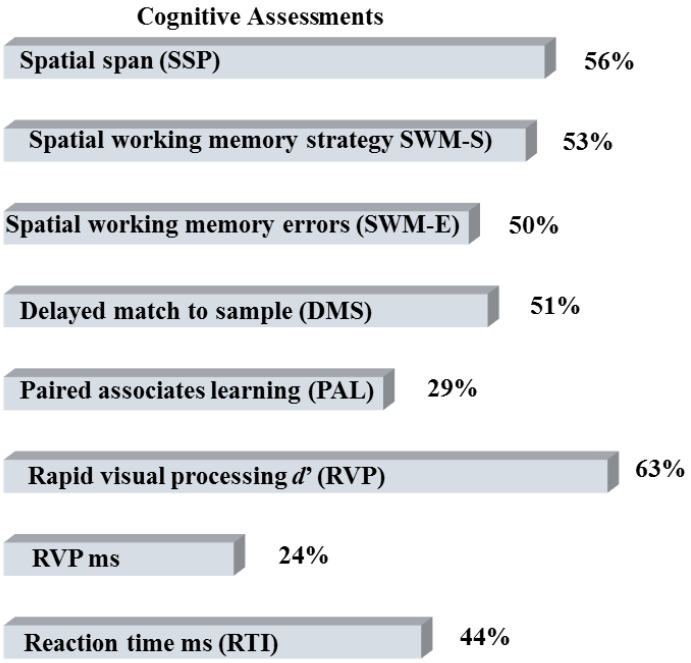


Figure 2.3. Relative incidence (%) of cognitive morbidity compared with normative data on the different subtests of the CANTAB battery.

Underlying Mechanisms

Core cognitive components. Next an EFA was conducted to identify which CANTAB tests appeared to probe to the same cognitive functions and which cognitive factors explained the most variance in participants' scores (e.g. spatial memory, attention). The factors identified in this analysis were then used in SEMs to test hypotheses about the mechanisms of vestibular-cognitive effects.

Initially, the factorability of the principal CANTAB outcome measures was examined. Firstly, it was observed that the majority of the measures shared significant moderate correlations (see Table 2.7) suggesting the data were suitable for EFA, although two exceptions were present. The SWM_S measure correlated negatively with the other positively indicated accuracy outcome measures because improved strategy performance is associated with fewer initial search positions. Since this is a crucial element of the measure which cannot be reverse coded and reflects an important cognitive dimension, the SWM_S was retained for further EFA analysis. In line with previous research, outcome measures indicated by response speed (Simple RTI and RVP) also tended not to associate with those measured by accuracy. This could potentially be due to a speed-accuracy trade-off or a dissociation between tasks with higher and lower mental processing demands. EFA was therefore completed upon the seven measures that were not time-based (including SWM_S) and excluded the two RT measures (since a separate EFA could not be completed with just two outcome measures).

Table 2.7
Zero-Order Correlations among the Principal CANTAB Outcome Measures

Measure	1	2	3	4	5	6	7	8	9
1. Reaction time (acc)	—	.12	.24*	-.15	.25*	.15	-.14	.31**	.27**
2. Reaction time (ms)		—	-.12	.42**	-.17	-.46**	-.03	-.06	-.10
3. Rapid visual processing (*d*')			—	-.53**	.38**	.26**	-.20*	.30**	.48**
4. Rapid visual processing (ms)				—	-.28**	-.35**	.16	-.29**	-.37**
5. Paired associates learning_%C					—	.14	-.28**	.50**	.41**
6. Delayed match to sample						—	-.20*	.30**	.23*
7. Spatial working memory strategy							—	-.73**	.23*
8. Spatial working memory_%C								—	.44**
9. Spatial span									—

Note. Non-redundant correlations presented (*N*= 101). The PAL and SWM_E were both reverse coded to obtain the percentage of trials that participants got correct (%C). Coefficients significant at $p<.05$ are displayed with a *, those significant at $p<.01$ are displayed alongside **.

The EFA used the Maximum Likelihood extraction method and applied Promax rotation. The Kaiser-Meyer-Olkin coefficient was 0.7 and the Bartlett test of Sphericity was significant [χ^2 (21)= 188.83, p<.001] indicating that the properties of the correlation matrix were suitable for EFA. Two factors emerged with eigenvalues above one (factor one= 2.92, factor two= 1.07), accounting for 32.17 and 13.45% of the variance respectively. Examination of the scree plot (see Figure 2.4) demonstrates that factor one appeared to explain the majority of variance. Further SEM analyses therefore proceeded with a single factor model (further interpretation of the extracted factor is provided in the next section).

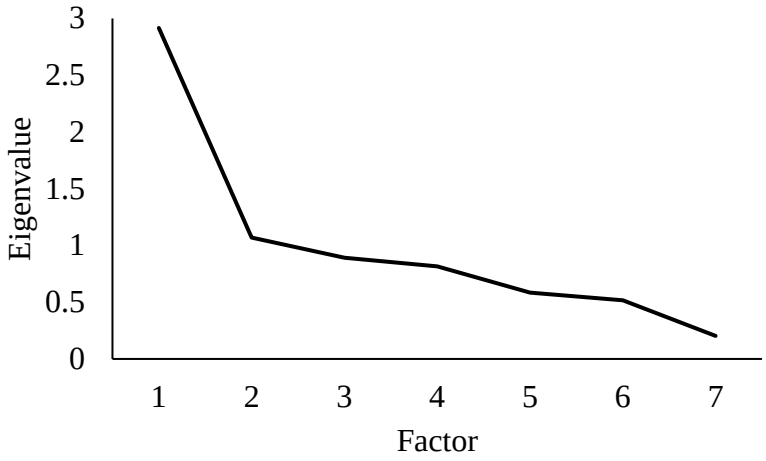


Figure 2.4. Scree plot displaying one clear cognitive factor.

Structural equation modeling. Once the model structure had been confirmed (single cognitive factor plus the two RT measures), a series of mediation models were then constructed using SEM in AMOS^{TM} 23. SEM can evaluate multiple causal relationships between latent and observed variables by combining confirmatory factor analysis with multiple regression. Unlike more traditional multivariate procedures, SEM simultaneously models multiple path outcomes and can correct for measurement error, thereby resulting in more accurate parameter estimations. Several recent studies have also adopted the technique and revealed interesting insights regarding vestibular contributions to cognition using survey

data (Bigelow et al., 2015a; Bigelow et al., 2015b; Semenov et al., 2016), highlighting the utility of the technique.

Following the guidelines of Holmbeck (1997), two stages of modeling were completed to address the key study questions. First the analysis tried to establish the impact of vestibular influences on cognitive function (direct effect), while taking in to account any age-related effects. That is, does vestibular function impact cognition over and above any age-related changes? To do so, SEM examined whether the association between age and cognitive performance was mediated by the different measures of balance (direct vestibular-cognitive pathway). The next step tested mediational effects for those balance measures which showed a significant unique contribution to cognitive function. Analyses estimated how much of this association was mediated by comorbid psychiatric and fatigue/ sleep symptoms, while adjusting for age (indirect vestibular-cognitive pathway).

Where relevant, standardised regression coefficients are reported to explore the loadings of the observed CANTAB variables on two cognitive factors: processing speed for the RT measures, and the accuracy-based cognitive factor identified by the EFA. Standardised coefficients are also reported for the mediation pathways to determine the strength of the associations between the variables of interest.

Prior to estimation, the raw data was checked for outliers and missing values. Of the 101 participants, 96% provided a complete set of data. Because there was no discernible pattern of missing data, listwise deletion was applied (N= 95). All models were estimated using Maximum Likelihood and bootstrapped (2000 resamples) to account for non-normality and acquire greater power (while controlling for type I error). p values and 95% bias corrected confidence intervals were used to ascertain significance, however no further corrections for multiple comparisons were applied. Instead, efforts were made to simplify the

models under investigion to reduce the number of statistical comparisons being estimated. Contrainsts were also introduced so that the more complex models were only tested if the paths of the initial basic model were significant (Holmbeck (1997).

Does vestibular dysfunction contribute to cognitive impairment over and above normal age-related changes? A total of eight structural equation models were tested, with each of the four balance assessments (balance platform and questionnaires: VAS, VSS_VS, DHI) acting as the mediator in separate models for both cognitive factors (accuracy-based and processing speed). Scores from the VSS_SA sub-scale were excluded from these analyses because the secondary autonomic symptoms which this scale assesses could be caused by psychiatric and somatic disturbances as opposed to vestibular dysfunction, thus distorting any estimates of vestibular-contributions to cognition (Yardley et al., 1992). The VSS_SA was included in later analyses where the influence of psychiatric mechanisms were considered. If vestibular function makes an independent contribution to cognition, then the indirect path which adjusts for age-related effects should reach significance in least one of the four models tested.

The measurement model revealed that all loadings for the cognitive accuracy factor were significant and moderate (positively indicated measures ß= 0.30 to 0.71 and SWM_strategy ß= -0.37; all *ps* <.01) across all of the balance tests, suggesting that the CANTAB tests were valid and reliable indicators of the factor. The indicators with the highest loadings required memorising spatial locations, thus this factor was termed visuospatial memory. The indicators for the processing speed factor did not have significant factor loadings (all *p*s>.50) across any of the balance assessments, therefore models concerning this factor are not discussed further.

Only postural ability on the balance platform appeared to mediate the relationship between age and visuospatial memory performance (all other indirect paths $p>.28$, see Appendix A). Self-rated perceptions of vertigo severity, visual disturbances (indicative of VOR impairments) and balance-related handicap did not significantly impact age-related effects on cognition.

A representation of the structural model involving the balance platform can be seen in Figure 2.5 (further measurement statistics are provided in Appendix A). A moderate direct path was observed between age and visuospatial memory performance such that older participants achieved lower scores on the visuospatial memory factor (ß= -0.45, $p<.001$). The indirect path showed that performance on the balance platform partially mediated this relationship (ß= -0.09, $p<.05$). Specifically, older participants showed increased sway and in turn worsened performance on the visuospatial memory factor, resulting in the larger overall total effect (ß= -0.54, $p<.001$). Importantly, performance on the balance platform mediated 17%[1] of the association between age and visuospatial memory, confirming that vestibular dysfunction contributes to cognitive impairment over and above any age-related changes.

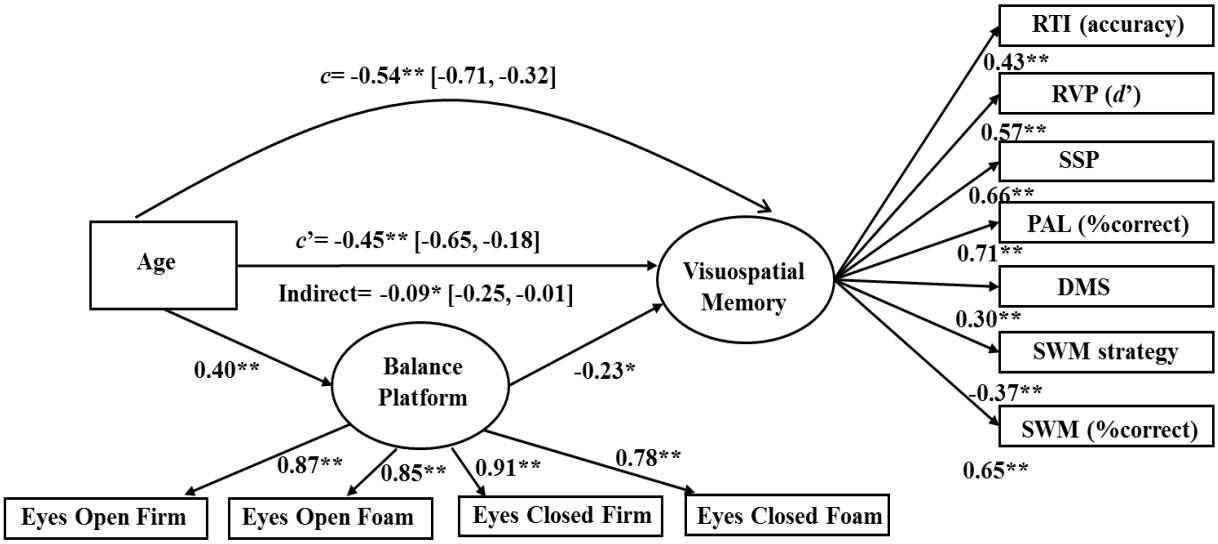


Figure 2.5. Mediation model between age, sway on the balance platform and visuospatial memory abilities. Latent factors (circles) used the scale of the most conceptually relevant

[1] The percentage of mediation is calculated as: (A x B)/ ((A x B) + C) x 100), where A x B is the indirect effect, C is the direct effect, and (A x B) + C is the total effect.

observed variable (rectangles) in accordance with the factor loadings. Errors from the SWM strategy and SWM (%correct) indicators were allowed to correlate (not drawn here) to account for method effects. Standardised coefficients are reported alongside bias-corrected 95% confidence intervals and significance values, *p<.05, **p<.01.

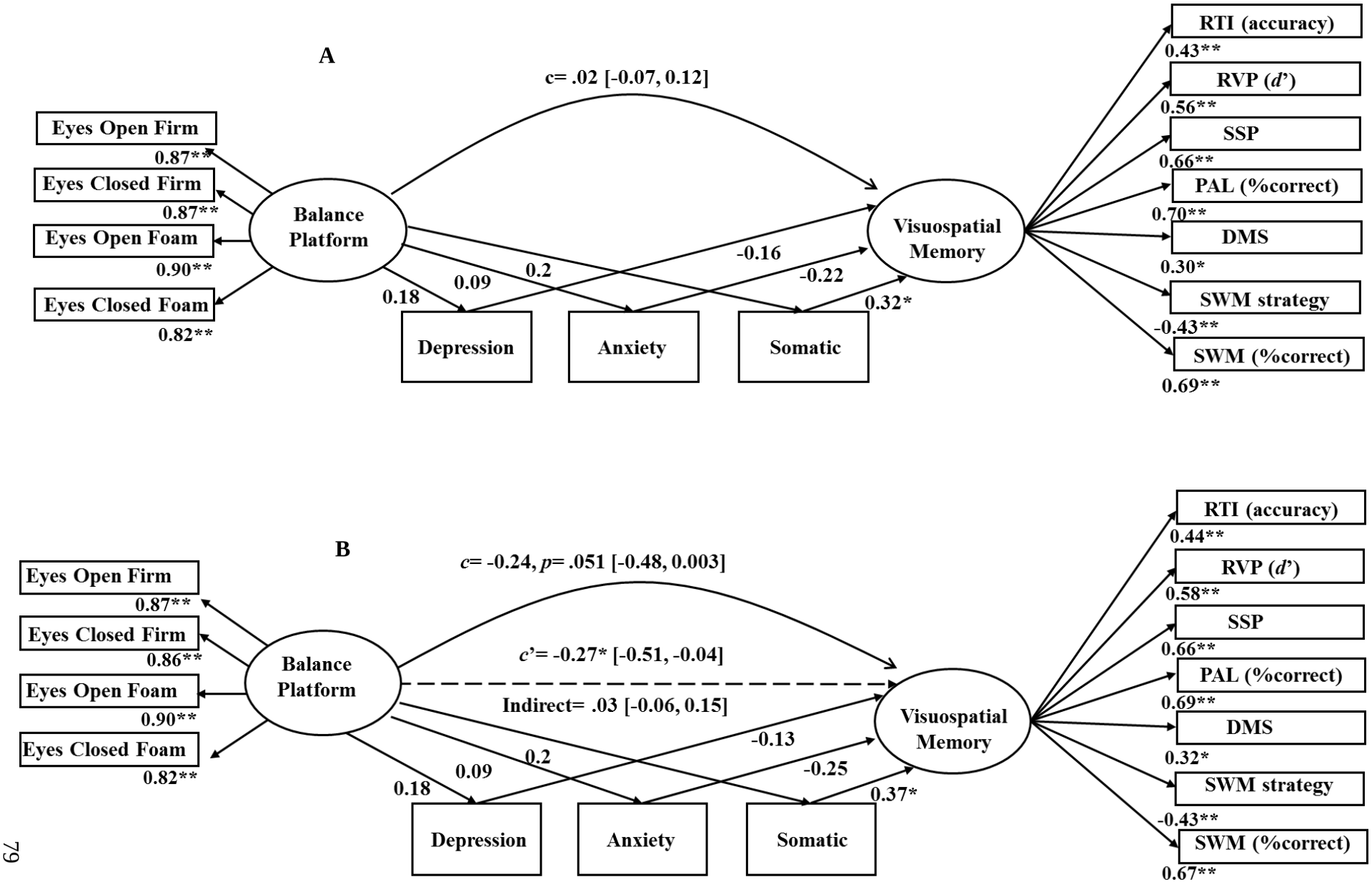
Do psychiatric and fatigue/ sleep symptoms mediate the relationship between balance and visuospatial memory performance? The next analysis aimed to determine the fraction of the association between posturography and visuospatial memory that could be explained by comorbid symptoms. Two combinations of mediators were applied in separate models (to reduce model complexity). The first combination examined the influence of psychiatric variables including the BDI, BAI and VSS_SA. The VSS_SA was treated as a mediator because the somatic anxiety symptomology assessed by this scale reflects patients' psychiatric and somatic responses to the balance problem (Yardley et al., 1992). Note that the CDS was excluded from the psychiatric model (to reduce model complexity) because few participants identified with its items, relative to the other questionnaires (just 12.87% met the clinical cut-off). The second combination estimated the influence of fatigue and sleep disturbance using the FSS, ESS and PQI. As these comorbid measures all involved self-reported perceptions of wellbeing, covariance paths were drawn between the three questionnaire residuals in each model to account for any shared variance not being estimated (i.e. response tendencies).

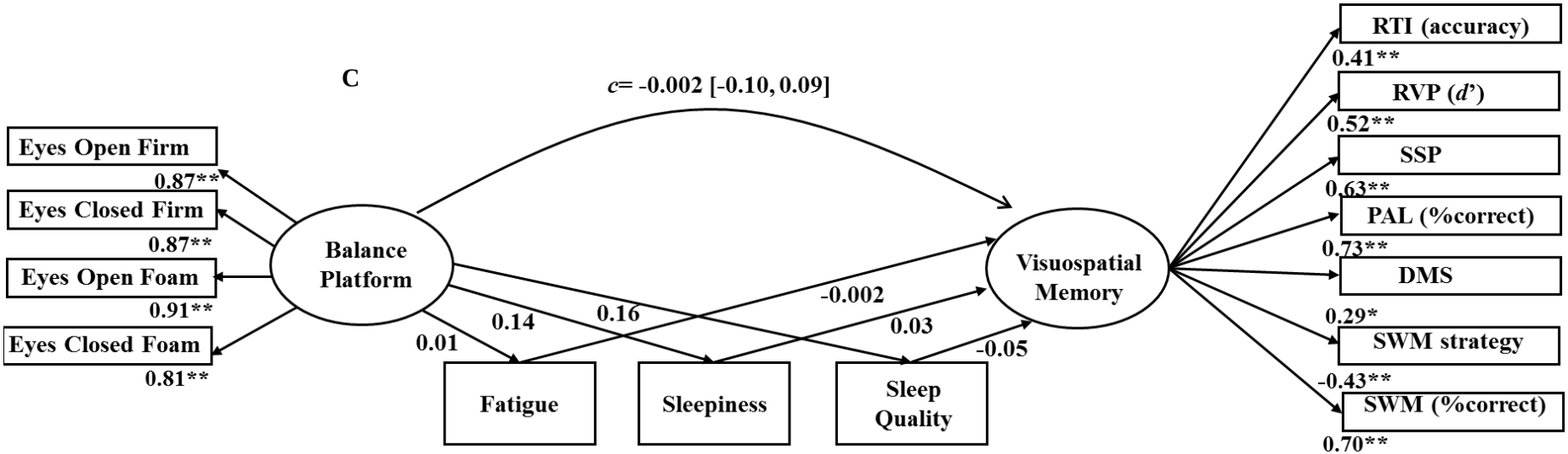
Mediational effects for the psychiatric and fatigue variables were tested under two conditions. Analyses first tested the strength of the indirect paths involving the mediators (psychiatric or fatigue), to establish whether a significant association was present between these variables and visuospatial memory (see Figures 2.6A and 2.6C). A second model then added the direct path to evaluate the strength of this indirect relationship, once the direct path between balance function and visuospatial memory was controlled for (see Figures 2.6B and 2.6D). If cognitive impairments in this cohort arise as a secondary consequence of psychiatric and fatigue disturbances, then this indirect path should reach and retain significance. Four

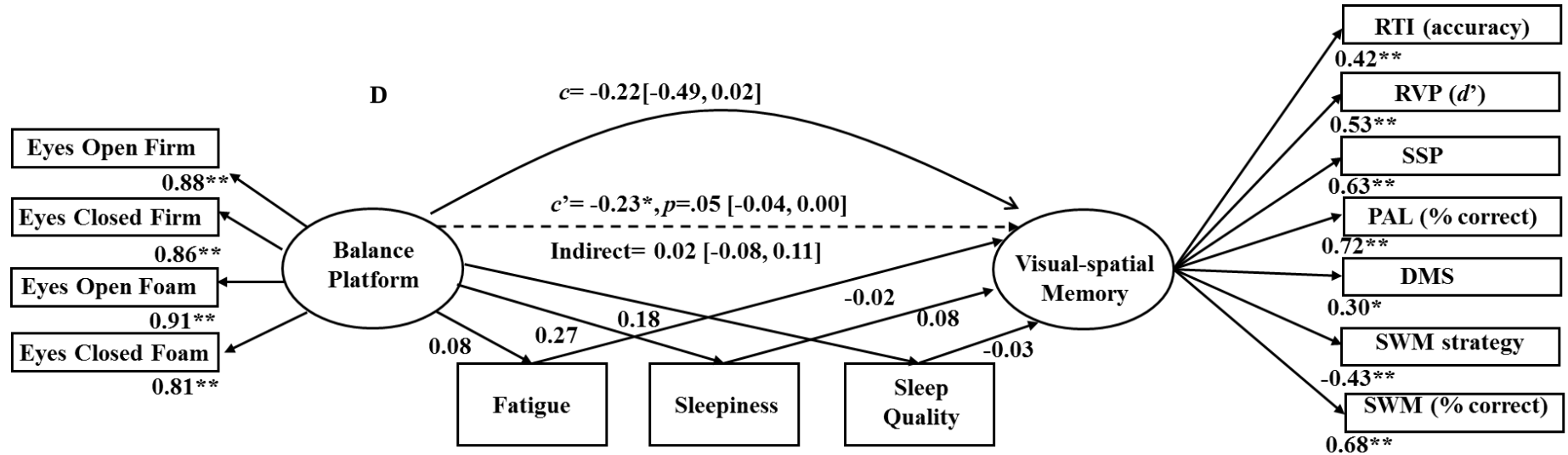
models were fitted and tested, again these models were adjusted for age (further measurement statistics are provided in Appendix A).

Neither the indirect effect of the psychiatric nor the fatigue variables reached significance, regardless of whether or not the direct path was controlled for (all ßs<0.03, all *p*s>.50). Combined depression, anxiety and somatic anxiety slightly supressed the effect of posturography on visuospatial memory performance therefore reducing the total path (direct ß= -0.27; total ß= -0.24). Similarly, fatigue severity, sleepiness and sleep quality somewhat supressed the association between posturography and visuospatial memory performance (direct ß= -0.23; total ß= -0.22). Importantly, the negative direct path between the balance platform and performance on the visuospatial memory factor accounted for the majority of variance within the total path across both mediator models. Additionally, the direct path remained significant across the psychiatric mediators (ß= -0.27, *p*<.05) and just missed significance for the fatigue mediators (ß= -0.23, *p*=.05).

Taken together the SEM analyses suggest that lower visuospatial memory performance was directly associated with unsteadiness on the balance platform (increased sway), independently of comorbid psychiatric and fatigue symptoms (and controlling for age).


A
c= .02 [-0.07, 0.12]
Eyes Open Firm
0.87**
Eyes Closed Firm
0.87**
Eyes Open Foam
0.90**
Eyes Closed Foam
0.82**
Balance Platform
0.18
0.09
0.2
-0.16
-0.22
0.32*
Depression
Anxiety
Somatic
Visuospatial Memory
RTI (accuracy)
0.43**
RVP (d')
0.56**
SSP
0.66**
PAL (%correct)
0.70**
DMS
0.30*
SWM strategy
-0.43**
SWM (%correct)
0.69**
B
c= -0.24, p= .051 [-0.48, 0.003]
c'= -0.27* [-0.51, -0.04]
Indirect= .03 [-0.06, 0.15]
Eyes Open Firm
0.87**
Eyes Closed Firm
0.86**
Eyes Open Foam
0.90**
Eyes Closed Foam
0.82**
Balance Platform
0.18
0.09
0.2
-0.13
-0.25
0.37*
Depression
Anxiety
Somatic
Visuospatial Memory
RTI (accuracy)
0.44**
RVP (d')
0.58**
SSP
0.66**
PAL (%correct)
0.69**
DMS
0.32*
SWM strategy
-0.43**
SWM (%correct)
0.67**


C
c= -0.002 [-0.10, 0.09]
Eyes Open Firm
0.87**
Eyes Closed Firm
0.87**
Eyes Open Foam
0.91**
Eyes Closed Foam
0.81**
Balance Platform
0.01
0.14
0.16
-0.002
0.03
-0.05
Fatigue
Sleepiness
Sleep Quality
Visuospatial Memory
RTI (accuracy)
0.41**
RVP (d')
0.52**
SSP
0.63**
PAL (%correct)
0.73**
DMS
0.29*
SWM strategy
-0.43**
SWM (%correct)
0.70**


D
c= -0.22[-0.49, 0.02]
c'= -0.23*, p=.05 [-0.04, 0.00]
Indirect= 0.02 [-0.08, 0.11]
Eyes Open Firm
0.88**
Eyes Closed Firm
0.86**
Eyes Open Foam
0.91**
Eyes Closed Foam
0.81**
Balance Platform
0.08
0.27
0.18
-0.02
0.08
-0.03
Fatigue
Sleepiness
Sleep Quality
Visual-spatial Memory
RTI (accuracy)
0.42**
RVP (d')
0.53**
SSP
0.63**
PAL (% correct)
0.72**
DMS
0.30*
SWM strategy
-0.43**
SWM (% correct)
0.68**

Figures 2.6A-D. Mediation models for the psychiatric (BDI, BAI, VSS_SA) and fatigue variables (FSS, ESS, PSQI), with (B, D) and without (A, C) the direct paths (dashed lines). Standardised coefficients are reported alongside bias-corrected 95% confidence intervals and significance values, **p*<.05, ***p*<.01. Errors from the SWM strategy and SWM (%correct) indicators were allowed to correlate to account for method effects, as well as errors from the self-report questionnaires. All results were adjusted for age.

In light of this association, a final more focused regression analysis was performed to determine whether the level of neuropsychiatric function could predict posturography performance. To this end, the neuropsychiatric variables (visuospatial memory factor from the EFA and the psychiatric and fatigue questionnaires) plus age were regressed against the Romberg ratio which is common balance parameter (Eyes-Closed/ Eyes-Open on a foam surface; Tjernström, Björklund & Malmström, 2015). This analysis was also limited to those patients with preserved peripheral function (i.e. excluding those with peripheral loss or Méniére's disease) since central aspects of vestibular symptomology (the combination of different sensory signals across multiple brain circuits) are more likely to exert a top-down influence than peripheral sensory transduction (Allen, Ribeiro, Arshad & Seemungal, 2017). Consequently, this analysis will inform on any central aspects of vestibular symptomology which affect balance beyond a loss of afferent input signal.

Table 2.8 shows that the variables entered into the regression model did not significantly predict balance using the Romberg Ratio, either individually (all $\beta<0.18$, *p*s>.10) or when combined [$F(8,76)= 0.83$, $p= .53$]. This suggests that the more complex models presented in Figures 2.5 and 2.6 may better describe the comorbidities found in the sample (both central and peripheral dysfunction).

Table 2.8
Multiple Linear Regression Analysis of the Neuropsychiatric Factors Predicting Balance Using the Romberg Ratio.

Predictor	β	*SE*	Sig
Age	0.18	.01	.10
Visuospatial memory Factor	0.05	.09	.70
Beck Depression	-0.11	.01	.44
Beck Anxiety	0.0	.01	.99
VSS_Somatic Anxiety	0.12	.01	.45
Epworth Sleepiness	-0.10	.02	.44
Fatigue Severity	0.16	.07	.27
Pittsburg Sleep Quality	-0.14	.02	.27

Note. N=87 (preserved peripheral function), R^2= 0.80.

Discussion

This study aimed to investigate whether specific memory, other memory-related cognitive operations and comorbid psychiatric/ fatigue symptoms were affected by vestibular dysfunction. Based on previous literature demonstrating the widespread connections that the vestibular system has within the cortex, cognitive impairments (notably those involving spatial memory) and other neuropsychiatric symptoms were expected to be prevalent amongst the sample. The mechanisms underlying these vestibular-cognitive effects were also explored using SEM. Several models tested whether cognitive performance was related to vestibular function via a direct (i.e. due to potential disruptions to key vestibular cortical networks related to cognition) or indirect pathway (i.e. through age, psychiatric or fatigue/ sleep-related effects).

Key Findings

With regards to the first aim, the results revealed that psychiatric, fatigue/ sleep and cognitive disturbances were all prevalent amongst the sample. Clinically significant levels of anxiety, fatigue and disturbed sleep quality were especially prominent on the questionnaire responses. Objective cognitive testing also revealed that over 50% of the sample performed below average, according to age-matched normative data, on the RVP (sustained attention),

SSP (working memory capacity), SWM (spatial working memory) and the DMS (short-term memory). Taken together these results show that vestibular dysfunction can induce a complex constellation of attention, memory and wellbeing deficits which extend beyond the traditionally recognised symptoms of vertigo, unsteadiness and impaired vestibular reflexes (Bisdorff et al., 2015). A second major finding revealed by the SEM analysis, was that postural stability on the balance platform accounted for a significant proportion of the variance (17%) in visuospatial memory performance, independent of any common causes related to aging. Moreover, this vestibular-cognitive effect could not be explained away by the presence of psychiatric or fatigue/ sleep symptoms. The fact that the direct pathway between balance function and visuospatial memory remained close to significance across the mediation models (just missed significance in the fatigue model), suggests that vestibular inputs could make a direct contribution to cognitive function. Importantly, since the psychiatric and fatigue/ sleep mediators only accounted for a small amount of variance within the total path, a direct rather than indirect mechanism could underlie the vestibular-cognitive effects reported in this study. A more focused regression analysis also showed that neuropsychiatric function did not predict postural performance, suggesting the more complex pathways predicted within the SEM (i.e. posturography as a direct predictor of visuospatial memory) may provide a better fit to the data.

Prevalence of Comorbidity

To my knowledge, there are no studies to date which have simultaneously investigated such a broad range of symptoms in patients with vestibular dysfunction using validated tests rather than uncontrolled self-report measures. The current findings support existing research which has demonstrated high prevalence rates of anxiety, self-reported cognitive dysfunction, and fatigue symptoms on general health questionnaires. Importantly, they also extend this literature to show that comorbid symptoms of fatigue and sleep

disturbance frequently occur in this patient group when measured using specialised scales adapted for use with other neurological conditions (Barbanti, Fabbrini, Aurilia, Vanacore & Cruccu, 2007; Herlofson & Larsen, 2002). Moreover, the data show that the cognitive impairments which patients have previously complained of on patient forums, subjective questionnaires and during clinical interviews (Bigelow et al., 2015a; Bisdorff et al., 2015; Grimm et al., 1989), were not simply self-perceived but manifested on actual objective tests of specific cognitive processes. Participants showed below-average performance on a number of specific cognitive processes, which included spatial memory as well as sustained attention, visual memory for object patterns and working memory capacity.

The current data demonstrate the extensive reach of the vestibular system and indicate that further efforts should now be dedicated to improving the screening and treatment of cognitive, psychiatric and fatigue symptoms within neuro-otology clinics. Vestibular testing could also be provided for individuals with impairments to those cognitive processes that are known to be vulnerable after vestibular dysfunction (e.g. elderly adults with spatial memory deficits: Bigelow et al., 2015b; Harun et al, 2016b). Both are likely to be important since vestibular patients with comorbid psychological symptoms have been shown to have worse outcomes than those who do not (Lahmann et al., 2014; Tschan et al., 2011).

Mechanisms of Vestibular-Cognitive Effects

Despite growing consensus that vestibular dysfunction can impair memory and other relevant aspects of cognition and wellbeing, the nature of these interactions has remained poorly understood. The significant associations that were identified here between balance function and those cognitive tests relating to visuospatial memory (independent of age and comorbid effects) are consistent with an emerging literature evidencing a direct vestibular-cognitive pathway. Although the mechanisms behind this direct pathway fall short of a

complete explanation, the main premise focuses on neuroanatomical links which show how vestibular signals could be passed to areas of the cerebral cortex involved in cognition and memory (Hanes & McCollum, 2006). Moreover, the fact that the vestibular cortical network includes several regions involved in visuospatial processing and memory (e.g. the hippocampus, insula, superior temporal gyrus and inferior parietal lobule), fits with clinical data where vestibular signals appear to be particularly relevant for spatial memory, navigation and orientation (Bigelow & Agrawal, 2015; Brandt et al., 2005). In line with this idea, the current data showed that visuospatial memory processes were affected by balance function. Moreover, the factor analysis revealed that the majority of cognitive variance within this patient sample was associated with visuospatial memory processes (as opposed to attention or information processing). Additional analysis failed to show that visuo-spatial memory capacity, of for that matter any other neuropsychiatric function measured here, predicted balance control (as measured by the Romberg ratio) as would be expected if there is a bi-directonal relationship.

If the direct pathway holds, then vestibular dysfunction could have disturbed regions within the vestibulo cortical network which are involved in visuospatial processing, resulting in changes related to the cognitive mapping of the environment within this sample (e.g. performing mental transformations: Lenggenhager, Lopez & Blanke, 2008; spatial memory and navigation: Brandt et al., 2005, Kremmyda et al., 2016, Shautzer et al., 2003; and path integration: Cohen, 2000). Thus although the effects of vestibular dysfunction appeared to extend to a range of cognitive processes and aspects of wellbeing, it could be argued that visuospatial processes, particularly memory, are especially reliant on vestibular signals. Also recall that vestibular-cognitive effects could actually extend to operations that are not typically associated with spatial information if the human brain carries out cognitive functions within a relational framework that resembles physical space (Hanes & McCollum,

2005). For example, functions which require information about the structure of space and movement such as orientation (Karnath & Dieterich, 2006), numerical cognition (Smith, 2012) and body ownership (Lopez, Halje & Blanke, 2008) could all be impeded by disturbances to the self-motion signals provided by the vestibular system (Bigelow & Agrawal, 2015).

However, it is important to note that the cognitive tests implemented here were all delivered visually and several required processing of spatial details either as an explicit instruction (e.g. PAL- memory for object-location associations), or more implicitly (e.g. DMS- memory for complex visual patterns where the configuration of the pattern features was altered). This decision was motivated by the fact that there is already strong clinical evidence to support a connection between vestibular inputs and visuospatial cognition (see Bigelow & Agrawal, 2015; Hanes & McCollum, 2006; Smith et al., 2005; Smith et al., 2016 for reviews), meaning the battery was likely to be sensitive to some of the deficits faced by the sample. More recently, Bigelow et al. (2015b) also studied a cross-sectional sample of elderly adults and showed that vestibular function was only associated with specific cognitive domains, mainly visuospatial abilities but also working memory and attention. Verbal memory was not associated with vestibular function. Nonetheless further insights might still be gained from investigating whether the specialisation of vestibular signals within visuospatial memory processes holds when compared to a more varied test battery which is less focused on visual cognition.

Further, although the SEM analyses indicated that vestibular signals may be particularly relevant for visuospatial memory processes, prevalence rates from the current and previous studies suggest that vestibular dysfunction can induce a wide range of comorbid symptoms, including sustained attention (RVP) and fatigue/ sleep disturbances. One hypothesis for the broad range of disturbances identified here is that patients with vestibular

dysfunction are having to allocate additional attentional resources to maintain postural stability and orient themselves during daily activities ("orientation first principle"), resulting in less availability for other mental processes (Redfern et al., 2004). These compensatory mechanisms could in turn lead to impaired performance on a range of cognitive tasks (not limited to visuospatial memory) which also extract resources from the same limited attentional capacity.

In line with this hypothesis, dual-task studies have already demonstrated that patients with vestibular dysfunction perform worse on a variety of spatial and non-spatial cognitive tasks when in a posturally challenging environment (see Hanes & McCollum, 2004; Bigelow & Agrawal, 2015 for reviews). These results suggest that vestibular-cognitive effects arise due to general capacity limitations which reflect the attentional demands of each task, rather than the specialisation of vestibular signals for visuospatial memory processes. The attentional hypothesis could also explain the more general complaints that have been described by vestibular patients such as feeling confused, fatigued and unable to concentrate which might reflect mental exhaustion or overload (Bigelow et al., 2015a; Yardley et al., 1998).

However, some caution should be exercised when interpreting dual-task studies like the above since there is no way of determining whether the spatial and non-spatial tasks being compared were equally difficult (Hanes & McCollum, 2006). For example, Shumway-Cook, Woollacott, Kerns and Baldwin (1997) previously examined the effects of a sentence-completion and visuospatial task (perceptual matching task) on postural stability amongst older adults with a history of falls and found that the dual-task effects were actually stronger for the sentence-completion task. Importantly, since the visuospatial task provided participants with a visual cue which could be used to maintain balance (fixation cross) while the sentence-completion task did not, the results seem to reflect the effects of visual

dominance rather than the attentional demands of particular sub-tasks. A specialisation for spatial cognition could therefore have been masked by previous research if the non-spatial task was particularly difficult or the spatial task easier. Further, several of the paradigms implemented within dual-task studies have involved cognitive processes which are organised spatially (e.g. counting: Nascimbeni, Gaffuri, Penno & Tavoni, 2010; arithmetic: Yardley et al., 2002; and reacting to visual stimuli presented in a given location: Andersson, Yardley & Luxon, 1998). Thus, any dual-task effects might still be explained by the specialised role of vestibular inputs in visuospatial cognition (Redfern et al., 2004).

All in all the literature above underscores the importance of vestibular inputs to memory. While attentional-based accounts would argue that vestibular-cognitive effects are driven by attentional capacity limits rather than the specialisation of vestibular signals within visuospatial processes, the methodological concerns associated with dual-task studies alongside existing clinical literature linking vestibular dysfunction to particular cognitive impairments, indicates that vestibular signals likely have a more distinct role in cognition perhaps by providing spatial structure in visuospatial processes like spatial memory, orientation and navigation (Bigelow & Agrawal, 2015; Hanes & McCollum, 2006). Overall, the current data provide tentative evidence of a specific effect of vestibular dysfunction on visuospatial processing and suggest that this association should not be downplayed as an indirect consequence of psychiatric/ fatigue impairments or general disorientation which draws attention away from the cognitive tasks (Hanes & McCollum, 2006).

Limitations

The above conclusions are limited by the cross-sectional study design, which cannot provide causal inferences about the mechanisms of vestibular-cognitive effects. Although the present SEM analyses provide valuable information about vestibular contributions to

cognition which will hopefully encourage further exploration of vestibular-cognitive pathways, they cannot provide a complete picture. Longitudinal study designs which monitor participants across the lifespan and assess their cognitive functioning prior to and after the onset of the balance problem would contribute useful insights into the temporality of effects (which mediation assumes but cannot test) (Semenov et al., 2016). More complex model designs could also be implemented which adjust for other relevant variables which could affect cognitive functioning (e.g. education, ongoing medical conditions, hearing loss) and were not modelled here. Some caution should however be exercised when increasing the number of model parameters to avoid false positives, particularly since the SEM tested here were already failry complex and yielded small effects (though these were comparable to previous studies Bigelow et al., 2015a; Bigelow et al., 2015b; Semenov et al., 2016). Increasing the sample size from the relatively small numbers recruited here (ideally SEM requires 200 cases or five participants per estimated parameter; Kline, 2011) would likely improve effect sizes and model fit. Finally, since the SEM showed that older participants were more unstable (increased sway) and had worsened visuospatial memory performance, future studies could also examine the influence of vestibular-cognitive effects on geriatric outcomes (e.g. falls risk, independence). Such efforts may help to provide more useful therapeutic strategies (e.g. navigation or spatial orientation tasks) for an increasingly aged population (Bigelow et al., 2015b; Semenov et al., 2016).

Another limitation relates to the focus on posturography (balance platform) as a measure of vestibular function. This is a routinely implemented clinical test which assesses one of the prominent, everyday vestibular symptoms (i.e. a patient's ability to maintain balance under varying levels of sensory input; Semenov et al., 2016). This was deemed to be the most appropriate neurophysiological test since the majority of the sample suffered with VM (rather than a peripheral dysfunction) which does not necessarily manifest on the

videonystagmography and vHIT. Additionally, Agrawal et al. (2009) demonstrated that postural performance was significantly associated with self-reported fall risk over a twelve month period, indicating the potential utility of the test as an indicator of chronic unsteadiness. This is relevant to the present sample where the most commonly reported constant symptom was unsteadiness, meaning vestibular impairments were more likely to be captured by the assessments on the day of testing.

However, it should be noted that postural performance can be affected by other non-vestibular factors such as participant compliance (e.g. anxiety at the higher postural demands) or ongoing medical conditions (e.g. arthritis, fibromyalgia) (Semenov et al., 2016). In this study, the gradual increase in postural demands and engagement with the consultant as well as the inclusion criteria should have minimised these concerns, but further research may still benefit from investing whether cognitive impairments are associated with other questionnaire (e.g. Vestibular Migraine Diagnosis Questionnaire; Celebisoy et al., 2016) or neurophysiological (e.g. using vestibular-evoked myogenic potentials to assess the effects of the saccule; Bigelow et al., 2015b, Furman et al., 2013) measures of vestibular function which can probe specific vestibular symptoms or end organs.

Vestibular Migraine

Finally as mentioned above, the majority of the sample were diagnosed with VM so the current findings offer the best new insights into comorbidities within this patient group. Traditionally vestibular-cognitive effects have been studied in small numbers of patients with bilateral or unilateral vestibular loss to isolate the specific contribution of the peripheral vestibular organs (Brandt et al., 2005; Hüfner et al., 2007; Schautzer et al., 2003). Here, a sample of unselected patients were tested to ensure that the results were representative of patients attending a tertiary neuro-otology clinic. Psychiatric, cognitive and fatigue/ sleep

abnormalities were prevalent amongst the sample. The intensity and unpredictability of VM attacks (on top of the constant problem that was already present in most of the sample), as well as disturbances to common neural circuitry including the PBN, trigeminal nucleus caudalis and serotonergic neurotransmission (Best et al., 2006; Furman, Balaban & Marcus, 2005; Lahman et al., 2014) could both be relevant in explaining these neuropsychiatric symptoms. More generally, VM is thought to disturb central vestibular structures including the vestibular nuclear complex and vestibulo-cerebellum. These regions integrate sensory information and enable sensory recalibration which forms the basis of several vestibular rehabilitation techniques (Furman, Balaban & Pollack, 1997; Furman & Whitney, 2000). It is therefore unsurprising that the current study demonstrated widespread morbidity, with fatigue/ sleep disturbance being confirmed as particularly relevant comorbidities (Mendel et al., 1999; Salhofer et al., 2010).

Although unselected opportunistic sampling helped to ensure that the present sample was representative of a neuro-otology clinic, it also meant that some vestibular syndromes were missed (e.g. vestibular paroxysmia and vestibular neuritis), or were less likely to be included (e.g. BPPV where the associated symptoms manifested in transient attacks which were no longer in an active state), thus prohibiting group comparisons. Recruiting from a tertiary care department relative to other services (e.g. general practitioner, ear nose and throat specialists) may have also reinforced the sampling bias if the most complex patients were being referred to the tertiary unit. In line with this idea, most of the current sample were referred to the clinic because they had not responded to the primary/ secondary care that they had already accessed. Both of the above could contribute to a selection bias that might favour VM, given that the disorder is under-recognised and diagnosis is largely based on exclusion (Furman & Whitney, 2000). Nevertheless, sampling was mostly in line with previous epidemiology reports where VM was shown to be more prevalent than other vestibular

disorders (Lempert & Neuhauser, 2009), and enabled a relatively large sample of patients to be tested.

Conclusion

The current study supports and extends upon previous findings in demonstrating that cognitive (particularly visuospatial memory and attention), psychiatric and fatigue/ sleep disturbances are prevalent in patients with vestibular dysfunction. Moreover, a significant proportion of the variance in participants' visuospatial memory performance could be explained by vestibular function (posturography), independent of any age, psychiatric or fatigue/ sleep-related (marginal) effects. These findings highlight the need for greater scientific and clinical attention to be focused on exploring the reach of vestibular dysfunction beyond balance symptoms, and on understanding the mechanisms underlying vestibular contributions to memory which should not be downplayed as an indirect consequence of other comorbidities (Hanes & McCollum, 2006).

Future research could apply longitudinal designs to larger samples of patients to further elucidate the relative contribution of direct and indirect (e.g. age, psychiatric, auditory impairment co-morbid illness) vestibular effects on cognitive performance (Bigelow et al., 2015a). These studies could also add to the battery of cognitive assessments used here to determine whether particular cognitive profiles are present (i.e. specialisation for visuospatial memory processes) across vestibular patients as whole (relative to matched controls), or just particular vestibular syndromes.

Chapter 3

Neuropsychiatric Outcomes in Individuals with Traumatic Brain Injury Following Caloric Vestibular Stimulation.

Chapter 2 showed that vestibular signals exert a direct influence over cognition and memory processes, such that when the vestibular system becomes dysfunctional, these processes are impeded. These results raise an important question: If down-regulating the vestibular system via disease or injury leads to cognitive loss, then does up-regulating the vestibular system lead to cognitive gain? This chapter aimed to test this hypothesis by artificially stimulating the vestibular system and examining whether there were associated improvements in the memory and cognitive symptomology (particularly visuospatial memory) that were shown to be relevant in patients with vestibular dysfunction. The same CANTAB tests and comorbid questionnaires were implemented to provide further evidence that the visuospatial memory processes identified in Chapter 2 really are affected by vestibular inputs, independent of comorbid psychiatric and fatigue symptomology. TBI patients were sampled given that they show neuropsychiatric impairments encompassing memory and attention as well as psychiatric and fatigue disturbances. Theoretical insights aside, TBI presents a significant global burden for which effective therapies are still lacking meaning the current findings will also be of relevance to neurorehabilitation. If successful, then the results would corroborate the findings of Chapter 2 and move closer towards understanding whether particular cognitive processes interact with the vestibular system (i.e. visuospatial memory) and the functional relevance of vestibular inputs within cognitive processes.

The following subsections will first provide an overview of TBI, including the disabling cognitive and memory symptoms that typically occur amongst TBI survivors and the existing treatments used to address these. CVS will then be proposed as a novel solution and the theoretical insights that can be gained from applying vestibular stimulation will be

reaffirmed. The introduction will close with an outline of the experimental approach and hypothesis.

Traumatic Brain Injury

TBI evolves longitudinally after an externally-inflicted trauma to the brain (via contact or inertial force) and is a field in medicine with great unmet needs (Vaishnavi, Rao & Fann, 2009). These injuries are a major cause of death and disability across the globe, especially within younger adults (15- 44 years) (Tagliaferri, Compagnone, Korsic, Servadei & Kraus, 2005) and veterans of modern warfare with exposure to blasts/ explosions (Scherer & Schubert, 2009). TBI places a huge burden on society, Coronado et al. (2012) estimated the costs within the USA during 2010 to be $11.5 billion for direct medical costs and $64.8 billion on indirect costs (e.g. loss of productivity), not to mention the great personal suffering experienced by survivors and their relatives. Despite this high prevalence and expenditure, TBI remains challenging to treat effectively (Rao & Lyketsos, 2000) and there are now global initiatives to improve the outcomes of TBI survivors (see https://intbir.nih.gov/).

The multi-faceted nature of TBI is thought to underlie this difficulty (Rao & Lyketsos, 2000). TBI often results in both focal and diffuse brain damage (including axonal injury), as well as disruptions to neurotransmitters involved in regulating cognitive and behavioural homeostasis (e.g. cholinergic, serotonergic systems) (McAllister, 2008). As a result survivors are left with a complex constellation of symptoms encompassing physical/ sensory disturbances (e.g. headache, paralysis, pain and seizures), mood disorders and cognitive dysfunction, including memory deficits (Demirtas-Tatlidede et al., 2012; Kinnunen et al., 2010; Rao & Lyketsos, 2000). In the past TBI therapies have often focused on observable physical/ sensory deficits, while ‘invisible’ neuropsychiatric symptoms frequently remained unaddressed (Fleminger & Ponsford, 2005; Koponen et al., 2002). However, there is now a

growing consensus that targeting these cognitive and emotional problems is essential to TBI rehabilitation (Flashman & McAllister, 2002).

Neuropsychiatric Sequelae

Cognitive deficits are amongst the most common complaints immediately after TBI as well as long-term (McAllister, 2008). Domains such as short-term memory, attention, information processing and executive functions are all frequently impaired, and patients typically present with multiple deficits (Arciniegas, Held & Wagner, 2002). When unaddressed, these cognitive changes can pose a significant barrier to community reintegration including independent living, vocational activities and social relationships (Wilson, Wienegardner & Ashworth, 2013).

Of particular relevance to this thesis are memory disorders, which are one of the cardinal features of cognitive dysfunction following TBI (Granacher, 2015). Immediately after injury, the duration of retrograde (memory for events/ information prior to the injury) and anterograde (ability to create new memories) amnesia can be used to predict eventual outcome (McCullagh & Feinstein, 2011). Later, impairments to the explicit declarative stores can also compromise important functions such as working memory which are known to persist (Schmitter-Edgecombe & Seeley, 2012). Working memory requires the maintenance of information in temporary storage while cognitive manipulations are simultaneously performed on the information, and is implemented in a number of cognitive processes (e.g. problem solving, active listening). Thus it is easy to conceive how memory deficits can restrict participation in everyday activities that are necessary for work and study (e.g. remembering the details of a telephone conversation while taking notes; Christodoulou et al., 2001).

Attentional impairments, particularly related to capacity limits, are also prevalent within TBI and can have a knock-on effect on other cognitive processes including memory.

Patients are often unable to ignore irrelevant stimuli which in turn affects their ability to process relevant inputs (Lavie, 2001). Unfortunately, these deficits regularly go unnoticed during rehabilitation and only surface once the patient has returned to their daily routines where additional cognitive demands are present and treatment is less accessible (Granacher, 2015). Impairments to executive functions which enable self-directed behaviours such as planning, volition, purposive action and self-monitoring are also particularly vulnerable. This is because the anterior portions of the brain, which are associated with executive functions, are generally more affected by TBI than the posterior regions. TBI can seriously handicap cognitive functions, including memory, by virtue of executive function. For example, consider prospective memory which involves remembering to perform a task in the future; if executive functions are impaired then the individual cannot formulate an earlier plan to complete the action (Granacher, 2015).

Other neuropsychiatric symptoms are also frequent amongst TBI survivors which can interfere with memory functioning. For example, post-traumatic fatigue is widely recognised as a central nervous system disorder which can impede cognition by slowing mental processing speed (Johansson, Berglund & Rönnbäck, 2009) and increasing the mental effort required to attend and memorise information (Belmont, Agar, Hugeron, Gallas & Azouvi, 2006), and thus can further contribute to disability (Juengst et al., 2013). Complaints of sleep-wake disturbances are also prevalent and while the mechanisms are thought to differ from fatigue (here the hypocretin system is implicated), the impact on quality of life is similarly negative (Culebras, 2007).

Personality changes, psychotic illness and mood disturbances are another potential source of disruption to memory following TBI. These symptoms are thought to be particularly prevalent amongst TBI survivors because several functions of social behaviour are associated with the frontal and temporal lobes which are especially vulnerable to TBI

(Fleminger, 2008). Major depression is a common sequelae, with around 20-30% of survivors becoming depressed during the first year (Jorge et al., 1993; Jorge, Robinson, Moser, Tateno, Crespo-Facorro, & Arndt, 2004), and some reports showing symptoms which persist for up to 30 years post-injury (Koponen et al., 2002). Importantly, temporal regions including the hippocampus have been shown to undergo atrophic changes following TBI and there is also evidence that major depression can reduce hippocampal volumes (Bremner et al., 2000). Consequently, those individuals with both a TBI and a mood disorder ("a double hit") have been shown to have significantly smaller hippocampal volumes than those without mood disturbance, which may in turn increase their susceptibility to memory deficits (Jorge, Acion, Starkstein & Magnotta, 2007). Anxiety disorders are also prevalent and can be associated with symptoms of panic and agoraphobia (Fleminger, 2008). When severe, these mood disorders can disrupt recovery, for example the social withdrawal associated with depression may reduce engagement in rehabilitation activities, while increased anxiety may aggravate symptoms such as headache or fatigue and lead to avoidance behaviours (McAllister, 2008).

These neuropsychiatric symptoms may be well-suited for treatment with vestibular stimulation because in the previous chapter similar deficits were prevalent amongst patients with vestibular dysfunction, suggesting some of these symptoms might be influenced by the presence of vestibular inputs. Another reason is that vestibular system diffusely projects to a variety of cortical and subcortical structures, while TBI causes widespread axonal injury (due to the shearing and tearing of nervous tissue) as well as more focal damage. The diverse cortical network activated by vestibular stimulation may therefore be equipped to alleviate TBI symptomology. One further implication is that many of the overlapping symptoms seen within TBI may stem from an undiagnosed balance disorder. This is especially likely amongst individuals with blast injuries (which induce global brain damage) who commonly suffer from vestibular symptoms, indicating that vestibular loss may also be a contributing

factor to TBI symptomology (Hoffer et al., 2010). Similar hypotheses have already been suggested for AD (Previc, 2013) and spatial neglect (see Karnath & Dieterich, 2006 for a review) which involve temporal-parietal brain areas that are shared with vestibular processing.

Existing Treatment Options

Despite the prevalence and persistence of neuropsychiatric deficits in TBI, current medical conceptualisations of these symptoms and evidence-based guidelines for their rehabilitation are incomplete (Warden et al., 2006). Patients will often receive cognitive neurorehabilitation focused on helping them to achieve realistic goals (Elliott & Parente, 2014; Williams, Evans & Fleminger, 2003). For example, errorless learning strategies which aim to eliminate memory errors during the learning process (e.g. breaking down the task, correcting errors and gradually removing prompts; Clare & Jones, 2008) have improved memory for specific but not generalised information (Cicerone et al., 2011). However, a major obstacle to these treatments is the lack of insight (anosognosia) that TBI patients have into their difficulties (Williams et al., 2003), particularly their neuropsychiatric symptoms (Sherer et al., 1998). Thus, asking patients to independently implement therapy strategies for problems of which they are unaware may not be sufficient as a stand-alone therapy (Flashman & McAllister, 2002).

Bottom-up approaches such as pharmacological treatments can also be combined with rehabilitation programs and require less autonomy (Vaishnavi et al., 2009). Beneficial effects have been demonstrated in several post-injury symptoms, such as sleep quality and depression using selective serotonin reuptake inhibitors (Larson & Zollman, 2010). Cholinesterase inhibitors (mainly used to treat AD) have also been useful in addressing memory impairments (Warden et al., 2006). However, pharmaceutical interventions have generally struggled to balance the benefits of managing one deficit, whilst not inducing side-

effects which worsen another. For example, anticonvulsants such as phenytoin have improved mood disturbances and post-injury epilepsy, while impairing cognitive function in TBI (Dikmen, Temkin, Miller, Machamer, & Winn, 1991; Trimble, 1987). These studies reflect the complex constellations of symptoms found within TBI and the demand for treatments which can tackle patients' multiple deficits (Williams et al., 2003).

Neurostimulation methods (NSM) are a drug-free, bottom-up treatment, which have shown potential in promoting recovery after TBI with less side-effects. During the acute stages post-injury NSM have been used to decrease maladaptive cortical hyperexcitability, then in later chronic stages NSM have been applied to promote synaptic plasticity and cortical reorganisation to restore previously damaged neural pathways (Demirtas-Tatildede et al., 2012; Villamar, Santos Portilla, Fregni, & Zafonte, 2012). Deep brain stimulation (DBS), a procedure which implants electrodes into targeted subcortical regions of the brain, has promoted spatial memory performance in neurological patients undergoing surgery when applied to the entorhinal cortex during learning (Suthana et al., 2012). Another study also improved spatial working memory deficits in a TBI patient, when DBS was applied to the medial septal neucleus which connects to the hippocampus (Lee et al., 2013). However, DBS is often considered an unappealing modern treatment for TBI due to its invasiveness (Miller & Ngo, 2007).

Non-invasive NSM such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which pass electrical current through electromagnetic coils placed on the scalp to facilitate or inhibit targeted brain structures (Pape, Rosenow & Lewis, 2006), have also shown therapeutic potential by steering neural plasticity (Page, Cunningham, Plow & Blazak, 2014). Temporary improvements in post-TBI depression have been demonstrated using TMS (Fitzgerald et al., 2011), as well as reduced attention deficits following tDCS to the left prefrontal cortex (Kang, Kim & Paik, 2012). However, a recent

review revealed that only one out of five studies showed a significant effect of tDCS/ repetitive TMS on memory performance in brain injury patients (Spreij, Visser-Meily, van Heugten & Nijober, 2014). The time consuming, condition-specific, application of these NSM to targeted areas of the brain may explain these findings, since the specificity in which they are administered means that it is difficult to address the multifaceted symptoms of TBI (Been, Miller, Ngo & Fitzgerald, 2007; Miller & Ngo, 2007).

Proposed Solution

If, as proposed, the vestibular system directly modifies memory and cognition then CVS may offer some benefit here. Recall that this procedure involves irrigating the external ear canal with thermal currents, which alters the density of fluid inside the semi-circular canals and in turn stimulates the peripheral vestibular nerve and vestibular nuclei (Been et al., 2007). CVS has been associated with the release of several important neurotransmitters including acetylcholine (Horii et al., 1994), GABA (Samoudi, Nissbrandt, Dutia & Bergquist, 2012), histamine (Horii et al., 1993) and serotonin (Ma et al., 2007). Functional neuroimaging has also revealed that CVS activates multiple cortical and subcortical structures including the ACC, temporoparietal cortex, insular cortex and the brain stem (Lopez et al., 2012, see Figure 3.1); Suzuki et al., 2001). Taken together, these findings indicate that CVS holds significant potential for the broad-scale modulation of several sensory and higher order functions including memory (Black et al., 2016; Miller et al., 2007).

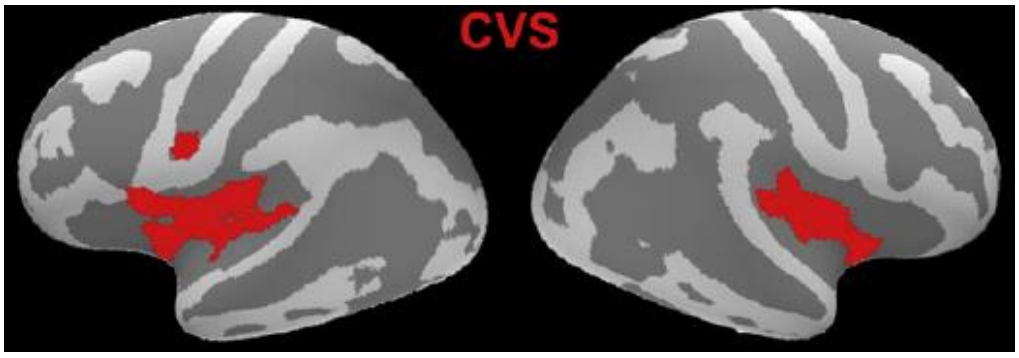


Figure 3.1. Clusters of brain activity (red areas) elicited by CVS as identified by a meta-analysis by Lopez et al. (2012).

While CVS has a long history of clinical safety, investigations into its therapeutic potential are sparse. Research has been limited by the unpleasant side-effects, lack of dose control and inconvenient administration procedures associated with the technique (Black et al., 2016). However, despite any discomfort that may have been experienced, small groups of patients with psychiatric illnesses and acquired brain injuries have shown significant improvements in the symptomology associated with mania (Dodson, 2004), anosognosia (insight into illness) (Cappa et al., 1987; Levine et al., 2012), pain (Ramachandran, McGeoch, Williams & Arcillia, 2007), hemispatial neglect (Adair, Na, Schwartz, Heilman & 2003) and hemianesthesia (Bottini et al., 2005). Delivering cold water CVS alongside verbal and spatial stimuli also sped the rate at which these items were later recalled in a sample of healthy participants (Bächtold et al., 2001).

Following the advent of more tolerable and practical solid-state CVS devices (Black et al., 2016), Wilkinson and colleagues have also managed to apply CVS longitudinally (over days or weeks). This has resulted in a number of lasting beneficial effects which could be observed offline across several neurological disorders including aphasia (Wilkinson et al., 2014) and Parkinson's disease (Wilkinson, Podlewska & Sakel, 2016). Importantly, a preliminary investigation by the research team also showed that CVS improved levels of awareness within two minimally conscious patients who had sustained a TBI (via hypoxia and surgically induced thalamic infarction) (Vanzan, Wilkinson, Ferguson, Pullicino & Sakel, 2016), highlighting the therapeutic potential of CVS in TBI.

Although the mechanism behind these effects is somewhat unclear, the fact that CVS induces broad-scale changes in blood flow across multiple cortical networks (insular cortex, basal ganglia, posterior thalamus, parieto-frontal operculum, superior temporal gyrus; Lopez et al., 2012) suggests that CVS could serve as an effective neuromodulator for a variety of clinical conditions. Importantly, the core circuits activated by CVS are often implicated in

TBI and are associated with memory, attentional, executive, mood and motor functions. Thus although previous research has focused on acquired brain injury, caloric induction is likely to be particularly suited to TBI where the diffuse and diverse nature of the injuries sustained means that there is often a constellation of symptoms which require treatment. CVS could target these symptoms simultaneously without relying on patients to implement strategies (Suzuki et al., 2001). The availability of newly developed CVS devices also means that stimulation can be delivered comfortably and within patients' homes (Black et al., 2016).

Clinical relevance aside, the study could also provide further support for the direct pathway between vestibular dysfunction and cognitive impairment (visuospatial memory) which was evidenced in Chapter 2. More specifically, if this direct vestibular-cognitive pathway holds, then any beneficial memory and cognitive changes seen within this TBI sample should not be confined to simultaneous increases in comorbid psychiatric or fatigue symptomology. In other words improvements in memory and cognition could occur in the absence of mood and fatigue-related changes.

The Current Study

An exploratory pilot study was conducted with eight community-based TBI patients who received repeated sessions of CVS for several weeks in their homes. The protocol consisted of four phases: baseline, sham stimulation (N= 6), active CVS (N= 8) and follow-up. Changes in memory, attention, information processing, executive functioning, mood, fatigue and general wellbeing were evaluated using behavioural assessments. Electrophysiological changes were also measured and are presented in the next chapter to avoid making this chapter exceptionally long.

Hypothesis. Blocks of CVS were predicted to trigger improvements in cognitive performance as assessed by objective behavioural tests (CANTAB), as well as in other

important symptoms that can impact cognitive performance such as psychiatric and fatigue disturbances according to self-report questionnaires. Some variability in responsiveness was predicted across all the measures given the heterogeneous nature of TBI.

Importantly, these beneficial effects were expected to onset during blocks of CVS, as opposed to the baseline or sham assessments. Additionally, if the effects of CVS are cumulative, then further improvements were anticipated to occur after eight rather than four weeks of CVS. Some of these facilitatory effects may also be present at follow-up if the changes are carried over. The protocol implemented within this study meant that all of these effects were expected to occur offline as opposed to during concurrent vestibular stimulation.

The following sections will describe the study protocol and any resulting changes that were shown on the behavioural outcome measures. To give an overview, CVS was well tolerated by all, but responses on the outcome measures were varied and commonalities were difficult to come by. Nevertheless, several participants showed CVS-related improvements on the visuospatial memory tests according to descriptive statistics, and nearly all participants improved on least one CANTAB test in response to CVS within the inferential analyses. Psychiatric and fatigue symptoms were largely unaffected by the stimulation. Taken together these findings suggest that CVS may exert a modulatory effect on some aspects of TBI symptomology. Importantly, any vestibular-cognitive effects that were present were not dependent on concurrent changes in comorbid symptomology, providing further evidence for a direct rather than indirect pathway.

Method

Design

This pilot study employed a multiple single cases approach. A cross-over design was implemented as opposed to a randomised placebo-controlled trial because it seemed more

appropriate to first establish whether any participants actually showed improvement, and for how long. If a favourable outcome was achieved, a subsequent study could implement a randomised placebo-controlled design. Another consideration was that the study was fairly long and compliance might be low within the true placebo arm where little change was predicted.

To ensure that natural recovery or placebo-effects were estimated, all participants received eight weeks of active CVS, but the majority also completed a four week block of sham stimulation prior to receiving active CVS (cohort B). Upon study registration participants were randomly allocated to one of two cohorts with a ratio of 3:1 (cohort B: cohort A). While the participants were blinded to this allocation, the researcher was not (single-blind) so that tolerance and safety could be monitored.

Recruitment

Patients were recruited via physician referral from two Kent based NHS trusts (East Kent Hospitals University NHS Foundation Trust, Kent and Medway NHS and Social Care Partnership Trust). All participants had suffered a moderate or severe TBI at least three months prior to study enrolment (average time since injury was 2.5 years), and were in receipt of out-patient support from either a neuropsychiatrist or a neurorehabilitation consultant. All TBI diagnoses were documented in the patient's medical records and had been made by clinicians on the basis of the initial Glasgow Coma Scale (GCS) score (Jones, 1979), neurological and/ or neuropsychological abnormalities, degree of amnesia for events surrounding the accident, decreased levels of consciousness and neuroimaging evidence of neurologic deficit (American Psychiatric Association, 2013; Thurman, Sniezek, Johnson, Greenspane & Smith, 1995; Wortzel & Arcinegas, 2014; World Health Organization, 1992).

Patients who met the criteria in Table 3.1 were invited to participate. The inclusion criteria were intentionally broad to ensure that our findings would generalise to heterogeneous TBI populations and to facilitate study recruitment. Given the exploratory nature of the study, the exclusion criteria were restricted to the necessary precautions to demonstrate a treatment-effect by minimising potentially confounding influences, while ensuring participant safety.

Table 3.1
Recruitment Criteria

Inclusion Criteria
•Participants must have received a diagnosis of TBI. •Participants must have sustained their injury ≥6 weeks prior to study onset (to allow for acute spontaneous recovery to subside) and within a five year window (capable of treatment gains). •Participants must have chronic difficulties in one or more of the core symptoms being studied (psychiatric, cognitive, fatigue/ sleep disturbances) as assessed by the referring clinician. •Capacity to consent to the study. •Motivated to comply with the protocol. •An understanding of English sufficient to comply with the protocol. •Spouse/ carer willing to support the participant throughout the study.
Exclusion Criteria
•Premorbid history of intellectual disability. •Pre-existing endocrine or metabolic dysfunction. •Premorbid or ongoing neurological illness which could also induce neuropsychiatric symptoms. •Premorbid psychiatric history for which treatment beyond primary care services was sought. •Premorbid history of diagnosed sleep disorder. •Premorbid history of neurasthenia (or Chronic Fatigue Syndrome). •Previous exposure to neurostimulation. •Diagnosed inner ear pathology

Twelve patients were recruited into the study, eight completed the protocol (two females, six males) and four were discontinued (see Figure 3.2). Of the patients which were discontinued, two individuals were offered additional therapies mid-study which could not be completed alongside another therapeutic intervention, one patient withdrew himself due to stressful life events, and the final patient was withdrawn for failure to comprehend and comply with the protocol.

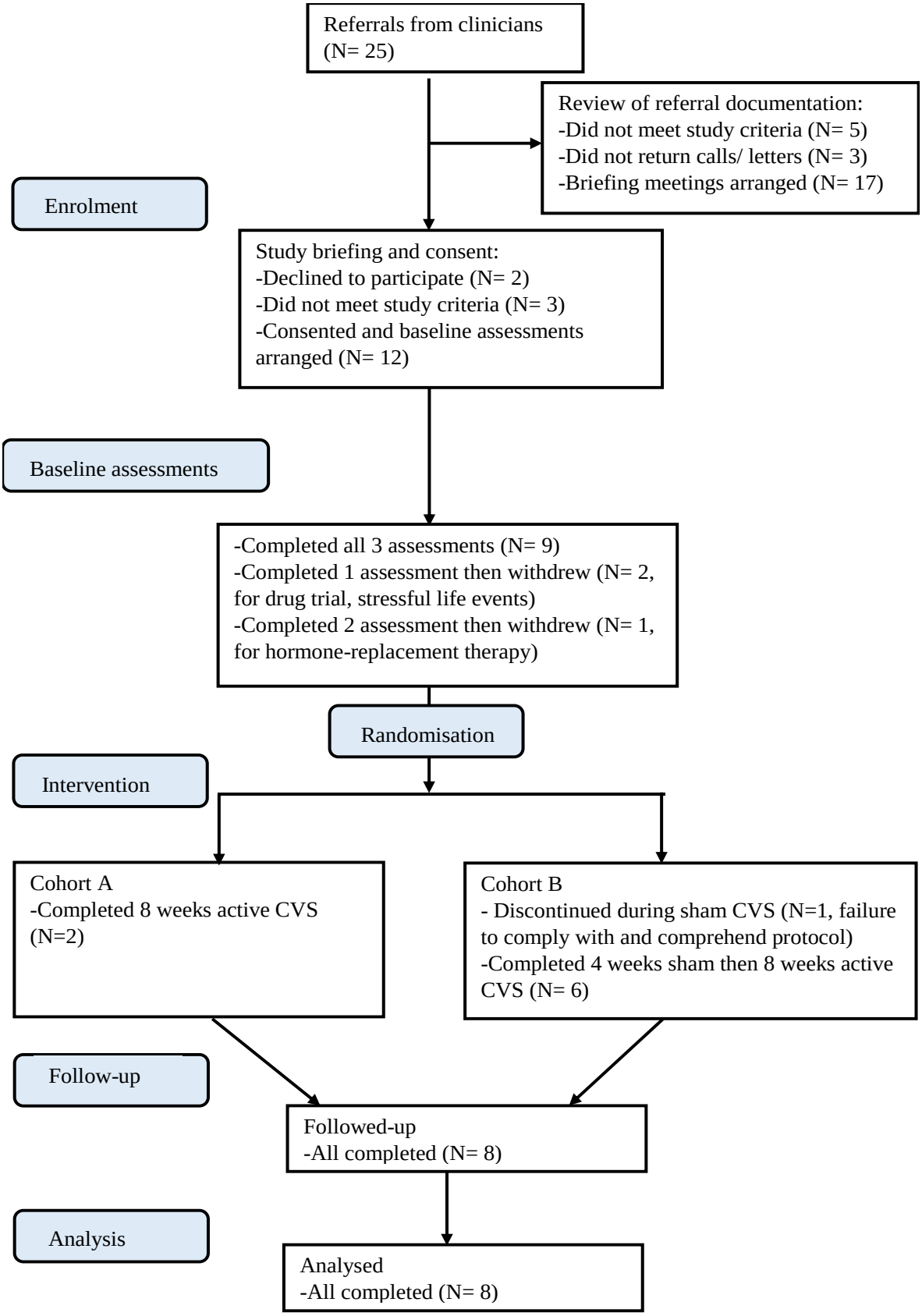


Figure 3.2. Consort statement showing the flow of participants throughout the study.

Identification numbers were assigned consecutively following referral, for simplicity, numbers 01- 08 will be used to describe the patients who completed the study. Individual case histories which summarise the key clinical features of each participant that completed the study can be found in Appendix B.

Ethical Considerations

The following study protocol was approved by the Cambridge Central NRES Committee.

Materials and Measures

Responsiveness to CVS was measured using behavioural and electrophysiological measures, the former are detailed below and the latter in the next chapter.

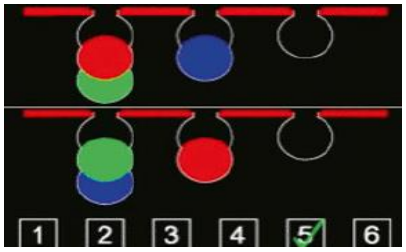
Behavioural measures. A variety of measures were included in the assessment battery to capture changes in the diverse symptomology of TBI. The measures fell into one of three broad categories: cognitive function, psychiatric/ fatigue symptoms, and general health status. Each category is described further below. All outcomes were selected on the basis of published research examining validity, reliability and applicability to TBI.

To fit within the overall aim of this PhD which was to investigate vestibular contributions to cognition, particularly memory, the majority of the battery was dedicated to assessing cognitive functions. These were measured using a customised battery of computer-interfaced tests from the CANTAB (CANTAB®- eclipse; Robbins & Sahakian, 1994). Recall from Chapter 2 that the CANTAB has been extensively used in research settings to infer brain-behaviour relationships (Wild & Musser, 2013). Many clinical trials with TBI samples have also implemented the CANTAB (e.g. Salmond, Chatfield, Menon, Pickard & Sahakian, 2005; Silver et al., 2009; Torgersen, Helland, Flaatten, & Wester, 2010), since the publishers now offer a "core battery" and bibliography relating specifically to TBI (see

http://www.cambridgecognition.com/academic/ccr-tbi).

Here eight tests were selected to determine whether any of the wide range of cognitive functions impaired by TBI (including information processing, executive functioning and memory) responded to CVS within individual participants. Six of these CANTAB tests were described in Chapter 2 (Delayed Match to Sample- DMS, Paired Associates Learning- PAL, Spatial Working Memory- SWM, Spatial Span- SSP, Reaction Time- RTI, Rapid Visual Processing- RVP); the remaining two tests were added to further address the complexity of TBI (One Touch Stockings, Affective Go-No-Go) and are described in Table 3.2.

Table 3.2
Two Additional Cognitive Assessments from the CANTAB.

Assessment	**Description**	**Example Trial & Key Outcome Measures**
One Touch Stockings (OTS)	Examines the use of executive functions to mentally solve a problem. Participants are shown two arrays containing coloured balls. Participants must work out (in their head) the minimum number moves required to achieve the top array by rearranging the bottom array and select the corresponding number.	 Number of problems solved correctly on first attempt.
Affective Go-No-Go (AGN)	Examines information processing biases for positive and negative verbal stimuli. Words are rapidly presented and participants must respond to a target category of words (positive or negative) across several trial blocks.	 Response bias and response time (ms).

Note. The remaining six assessments are described in full within Chapter 2 (see Table 2.5).

The CANTAB was selected for several reasons. On a theoretical level, the battery had already been used to uncover cognitive processes which the vestibular system might be likely to contribute to within Chapter 2. On a more practical level, all tests (except the Affective Go-No-Go) are language independent, meaning the test results are globally valid (Levaux et

al., 2007). Secondly, the instructions and stimulus presentations are all standardised during test delivery, therefore reducing intra-assessor unreliability between test repetitions. Some of the CANTAB tests also have parallel forms (DMS, PAL) which were implemented to enable more accurate repeat testing (reduced risk of practice/ learning effects). The administration times of the CANTAB tests are also brief (SSP, SWM and PAL additionally adjust to the level of performance) enabling reliable assessment of multiple cognitive processes (Collie, Maruff, Darby & McStephen, 2003). Lastly, no professional body membership is required to administer these tests (unlike some traditional neuropsychological assessments).

Several of the CANTAB outcome measures also have normative data available which is matched on age, gender and IQ according to the National Adult Reading Test (NART) (Nelson & Willison, 1991). The NART consists of 50 words with irregular pronunciation that participants must read aloud. The number of incorrectly pronounced words are used to calculate a full scale Wechsler Adult Intelligence Scale (WAIS-revised) IQ score. This score can be used as an indirect guide to TBI participants' premorbid intellectual functioning, based on the finding that reading ability is maintained near its premorbid level in individuals with dementia (Nelson & McKenna, 1975). The NART was therefore completed during participants' first assessment session.

Two different test orders were used to administer the CANTAB assessments, half the sample received the tests according to order one (PAL, RVP, SWM, OTS, SSP, AGN, DMS, RTI), the other in order two (RTI, DMS, AGN, SSP, OTS, SWM, RVP, PAL). These orders were selected to counterbalance serial position effects while avoiding placing similar tasks next to each other to prevent the session from becoming too taxing. Rest breaks were given after every two cognitive assessments, one or two questionnaires were usually completed during these rest breaks.

To contextualise any changes in cognitive function, five questionnaires examining psychiatric and fatigue symptoms were also administered. These included the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), a state version of the Cambridge Depersonalisation Scale (CDS-S), the Epworth Sleepiness Scale (ESS) and the Fatigue Severity Scale (FSS). These assessments are described in Chapter 2 (see Table 2.5), with the exception of the CDS-S which monitors daily changes in depersonalisation symptoms (see Table 3.3) as opposed to over a six month period as in the previous chapter.

Activities of daily living and health status were also measured as secondary study outcomes. Five questionnaires were used to determine whether CVS had induced any generalised health benefits (see Table 3.3). The EQ-5D and the Work and Social Adjustment Scale (WSAS) were both included to provide broader insights into functional recovery. The Dizziness Handicap Inventory (DHI) was also administered to monitor any changes in balance symptoms, which could occur as a result of the TBI but also as a side-effect of the CVS. Lastly, pain was monitored using a scale that was already implemented by the collaborating NHS trusts (Verbal Pain Intensity Scale- PIS).

Electrophysiological measures. These measures are detailed in separate sections (see Chapter 4) to avoid lengthening this chapter. In terms of the test schedule, all participants completed four EEG recording sessions, two recordings were taken during the pre-CVS period and two during active CVS. The recordings during active CVS were taken after four and eight weeks active CVS for both cohorts. The pre-CVS recordings were taken after the first (week 1) and third baseline (week 7) for cohort A, and after the third baseline (week 7) and sham stimulation (week 12) for cohort B.

The behavioural and electrophysiological assessments were administered during separate sessions, each lasting approximately two and a half hours (depending on the participant and the amount of rest breaks taken).

Table 3.3
Additional Wellbeing Questionnaires.

Assessment	Scale	Example Item
Cambridge Depersonalisation Scale- State version (Sierra & Berrios, 2000).	Measures current feelings of depersonalisation. 22 items are rated on visual analogue scales (VAS) ranging from 0% (I'm not having it at all) to 100% (it's as bad as it can get). No clinical cut-off available.	-I'm feeling strange, as if I were not real or as if I were cut off from the world. -I'm now having the feeling of being a "detached observer" of myself.
EQ-5D (Euro-QoL Group, 1990).	Five domains of health status are measured using a five point Likert scale describing problems with completing daily activities (no problems – unable). A VAS, also records patients' perceptions of their overall health (scored 0= worst imaginable health state – 100= best imaginable health state). No clinical cut-offs are available.	Usual activities *(e.g. work, study, housework, family or leisure activities):* I have no problems doing my usual activities I have slight problems doing my usual activities I have moderate problems doing my usual activities I have severe problems doing my usual activities I am unable to do my usual activities
Work and Social Adjustment Scale (Mundt, Marks, Shear & Greist, 2002).	Five domains of functional impairment are assessed using an eight point Likert scale (0= not at all - 8= very severely). Total scores >20 suggest moderately severe or worse psychopathology.	Family and relationships (form and maintain close relationships with others including the people that I live with).
Dizziness Handicap Inventory (Jacobson & Newman, 1990).	25 items are assessed on a three point Likert scale (yes, sometimes, no). Total scores ≥36 indicate a moderate handicap.	Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?
Verbal Pain Intensity Scale (Melzack, 1971).	Likert scale (VAS) with six points ranging from no pain to worst possible pain. No clinical cut-off available.	Participants complete the same VAS for each region of the body where they feel pain (Portenoy & Tanner, 1996).

Test Schedule

All TBI participants completed an initial full baseline assessment during the first week

of enrolment, encompassing all of the behavioural assessments, as well as the electrophysiological measures for cohort A only (see Figure 3.3).

The cognitive tests were then repeated two weeks later (week three). This short retest interval was included in response to findings from Collie et al. (2003) who demonstrated that practice-effects mostly occurred between the first and second administration of a similar computerised test battery, with only smaller nonsignificant improvements present between the second, third and fourth administrations. It was anticipated that this retest interval would help to reduce the magnitude of practice-effects present within the latter test-repetitions. All participants then completed a final full baseline assessment during the eighth week of the study which included all of the behavioural and electrophysiological measures for both cohort A and B.

Cohort A then proceeded to receive four weeks of active CVS, while cohort B received four weeks of sham stimulation (see Figure 3.3). Core symptomology were monitored after this stimulation block using behavioural (cognitive, psychiatric and fatigue) and electrophysiological measures within both cohorts. All participants then received a further four weeks of active CVS. The effects of CVS were then assessed in cohort A by repeating all of the behavioural and electrophysiological measures, while cohort B performed an intermediate behavioural assessment of the core symptoms (cognition, psychiatric and fatigue) as well the electrophysiological measures. Cohort B then completed one final four week block of active CVS before repeating all of the behavioural and electrophysiological measures.

All participants were followed-up four weeks after their active CVS treatment had ceased (week 20 cohort A/ week 24 cohort B), and the core cognitive, psychiatric, and fatigue behavioural measures were re-administered.

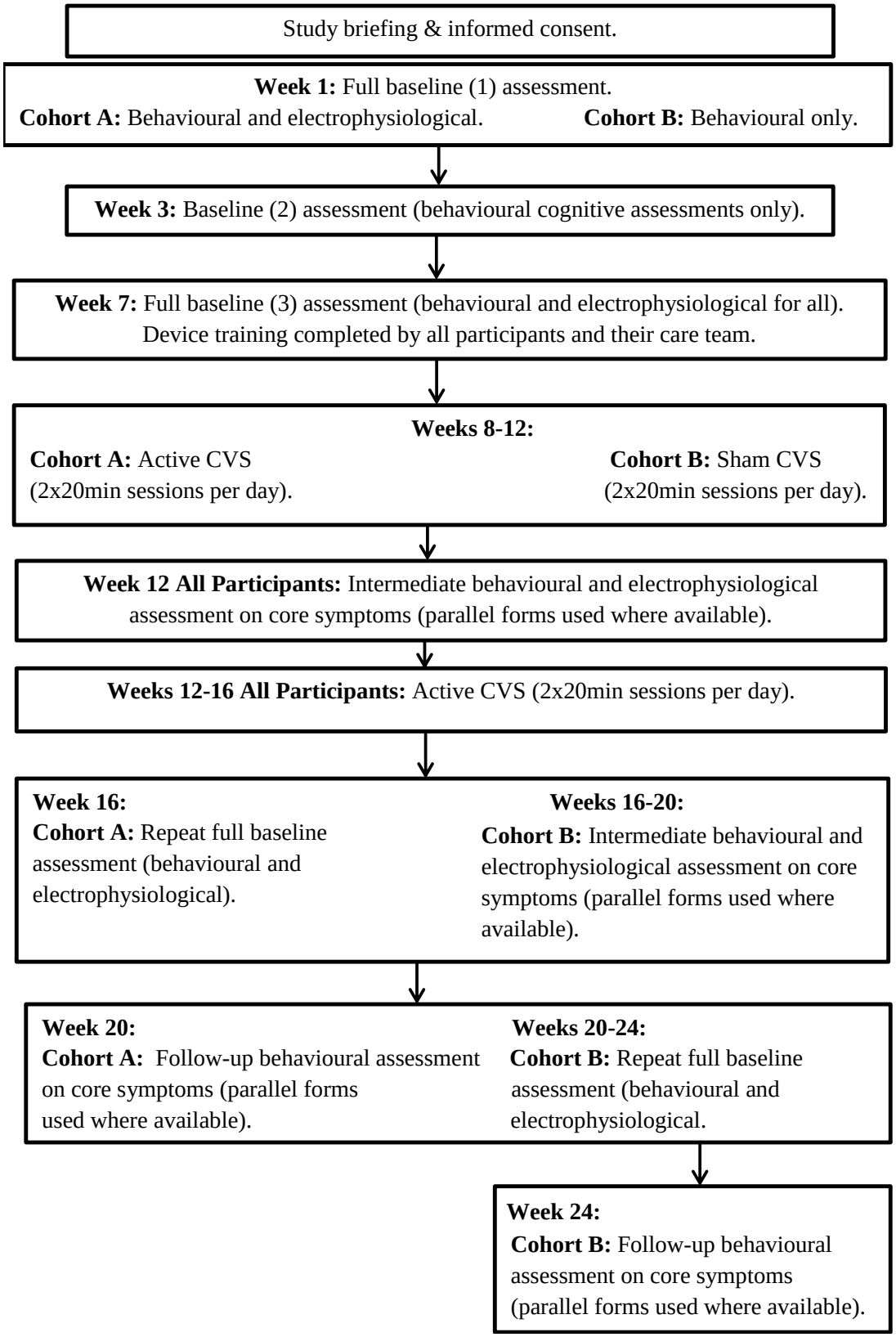


Figure 3.3. Summary of the study protocol for cohorts A and B respectively.

Stimulation

Intervention. The conventional method of CVS involves irrigating the external ear canal with ice-cold water which typically induces nausea and produces a swift habituated response, making it unsuitable for repeated or therapeutic administration.

To overcome these problems, CVS was administered via a custom-built, experimental device which modulates the temperature of small, thermo-electric, solid-state probes inserted into the external ear canals. The probes are too large to enter the bony portion of the canal, resting instead on the outer fleshy portion, thus ensuring that the tympanic membrane is not impacted. The mode of action is identical to that of conventional caloric irrigators in that thermal waves are conducted via the temporal bone, to and from the wall of the inner ear, into which the semi-circular canal protrudes (Black et al., 2016). However, unlike traditional caloric irrigators, with this device the laterality, duration, and temperature range of the CVS waveforms can all be regulated to maximise vestibular response and reduce physiological habituation. Controlling the time-rate-of temperature also mitigates unpleasant side-effects and potential adverse events.

The vestibular response elicited by this new device has been demonstrated through the analysis of nystagmus induction. An electronystagmography (see Figure 3.4) recorded by the device supplier (Scion NeuroStim, LLC) during a stimulation session where temperatures alternated between 20°C and 34°C showed that the solid state device induced the characteristic VOR just like irrigation-based CVS. However, unlike in the traditional procedure, the nystagmus does not fade away within the first two to four minutes, but persists until stimulation terminates. No other form of cranial nerve stimulation that could have been evoked by the device is known to induce this characteristic VOR (Black et al., 2016).

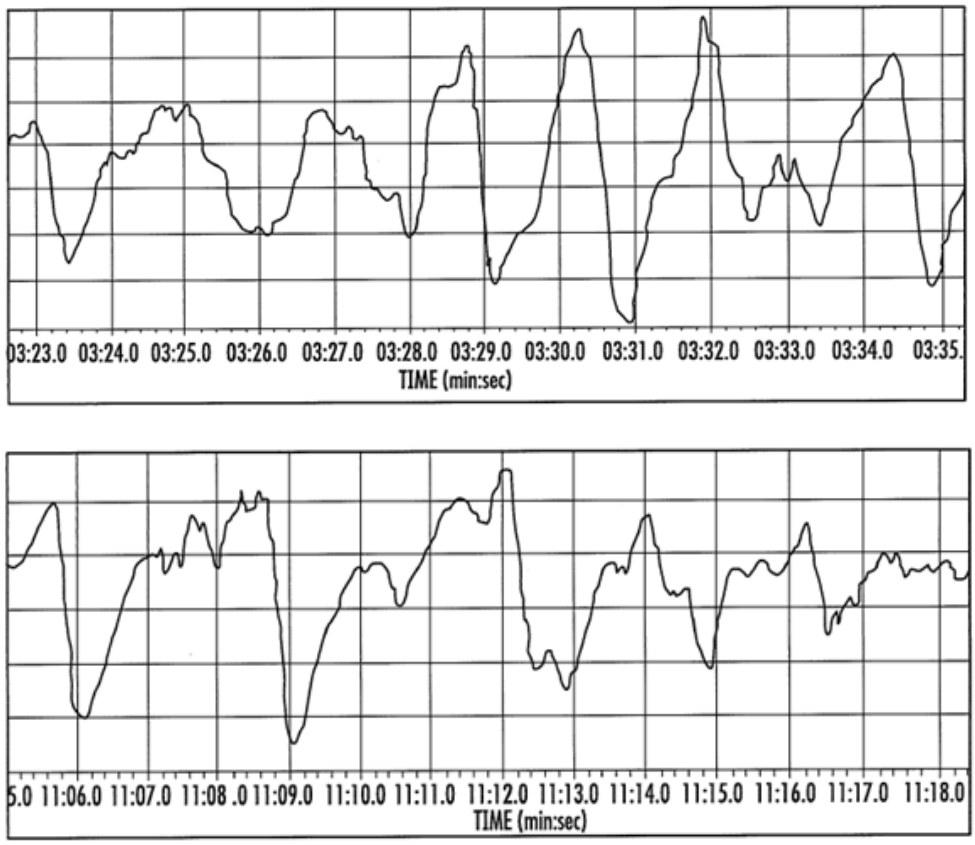


Figure 3.4. Electronystagmography of a subject undergoing CVS delivered with the solid-state device. Top: around 3.30 minutes into stimulation, ocular movements are similar to those elicited by traditional CVS. Bottom: unlike with irrigation-based CVS, the nystagmus is still present after 11 minutes.

The device equipment consists of the aluminium probes which are mounted within a headset, as well as a small hand-held unit which powers the device (Scion NeuroStim, LLC) (see Figure 3.5). Setup is very simple, the headset is placed on the participant's head, carefully ensuring the ear pieces are comfortably fitted, and then the unit is switched on. After a brief training session, treatments can therefore be administered independently by participants in their own homes, easing use and integration into daily routines. The device is equipped with patient-lockout protections, so that participants can only activate programmed waveforms twice daily.

Actual earpiece temperature is monitored by an embedded thermistor (in the tip of the earpiece). The device is programmed to shut-down if the temperature falls outside the selected waveform range. As an additional safety feature, the emitted temperatures are

recorded onto a secure digital (SD) card and a log-file can be downloaded to confirm correct functioning. Device functioning was checked by the researcher using these log-files before a device was given to the participant (as a pre-test) and at each assessment meeting. Moreover, these files were used to monitor participant compliance with the stimulation regime.

Figure 3.5. Illustration of the thermo-modulation device.

Waveform. CVS was applied to both the right and left ear canals. One earpiece delivered a cold sawtooth waveform, and the other a warm sawtooth. Given the diversity of injuries encountered by the sample, it was necessary to ensure balanced hemispheric activation over the course of the study (warm currents primarily activate the ipsilateral cortex, while cold currents primarily activate the contralateral cortex). Therefore, the waveform assigned to each ear was switched every two days to account for the bilateral nature of participants' injuries.

The temperatures of the cold and warm waveforms were selected with participant comfort in mind. Previous research has demonstrated that the vestibular nerves reach asymptote at 15°C and irrigating at temperatures below this induces unpleasant side effects (Reker, 1977), therefore waveforms were programmed to emit temperatures between 17 and 42°C to allow participants to fully benefit from CVS while remaining comfortable.

Although vestibular adaptation to sustained rotational stimulation is well studied, there is less appreciation of adaptation to CVS. A continuous time-varying CVS session (lasting 20 minutes) was therefore implemented to minimise adaptation. The cold sawtooth waveform cycled between ear canal temperature (37°C) and 17°C every two minutes, while the warm sawtooth cycled between ear canal temperature and 42°C every one minute (see Figure 3.6). This transition between warm and cool over time makes the procedure easy to tolerate, while inducing a demonstrable CVS effect (see Vanzan et al., 2016; Wilkinson et al., 2013; Wilkinson et al., 2016 for previous examples).

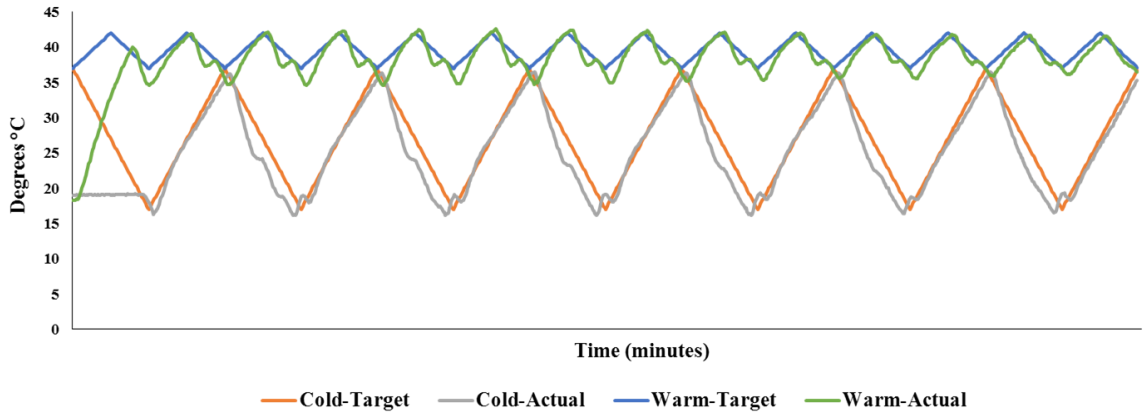


Figure 3.6. Example temperature data from a CVS log-file during a 20 minute active stimulation session. Both target (blue, orange) and actual (grey, green) temperatures are plotted. The starting temperature is the temperature of the room.

Cohort B began with a block of sham stimulation, followed by eight weeks of active CVS. In the sham condition, the unit was operated in exactly the same way, but both earpieces remained at 34° throughout the session. Participants were informed that different CVS waveforms would be administered over the study duration, and that although there may be times when temperature changes were more noticeable (i.e. during active CVS), this should not be taken as evidence that the device was working less effectively. The blinding of the CVS and sham stimulation blocks was aided by the fact that none of the participants knew how the CVS device was supposed to work or what the stimulation would feel like. As the sham stimulation was always completed first, the participants did not have any prior

perceptions with which the stimulation could be compared. Moreover, during the sham stimulation a degree of temperature change was likely to have been felt as the cool earpieces warmed to ear canal temperature. This slow rate of change in temperature means that any sham-induced CVS effects will be small (if any) but may help blind participants to the study protocol.

Throughout active and sham stimulation sessions, participants sat upright or lay passively supine with their head resting on a wedge-shaped pillow angled at 30°C (a position which has improved CVS efficiency; Storrie-Baker et al, 1997). After an initial supervised period of training, two 20 minute CVS sessions, spaced at least one hour apart, were administered by the participant (with supervision from a carer/ spouse) per day, seven days a week for two (cohort A) or three months (cohort B).

This longitudinal dosage plan was selected to maximise the chances of remediating the multiple, chronic and severe symptoms present within this patient group. Various intervention studies with TBI survivors are often conducted over similar periods for the same reasons (e.g. cognitive rehabilitation for eight weeks as an inpatient, Salazar et al., 2000; two x 50 minute slots of neuropsychological therapy delivered three times a week for eleven weeks, Tiersky et al., 2005; anti-depressants administered daily for ten weeks, Ashman et al., 2009). Because CVS is a safe, portable and low-cost technique with minimal side-effects, multiple exposures can be used to encourage plastic change in a way that is not possible with other rehabilitation techniques. The session length of 20 minutes was selected after previous research demonstrated significant effects in response to similar durations of GVS and CVS (e.g. Rorsman, Magnusson & Johansson, 1999; Wilkinson et al., 2009; Wilkinson et al., 2013).

Otoscopic inspection was performed prior to the first session of stimulation to check

for excessive cerumen (which may limit temperature transfer) and to confirm that the external ear canal and tympanic membrane were normal in appearance.

Results

Statistical Approach

The primary objective of this pilot study was to assess whether TBI patients responded to CVS. Given the small sample size, a test-retest design using a multiple-single cases approach was employed. Assessments taken after active blocks of CVS were predicted to show improvements in symptomology relative to the baseline period, while those assessments taken after sham stimulation were not.

Several researchers have questioned whether pilot studies aiming to provide preliminary evidence of the efficacy of an intervention should be assessed using traditional hypothesis testing (i.e. $\alpha = .05$, 95% confidence interval), since they are not formally powered to do so (Altman & Bland, 1995; Lee, Whitehead, Jacques & Julious, 2014). Instead, descriptive statistics as well as larger confidence intervals and error rates ($\alpha = 0.2$) have been recommended for the evaluation of clinical endpoints and feasibility (Lee et al., 2014a; Stallard, 2012).

The present analysis attempted to address these concerns by reporting descriptive statistics alongside an inferential statistical technique from the neuropsychological literature which has been designed to deal with the limitations of case-studies (Crawford & Howell, 1998). Further information regarding the statistical analyses conducted for the cognitive, psychiatric and general health outcome measures is provided below.

Cognitive measures.

Descriptive statistics. *z*-scores were first plotted to give an indication of each participant's cognitive trajectory across the study. These scores were based upon normative

data made available by CANTAB® and represent the number of standard deviations that the participant's test score lies from the normative group mean (age, NART and gender-matched where available). Negative *z*-scores indicate performance below the normative mean, and positive scores suggest better performance than the normative average.

Since these scores are standardised, the different tests can be displayed together. Two figures are presented for each participant, the first shows scores from the memory-based assessments (PAL, DMS, SSP, SWM) and the second displays the attentional assessments (RVP, RTI). Unfortunately, no normative data was available for the AGN or OTS. Six repetitions of the assessments are presented for cohort A (participants 01 and 04) and seven for cohort B (participants 02, 03, 05, 06, 07, 08) (see Figure 3.3 for test schedule).

Inferential statistics. Further analyses then determined whether any statistically significant changes in cognitive performance had occurred throughout the study. Of particular relevance to the hypothesis was whether any changes in performance had occurred during active CVS (four and eight weeks) and whether this upward trend had already begun prior to the onset of CVS (i.e. during sham stimulation), in which case it could not be confidently interpreted as CVS-related.

Repeated assessments are commonly conducted by neuropsychologists to track an individual patient's progress (e.g. forensic evaluations, deterioration with a neurodegenerative diagnosis), or to evaluate the effectiveness of an intervention (Duff, 2012). Several different methods are available to analyse the difference between these scores. Commonly implemented approaches include the reliable change index (RCI; Jacobson & Traux, 1991), and regression-based equations (McSweeney, Naugle, Chelune & Luders, 1993). The RCI calculates the discrepancy between two test scores, and divides this value by the standard error of the difference (X2 – X1)/ SED. This produces a *z*-score which can be

compared with a normal distribution table. Confidence intervals can then be used to describe the spread of the distribution of difference scores that would be expected if no change had actually occurred. Although several versions of the RCI now offer some control of test-reliability, the RCI is generally limited by its one-size-fits-all approach to assessing change, which does not account for differences between individuals (e.g. baseline performance, differential practice effects). Alternatively, simple regression-based equations can be built from published summary data (usually with healthy samples), to predict a patient's level of performance on a cognitive assessment at retest (Y), from their score at baseline (X) (McSweeney, Naugle, Chelune & Luders, 1993). An obtained retest score that is markedly lower than the predicted score suggests cognitive deterioration, whereas a markedly higher retest score suggests cognitive improvement (Crawford & Howell, 1998).

Unlike the RCI, the regression-based approach considers other variables in the prediction of the retest score. For example, by taking into account baseline performance, regression equations can simultaneously factor in extreme scores (i.e. if the baseline score is very high, retest scores may show little improvement due to ceiling effects), and regression to the mean (i.e. extreme baseline scores will likely become less extreme at retest, also low baseline scores are likely to regress upward and vice versa; Duff, 2012). Regression equations also incorporate the psychometric properties of the test, providing a more precise estimate of change by correcting for practice effects (scores are typically higher at retest), and the strength of the test-retest correlation (smaller discrepancies expected for more reliable tests; Crawford & Garthwaite, 2007). This is especially relevant in this study where serial assessments are being applied to a heterogeneous group of individuals (McSweeney, et al., 1993).

Computerised software[2] was used to apply the regression-based approach which tested whether there was a significant discrepancy between an individual's obtained and predicted retest score by evaluating a normalised *z*-score of change ((Y observed-Y predicted)/SEE (standard error of the predicted score for a new case)) against a *t*-distribution (Crawford & Garthwaite, 2006). This software also provides a point estimate of abnormality or rarity for the discrepancy (i.e. the percentage of the population exhibiting a larger discrepancy) and accompanying 95% confidence limits, as an indication of the uncertainty attached to the estimate.

t-tests were used to evaluate the discrepancy (*z*-scores) between a participant's predicted and observed scores based on their performance at baseline. To obtain a more reliable baseline estimate of cognitive ability and to account for any initial practice effects, the three baselines were averaged into a combined estimate of pre-CVS performance (Collie et al., 2003; Weller, 2007). This combined baseline was then used to predict participants' scores at each retest sessions (sham stimulation- cohort B, four weeks CVS, eight weeks CVS, follow-up). The exploratory nature of this study meant that a large number statistical tests were run: three/ four *t*-tests were completed for each cognitive assessment (nine measures) within each participant. The *t*-test results are summarised below but a full breakdown of each *t*-test can be found within Appendix B. *t*-tests occurring during active CVS will be focused upon. Any notable discrepancies or trends between the three baselines (e.g. an upward trend that begins between the three baselines) will also be considered in the interpretation of the data.

Two rather than one-tailed *t*-tests were implemented to explore any potential declines (as well as improvements) in cognitive performance following CVS. This is relevant, to monitor participant tolerance and to account for random performance variations (e.g. fatigue,

[2] Available from, http://homepages.abdn.ac.uk/j.crawford/pages/dept/regbuild.htm

environmental distractions). *t*-tests that were significant at the 20% or 5% level are highlighted since the utility of the traditional 5% level has been questioned in pilot studies (Stallard, 2012). Corrections for multiple comparisons were not applied to avoid risking type two errors in the application of this already conservative approach (see paragraph below) given the explorary nature of study. Instead, the focus will be on the point estimate of abnormality (and the 95% confidence interval around this), which provides more information about the range of possible responses to CVS (Lee et al., 2014a). Estimates of abnormality that were less than 10% are interpreted, since this means that 90% of the healthy population would be unlikely to exhibit a larger discrepancy than the participant, indicating that the participant's score is unusual or extreme. Tables 3.13 and 3.14 (within the chapter discussion) provide an overview of the number of participants that showed a CVS-related improvement on each of the CANTAB tests according to these criteria.

Ideally, the published data used to build the regression equation should resemble that of the participant in terms of diagnosis, retest interval and the neuropsychological measures used. The more similar the published data is to the participant and study protocol, the better the inferences of reliable change (Heaton et al., 2001). Although some studies have looked at the test-retest properties of the CANTAB in TBI samples, this has been limited to one or two assessments, does not present the necessary statistics or is contaminated by an intervention (Salmond et al., 2005; Silver et al., 2009; Mehta, Swainson, Ogilvie, Sahakian & Robbins, 2001; Wäljas et al., 2014). Therefore, data from healthy participants (*N*= 100, *M* age= 44, made available by CANTAB®, 2008) retested over a similar interval (one to eight weeks apart) on multiple CANTAB tests (including seven of the eight implemented here), were inputted into the equation to provide a closer estimate of reliable change. This equation therefore indicates whether the observed changes in performance between testing occasions in a TBI participant differ significantly from that seen in cognitively healthy persons who

have not been exposed to an intervention (Crawford & Garthwaite, 2006, 2007; Duff, 2013). Although this equation will not be able to determine whether any changes that the participants show from test to retest are unusual for patients with TBI, comparisons with healthy samples can still provide useful inferences. Moreover, it has yet to be determined whether clinical or healthy participants make the ideal comparisons group for these methods, since the two data sets are likely to complement one another (Duff, 2012).

Here, the raw test scores were analysed to match the metric of the normative comparison sample (CANTAB®, 2008). Thus, for those outcome measures which indicate accuracy or correct responses, a negative discrepancy/ difference *z*-score indicates performance below the normative mean and a positive score suggests performance above the normative average. The opposite is true for the negatively indicated measures (PAL, SWM_E, SWM_S) and latencies (RVP_ms, RTI_ms). Note that these raw test scores do not correspond with the standardised *z*-scores plotted in the descriptive statistics section of the analysis. While the descriptive statistics show how participants performed relative to a different normative sample across the six/ seven assessment sessions, inferential statistics are comparing raw test scores (for the available outcome measures) during active CVS sessions to an average of the three baselines and evaluate this discrepancy relative to another normative sample and thus may not map onto the descriptive plots.

Questionnaire responses. Established clinical cut-offs/ categories were available for the majority of the implemented questionnaires (but not the CDS, EQ-5D and PIS), which enable inferences about how a participant's score relates to a clinical condition/ symptom. Importantly, these cut-offs already incorporate calculations of minimally clinically significant differences. Any shifts between clinical categories or cut-offs were therefore reported with particular focus on those that occurred during active CVS.

Participants' questionnaire scores are displayed in tables. The psychiatric and fatigue questionnaires were administered at all sessions (except baseline two), while the general health questionnaires were only administered at baselines one and three and after eight weeks CVS. To provide broader insight into wellbeing and functional recovery, several written testimonials from participants and their relatives are also presented. These testimonials are anecdotal and subjective, but nevertheless hold corroborative value.

Participant 01

Descriptive statistics. CANTAB *z*-scores for the six sessions (three baselines, four weeks CVS, eight weeks CVS, follow-up) are presented in Figure 3.7. Participant 01's performance on the memory-based assessments remained above the normative average for the entirety of the study (with the exception of the DMS at baseline one, *z*= -0.36), indicating her visual memory was relatively well preserved. Simple information processing as indexed by the RTI assessment also remained close to the normative mean across the study (see Figure 3.7 bottom). However, sustained attention on the RVP (RVP_A) was consistently performed below the normative mean.

Cognitive performance appeared to be facilitated across most of the tests between the first and second baseline. No noticeable changes in memory performance appeared to be driven by CVS. Within the attention-based measures, descriptive statistics showed that RVP response times were shortest during CVS (four weeks *z*= -0.26; eight weeks *z*= 0.19), before returning to the baseline level at follow-up (*z*= -1.27). However, the *d'* prime measure for the RVP (RVP_A) fluctuated across the study and peaked at follow-up (*z*= -0.9), suggesting any potential treatment effects may not have generalised to RVP task-performance as a whole.

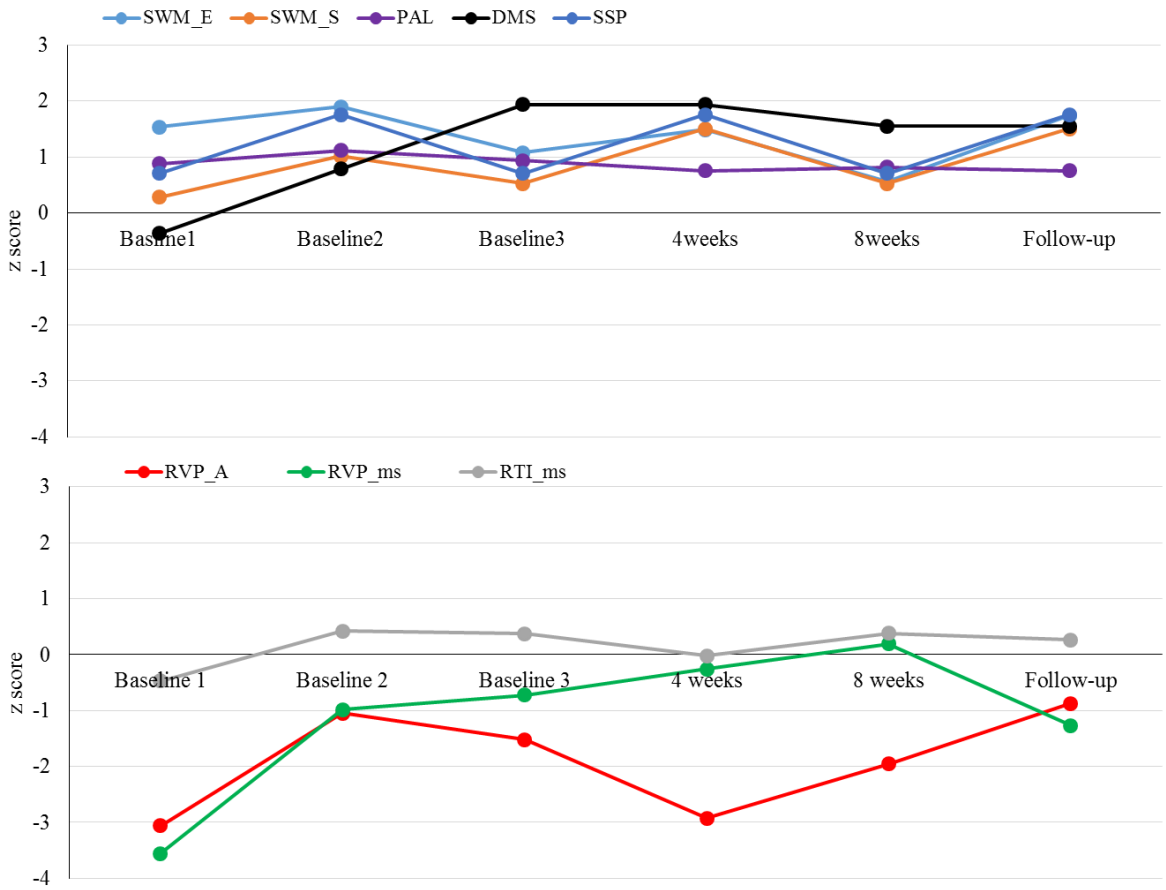


Figure 3.7. Descriptive statistics for the memory (top) and attention-based (bottom) assessments for participant 01. Negative scores indicate performance below the normative mean.

Inferential statistics. Analyses of reliable change revealed unusual changes from the pre-CVS baseline during active CVS across several tests (see Appendix B). In line with the hypothesis, some improvements were present following CVS. After eight weeks CVS processing speed on the RTI was significantly shorter than predicted based on the combined pre-CVS baseline [$t(98)= -2.48$, $p<.05$], and the discrepancy was estimated to be unusual, 0.74% [0.19, 1.83%]. However, descriptive statistics showed that RTs were actually shortest during the second baseline and thus the enhancement may have begun prior to CVS. Participant 01 also showed an improvement in the number of problems solved on the OTS after four weeks CVS, relative to the predicted score [$t(98)= 1.95$, $p<.05$], with only 2.9% [1.08, 5.24%] of the normative sample being likely to exhibit a larger discrepancy. Working memory capacity on the SSP was also greater than expected after four weeks CVS and at

follow-up [both $t(98)= 1.39$, $p= 0.17$]. However this improvement was limited by the considerable uncertainty associated with this estimate, 8.37% [1.90 to 20.51%], and the lack of effects present after eight weeks CVS.

Unexpectedly, RVP_hit detection was reduced after active CVS relative to the predicted retest score, after both four [$t(98)= -2.85$, $p<.05$] and eight weeks of CVS [$t(98)= -1.97$, $p<.05$]. Both estimates were considered to be abnormal within the normative sample: four weeks CVS= 0.26% [0.02, 1.01%], eight weeks CVS= 2.57% [0.55, 6.74%]. The number of errors made on the SWM (SWM_E) after eight weeks CVS was also greater than expected given the participant's baseline score [$t(98)= 1.66$, $p=0.10$], again the discrepancy was fairly unusual [5.04%: 2.27, 9.14%]. No further changes were present during active CVS and none of the negative changes described above continued at follow-up (all estimates of abnormality >13.67%).

Questionnaire responses. Contrary to the hypothesis, no shifts from clinical cut-offs or categories occurred during CVS (see Table 3.4). Symptoms of depression remained above the BDI clinical cut-off across the study but were worst at study onset. Clinically significant symptoms of sleepiness (ESS) and functional impairment (WSAS) also persisted across the study. Fortunately, dizziness and pain symptoms appeared to reduce throughout the study, although the onset of this improvement occurred prior to CVS.

Summary. Descriptive statistics showed that participant 01's cognitive performance largely fell within normal limits across the study. The majority of the inferential statistics also revealed stable performance at re-test. Performance on the SSP, OTS and RTI were temporarily facilitated after a block of CVS, however the fact that these improvements began prior to CVS or were not consistently present across blocks of CVS reduces the likelihood that they were CVS-related. Conversely scores on SWM_E and RVP_hit were declined,

indicating CVS did not have a significant generalised impact on cognition. No clinically significant shifts on the questionnaires occurred during CVS.

Table 3.4
Questionnaire Responses at Each Session for Participant 01.

Questionnaire	Baseline1	Baseline3	4 weeks	8 weeks	Follow-up
BDI	36* (sev)	23* (mod)	25* (mod)	27* (mod)	33* (sev)
BAI	1 (min)	15 (mild)	14 (mild)	10 (mild)	20* (mod)
CDS	275	165	220	250	100
FSS	6*	3.22	4.11*	3.11	4.67*
ESS	19*	17*	18*	17*	18*
EQ-5D (%)	30	0		10	
EQ-5D	43453	43553		43553	
WSAS	36*	38*		34*	
DHI	66*	12		12	
PIS	6	4		4	

Note. * indicates a score that falls above the clinical cut-off. sev= severe, mod= moderate, min= minimal. Secondary symptoms were not measured after 4 weeks CVS and follow-up (grey areas).

Participant 02

Descriptive statistics. CANTAB *z*-scores for participant 02 are presented in Figure 3.8. Several scores fell below the normative the mean throughout the study. Performance on the PAL and DMS were particularly impaired, simple RTs on the RTI also remained below average. On a positive note, performance peaked on the PAL, DMS and SWM tests during a block of active CVS. These improvements are echoed in the testimonial below from the participant.

"There have been some developments in my memory. I can remember bits of information that I couldn't before. I am better at day to day things, like remembering what I need to do on the next day and then actually doing it."

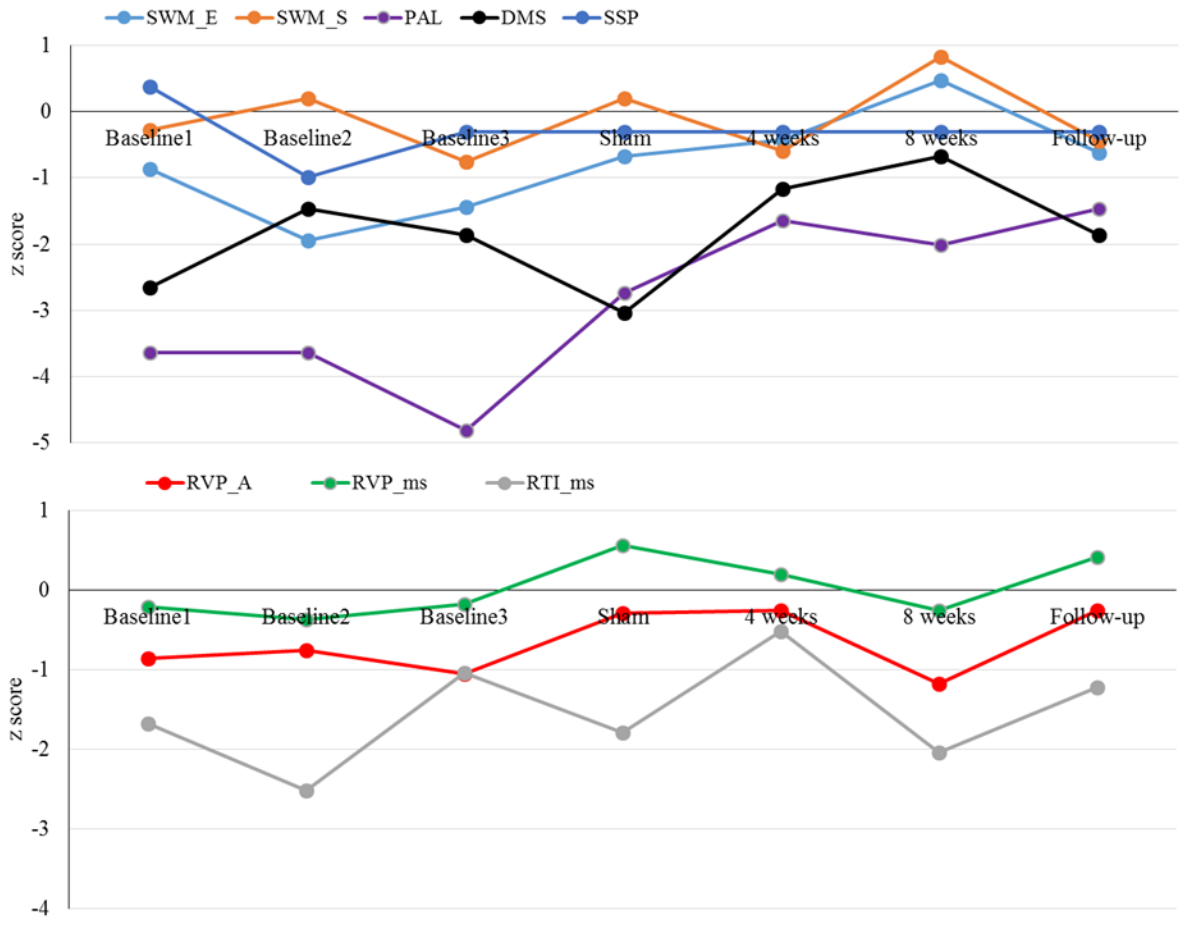


Figure 3.8. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 02.

Inferential statistics. Contrary to the hypothesis, the majority of the observed and predicted retest scores for participant 02 were similar suggesting his performance had remained stable across the retest sessions (see Appendix B). Nonetheless, several unusual discrepancy scores were observed. In line with the hypothesis, scores on the SWM_S [$t(98)$= -1.31, p= .19] and SWM_E [$t(98)$= -1.69, p=.09] were both better than expected after eight weeks CVS given the participant's pre-CVS baseline. The improvement on the SWM_E measure was more unusual (4.70%) with less uncertainty attached to estimate [1.99, 8.82%], than the SWM_S score [9.62%: 5.62, 14.75%]. Improvements from the baseline were also observed on the OTS after eight weeks CVS, such that the number of problems solved was significantly greater than the predicted score, $t(98)$= 1.95, p<.05. Only 2.69% [1.08, 5.24%]

of the healthy control sample were estimated to exhibit a greater discrepancy. Unfortunately, the improvements that were observed on the DMS and PAL within the descriptive statistics did not reach significance (see Appendix B).

Contrary to the hypothesis, the participant's RVP_hits score was significantly lower than predicted after four weeks CVS given his pre-CVS baseline, $t(98)= -2.08$, $p<.05$. This result suggests that an unusual decline [2.01%: 0.65, 4.39%] in sustained attention had occurred after four weeks CVS. This decline did not persist into the latter re-test sessions and no other reliable differences were present during active CVS (all estimates of abnormality >12.72%).

Questionnaire responses. Contrary to the hypothesis, no shifts from clinical cut-offs or categories appeared to occur in response to CVS (see Table 3.5). Participant 02 presented with clinically significant levels of fatigue (FSS) and sleepiness (ESS) throughout the study, while depression (BDI) and anxiety (BAI) symptoms remained minimal during sham and active CVS. Clinically significant dizziness symptoms were also reported (DHI) at all three assessments.

Table 3.5
Questionnaire Responses at Each session for Participant 02.

Questionnaire	Baseline1	Baseline3	Sham	4 weeks	8 weeks	Follow-up
BDI	21* (mod)	20 (mod)	2 (min)	4 (min)	11 (min)	17 (mild)
BAI	5 (min)	11 (mild)	4 (min)	4 (min)	7 (min)	10 (mild)
CDS	50	0	0	0	0	0
FSS	6.22*	5.33*	6.44*	6.33*	6.56*	6.56*
ESS	13*	17*	12*	13*	13*	13*
EQ-5D (%)	85	85			80	
EQ-5D	32212	32211			32421	
WSAS	22*	22*			14	
DHI	74*	70*			68*	
PIS	3	3			3	

Note. * indicates a score that falls above the clinical cut-off.

Summary. Inferential statistics revealed significant improvements from the baseline on the SWM (errors and strategy) and OTS following eight weeks CVS. Yet, no attentional

improvements were present and the number of hits on the RVP was temporarily declined after four weeks CVS. Scores on the questionnaire measures were also unaffected by CVS. There may have been a selective cognitive improvement on those tasks involving spatial working memory and problem solving after eight weeks of stimulation which ceased at follow-up.

Participant 03

Descriptive statistics. As can be seen in Figure 3.9, participant 03's scores generally fell above or close to the normative mean, with the exception of the SWM_S which remained below average throughout the study.

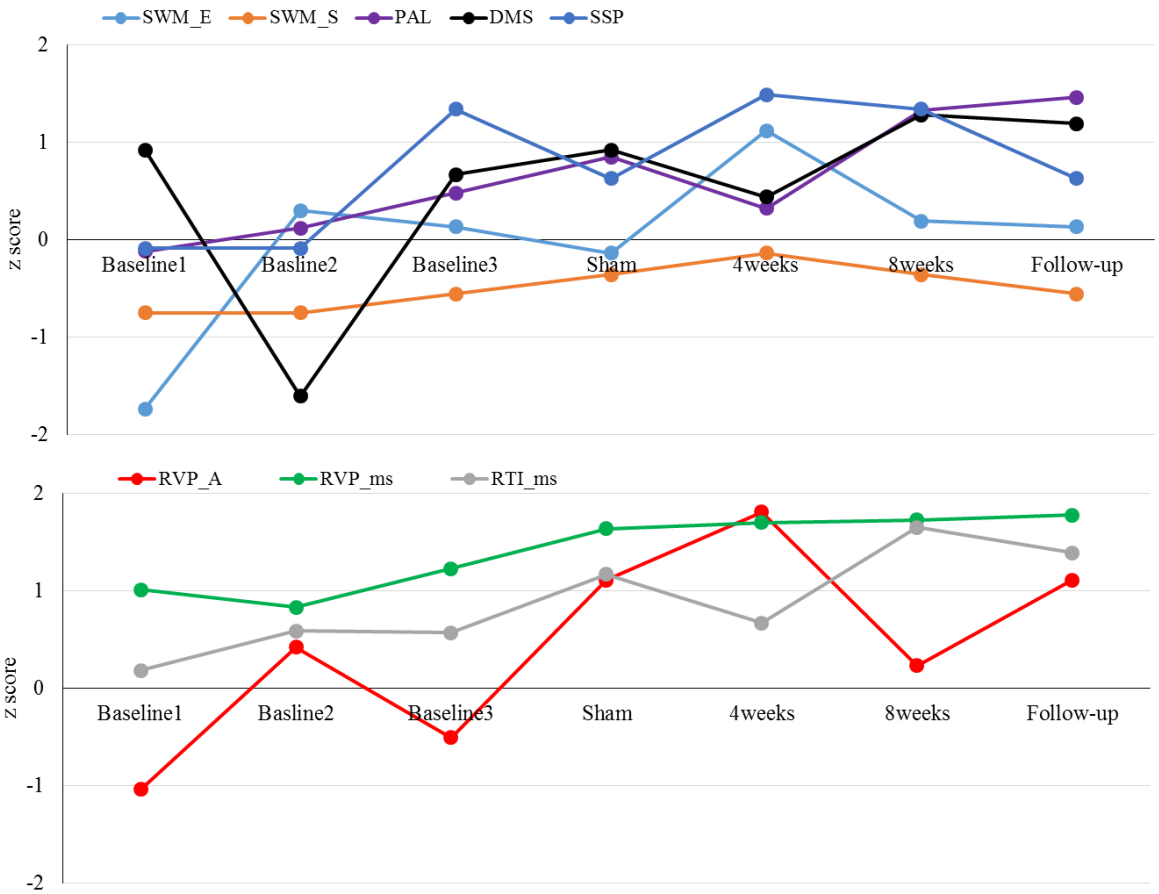


Figure 3.9. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 03.

Although participant 03's performance was variable, several test scores peaked after four weeks CVS (RVP_A, SWM_E, SWM_S, and SSP) in line with a CVS induced effect. However, these improvements were not sustained after eight weeks CVS or at follow-up contrasting with the expected pattern of results.

Inferential statistics. Unexpectedly, the majority of participant 03's scores remained stable across the four retest intervals (see Appendix B). Improvements in response to CVS were observed on the RTI_ms such that, RTs were shorter than expected after four [$t(98)= -1.57$, $p=.12$] and eight [$t(98)= -1.67$, $p= .10$] weeks of CVS, as well as at follow-up [$t(98)= -1.40$, $p=.17$] given the participant's pre-CVS baseline. However, these effects were somewhat limited by the considerable uncertainty associated with these estimates, particularly after four weeks CVS [5.93%: 2.92, 10.19%] and at follow-up [8.26%: 4.47, 13.32%]. Moreover, the improvement also appeared to begin before active CVS, during the third baseline and sham stimulation (see Figure 3.9).

A brief improvement on the RVP_hits score was also observed after four weeks CVS relative to the predicted score [$t(98)= 1.39$, $p= 0.17$]. This discrepancy was considered to be fairly unusual (8.37%), although again there was some uncertainty attached to the estimate [4.40, 13.75%] and the discrepancy did not persist after eight weeks CVS where performance fell within the predicted limits (31.13%). Unexpectedly, no other reliable differences were present during active CVS (all estimates of abnormality >13.02%), including those test scores that had appeared to peak after four weeks CVS within the descriptive statistics (SWM_E, SWM_S, and SSP).

Questionnaire responses. Contrary to the hypothesis, depression (BDI), fatigue (FSS) and sleepiness (ESS) symptoms were unaffected by CVS, and remained above the respective clinical cut-offs throughout the study (see Table 3.6). Anxiety symptoms (BAI) were lowest

after eight weeks CVS and subsequently increased again at follow-up. However, these symptoms were also minimal after sham stimulation therefore reducing the likelihood that this reduction was driven by CVS. Clinically significant dizziness symptoms were also present on the DHI across all three assessments. The comments from participant 03 are consistent with the findings above.

"I haven't noticed any significant benefits of the stimulation, only that I can sleep more through the night".

Table 3.6
Questionnaire Responses at Each Session for Participant 03.

Questionnaire	Baseline1	Baseline3	Sham	4 weeks	8 weeks	Follow-up
BDI	23* (mod)	25* (mod)	24* (mod)	24* (mod)	21* (mod)	23* (mod)
BAI	10 (mild)	8 (mild)	5 (min)	8 (mild)	2 (min)	11 (mild)
CDS	0	0	0	0	0	0
FSS	5.33*	5.22*	6.11*	5*	6.11*	6.11*
ESS	20*	19*	18*	16*	17*	17*
EQ-5D (%)	70	50			50	
EQ-5D	11321	11122			32231	
WSAS	19	21*			19	
DHI	46*	40*			41*	
PIS	3.5	3.5			3.5	

Note. * indicates a score that falls above the clinical cut-off.

Summary. Descriptive statistics revealed a variable, but generally above average pattern of performance. Inferential statistics also identified several improvements on the attention-bases measures (RTI and RVP_hits), although the uncertainty attached to these estimates limits their robustness. Importantly, no significant decreases from the pre-CVS baseline were present during CVS suggesting the treatment had not been detrimental. Responses on the questionnaire measures did not appear to change in response to CVS.

Participant 04

Descriptive statistics. Figure 3.10 presents the CANTAB *z*-scores for participant 04 which evidence a persistent attentional-impairment. Although, latency scores on the RVP (but not the RVP_A) did appear to improve after four (z= -0.98) and eight weeks CVS (z= -

0.44).

Visuospatial memory functions appeared to be better preserved in participant 04, with scores on most of the memory-based tests nearing the normative mean (see Figure 3.10- top). Several scores also peaked during CVS (SWM_E, PAL, SSP, DMS), although these improvements were not maintained (either into the second block of CVS or at follow-up).

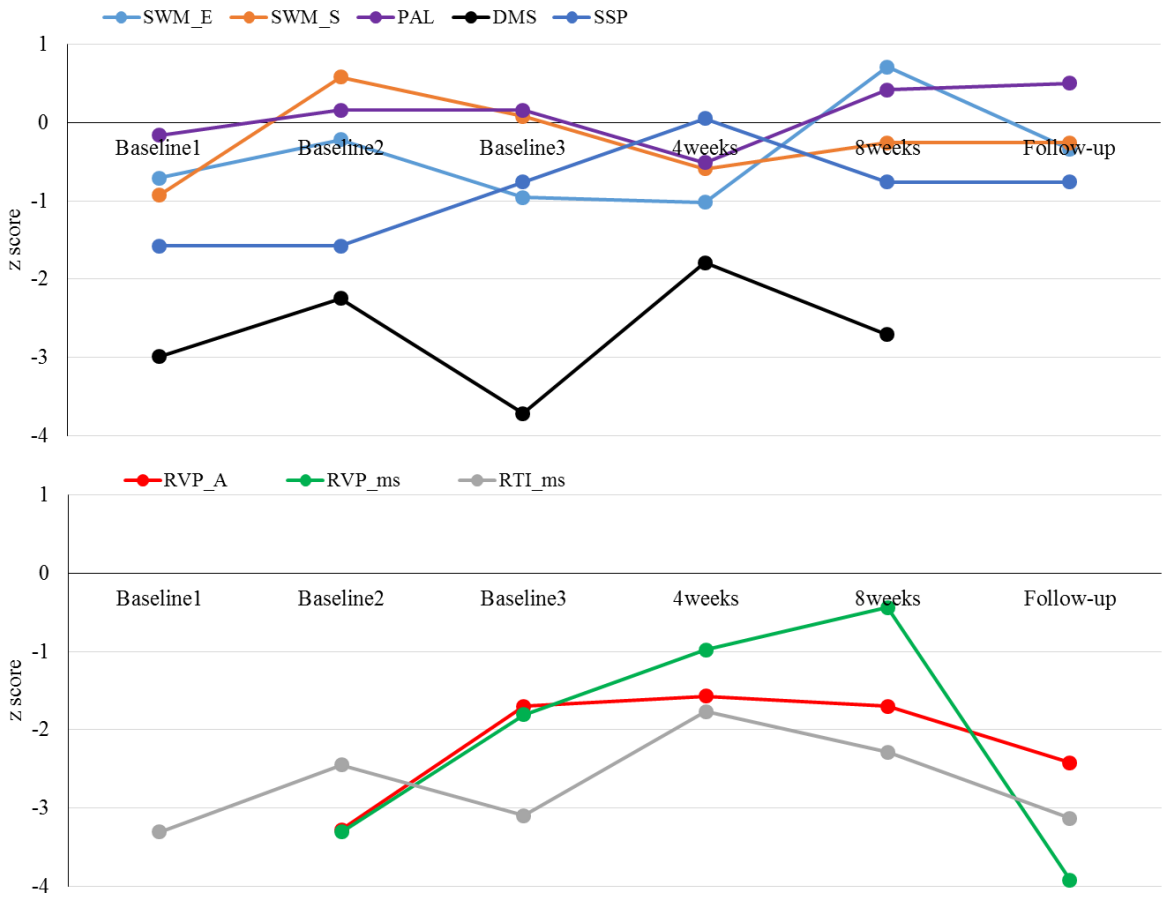


Figure 3.10. Descriptive statistics on the memory (top) and attention based assessments (bottom) for participant 04. *Note*. The RVP was discontinued at the initial baseline assessment due to the participant's information processing difficulties, but was completed from the second baseline onwards. The DMS was abandoned at follow-up due to participant disengagement.

Inferential statistics. Contrary to the hypothesis, analyses of reliable change revealed that participant 04's scores had largely remained stable following CVS. Only the SWM_E showed an improvement whereby fewer errors than predicted were observed after eight weeks CVS [$t(98)$= -1.30, p= 0.19]. Only 9.77% [5.63, 15.11%] of the normative sample were expected to exhibit a larger discrepancy between baseline and retest. No other

improvements during CVS that were noted within the descriptive statistics (PAL, SSP, DMS) reached significance.

Unexpectedly, several comparisons also revealed that the participant's performance during the CVS blocks was lower than expected given her pre-CVS baseline. The number of hits on the RVP was significantly reduced after eight weeks CVS and at follow-up, relative to the score predicted from the pre-CVS baseline [both $t(98)= -2.15$, $p<.05$], and the discrepancy was estimated to be unusual [both 1.72%: 0.23, 5.41%]. Performance on the DMS was also lower than predicted (based on the pre-CVS baseline) after four [$t(98)= -1.38$, $p=.17$] and eight [$t(98)= -2.58$, $p<.05$] weeks CVS. The results indicate that a healthy control participant would be expected show a greater improvement on the DMS at retest, particularly the discrepancy after eight weeks CVS [0.58%: 0.05, 2.18%]. No other changes were present during active CVS (all estimates of abnormality >11.81%).

Questionnaire responses. Participant 04 did not experience clinically significant psychiatric or fatigue symptoms over the course of the study (see Table 3.7). The high scores on the EQ-5D and the WSAS represent the significant ongoing rehabilitation needs of this participant (e.g. walking, dressing, occupational tasks), which remained in place throughout the study.

Summary. Descriptive statistics suggested that several memory test scores had peaked during CVS. However, inferential statistics calculated that only the SWM_E showed an unusual enhancement from the baseline. Scores on the DMS and RVP_hits were also temporarily reduced during CVS, contrasting with the hypothesis. Functional impairments were unaffected by CVS according to the questionnaires. Nevertheless, a testimonial from participant 04's father indicated that the family found the CVS beneficial.

"The fact that she did achieve improved levels on most of the repeats in the testing cycle does give us an upward trend. The CVS process itself, the cooling and heating of the inner ear,

may be responsible. The conclusion on that point can only be, as we have said all along "stimulation" is good and of course direct stimulation via the inner ear is yet another form of stimulation and a pretty unusual type of stimulation, one that we are fortunate to have had the chance of experiencing".

Table 3.7
Questionnaire Responses at each Session for Participant 04.

Questionnaire	Baseline1	Baseline3	4 weeks	8 weeks
BDI	8 (min)	6 (min)	0 (min)	5 (min)
BAI	1 (min)	0 (min)	0 (min)	0 (min)
CDS	0	50	0	50
FSS	1.89	2.11	1.22	0.78
ESS	1	2	1	1
EQ-5D (%)	90	90		90
EQ-5D	54421	55211		55511
WSAS	34*	28*		32*
PIS	3	2		0

Note. * indicates a score that falls above the clinical cut-off. General health questionnaires only administered at baseline and after eight weeks CVS due to participant disengagement.

Participant 05

Participant 05 missed several sessions of CVS during his first four weeks of treatment (sham stimulation), but subsequently maintained the treatment protocol following extra reminders from the researcher. The participant was also unable to complete the general health questionnaires at follow-up due to his busy schedule.

Descriptive statistics. CANTAB *z*-scores are presented in Figure 3.11. Several of the memory test scores (i.e. PAL, DMS) were extremely abnormal and fell five or more standard deviations below the normative mean. Performance on the attention measures was less unusual, although responses on the RTI_ms were longer than the normative average throughout the study.

Responses to the RVP_A and RTI_ms measures appeared to improve during CVS and these facilitations were sustained into the follow-up period. PAL and DMS scores also peaked during active CVS (after eight and four weeks of CVS respectively), although these improvements were not maintained (either across blocks of CVS or at follow-up).

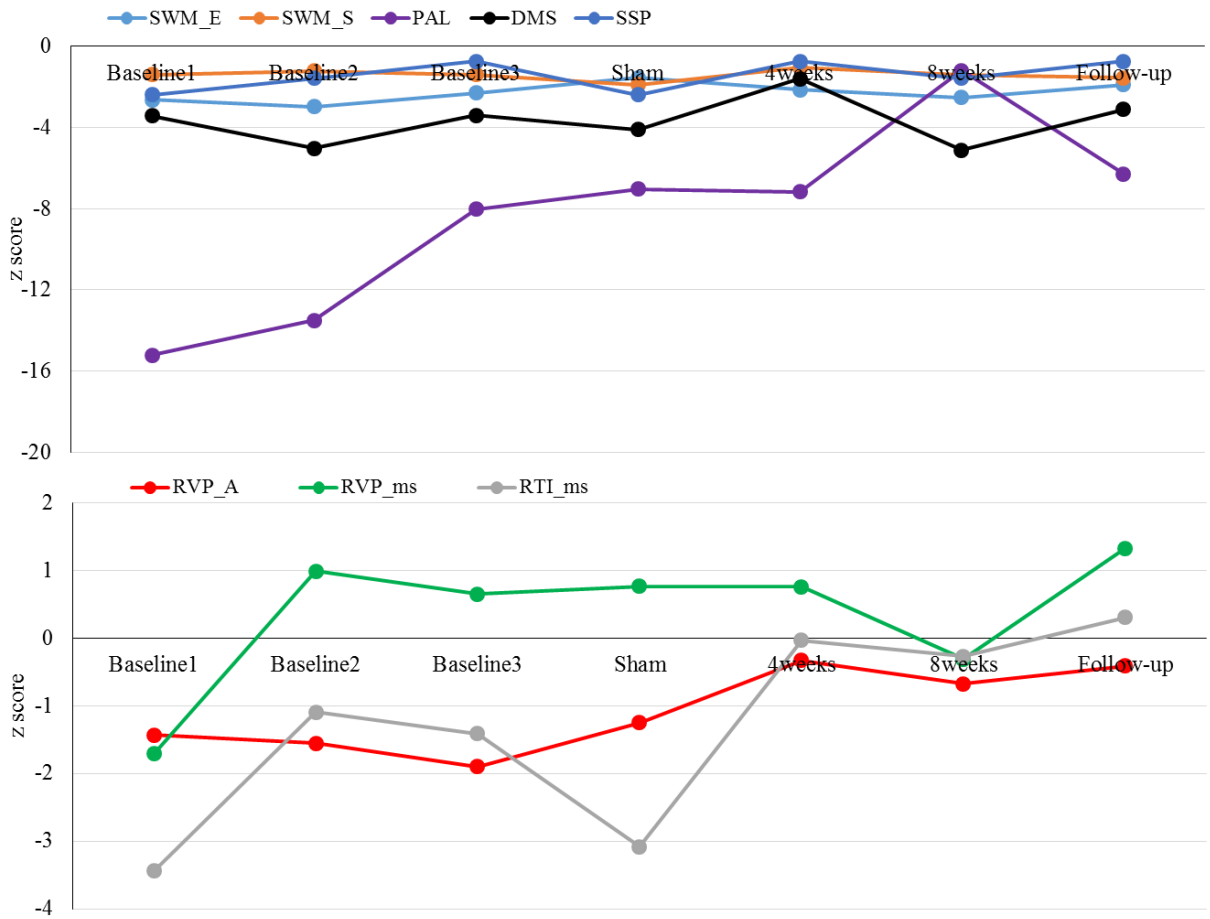


Figure 3.11. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 05. Note the use of different scales to account for the extreme memory scores.

Inferential statistics. Analyses revealed that the observed and predicted scores for the PAL differed across all four retests (all *p*s<.05). The largest discrepancies occurred during CVS (see Appendix B), such that the error rate was significantly higher than predicted after four weeks CVS [*t*(98)= 23.40, *p*<.05] indicating an unusual [0.27%: 0.001, 1.80%] decline in performance based on the pre-CVS baseline. However, in line with the hypothesis, the observed retest score was significantly improved (less errors) after eight weeks CVS relative to the predicted retest score [*t*(98)= -24.60, *p*<.05], with only 0.18% [0.001, 1.23%] of the normative sample expected to exhibit a larger discrepancy. This improvement was not sustained at follow-up, where the error rate was again greater than expected [*t*(98)= 16.40, *p*<.05] and was unlikely to be found within the normative sample [2.73%: 0.06, 11.58%]. The

facilitations in attention during CVS that were noted in the previous section (RVP_A, RTI_ms) did not reach significance here (RVP_hits, RTI_ms).

Contrary to the hypothesis, statistically significant declines in performance were also observed on the DMS after sham stimulation, eight weeks CVS and follow-up (all estimates of abnormality <2.34%, all *p*s<.05), but not after four weeks CVS (*p*= 0.84, abnormality= 41.94%) (see Appendix B). The largest discrepancy occurred after eight weeks CVS [*t*(98)= -4.27, *p*<.001], where the observed score was lowest relative to the predicted score. This estimate of abnormality was estimated to be highly unusual, with less than 1% [0.00, 0.02%] of the normative sample expected to exhibit a larger discrepancy. Unexpectedly, scores on the SWM_E were also worsened after eight weeks CVS given the pre-CVS baseline [*t*(98)= 1.79, *p*= .08], once again the discrepancy was estimated to be fairly unusual [3.82%: 0.84, 9.85%]. No other changes were present during active CVS (all estimates of abnormality >12.46%).

Questionnaires responses. Contrary to the hypothesis, no shifts from clinical cut-offs or categories were present during CVS (see Table 3.8). Clinically significant symptoms of fatigue (FSS) and sleepiness (ESS) symptoms continued to burden the participant throughout the study. Depression (BDI) and anxiety (BAI) symptoms also remained within the moderate range during CVS and fell above the clinical-cut off throughout the study. Additionally, clinical levels of functional impairment (WSAS) and dizziness symptoms (DHI) were reported at baseline and after eight weeks CVS.

Summary. Descriptive statistics showed that this participant's performance largely fell outside of normal limits and contained several extreme scores. Some CVS-related improvements initially appeared to be present on the attentional measures (RVP_A, RTI_ms). However, these facilitations were not significant within further inferential analyses

(RVP_hits, RTI_ms). Inferential statistics also revealed a temporary improvement on the PAL, alongside worsened performance on the DMS and SWM_E after eight weeks CVS. This participant's cognitive performance was highly variable (particularly on the DMS and PAL) but these changes did not appear to be driven by CVS alone. No CVS-related shifts from clinical cut-offs were present on the questionnaires.

Table 3.8
Questionnaire Responses at Each Session for Participant 05.

Questionnaire	Baseline1	Baseline3	Sham	4 weeks	8 weeks	Follow-up
BDI	26* (mod)	19 (mild)	27* (mod)	25* (mod)	24* (mod)	20 (mod)
BAI	17* (mod)	27* (sev)	24* (mod)	22* (mod)	20* (mod)	23* (mod)
CDS	300			165	450	
FSS	7*	6.44*	6.67*	6.22*	6.78*	7*
ESS	17*	18*	19*	16*	16*	17*
EQ-5D (%)	75	75			50	
EQ-5D	22233	11233			11333	
WSAS	18	26*			21*	
DHI	50*	72*			48*	
PIS	4	5.5			4	

Note. * indicates a score that falls above the clinical cut-off. The CDS was not completed at the third baseline, after sham stimulation or at follow-up as the participant felt the questionnaire did not apply to him.

Participant 06

Participant 06 missed several CVS treatments throughout the study due to his cognitive impairments and the availability of support workers to help him maintain the treatment protocol.

Descriptive statistics. As can be seen in Figure 3.12, participant 06's scores on the memory based tests fell below that of the normative sample across the study. Performance on the PAL was particularly impaired and did not appear to improve. Scores on the attention-based measures were also below average but showed some progression over the study, especially on the RVP_A where an upward trend was present from the second baseline onwards.

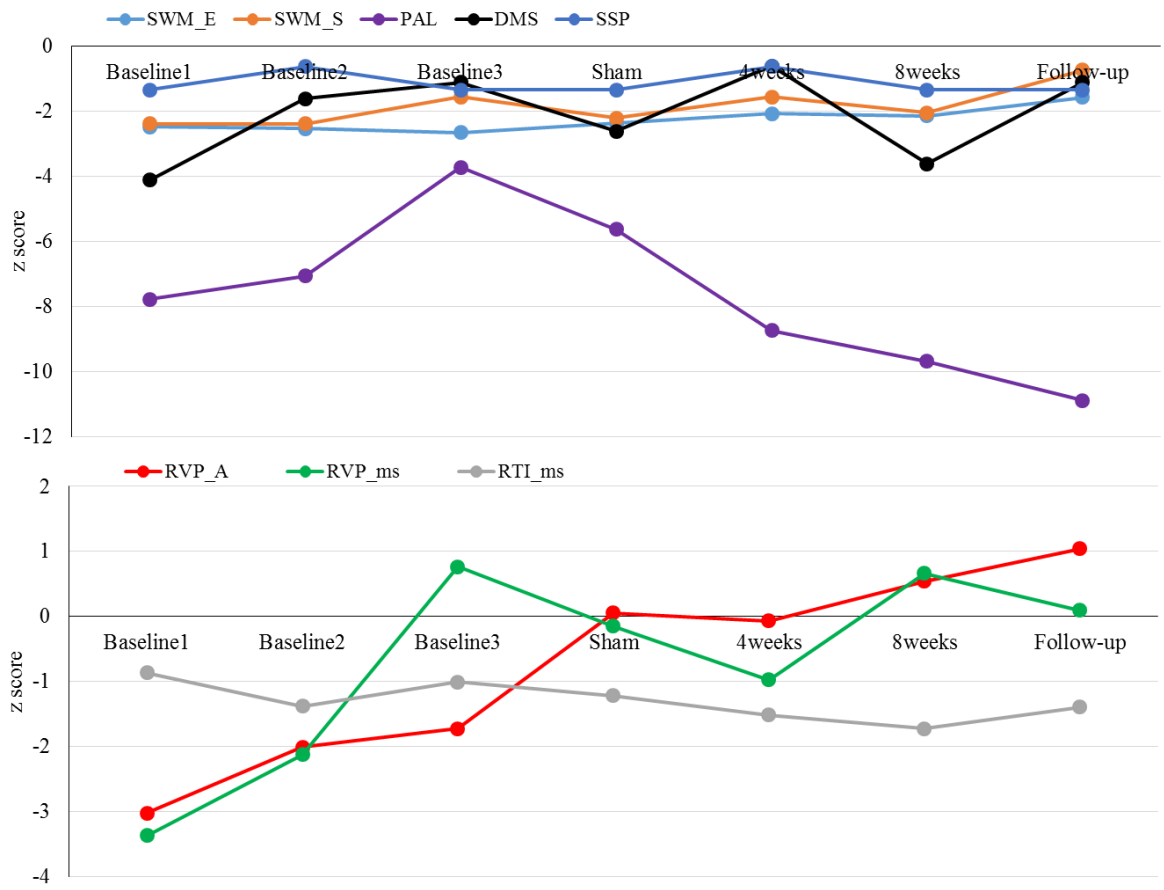


Figure 3.12. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 06. Note the use of different scales to accommodate the extreme memory scores.

Inferential statistics. Analyses revealed significant discrepancies between the observed and predicted retest scores of several tests (see Appendix B). Only the RVP_hits measure showed statistically significant improvements from the baseline assessments. Participant 06 responded to significantly more targets than expected after eight weeks of CVS [$t(98)= 2.17$, $p<.05$], this was also maintained at follow-up [$t(98)= 2.75$, $p<.05$]. These results support the hypothesis and indicate that a member of the healthy control sample would be unlikely to exhibit this large improvement between testing occasions [eight weeks 1.64%: 0.23, 5.13%; follow-up 0.36%: 0.02, 1.44%]. However, it should be noted that this facilitation appeared to begin prior to CVS (see Figure 3.12 for RVP_A).

Conversely, RTs for the RVP were significantly longer than expected after sham stimulation [$t(98)= 5.95$, $p<.001$] and four weeks CVS [$t(98)= 2.61$, $p<.05$], relative to the pre-CVS baseline. The point estimates of abnormality for both discrepancies were highly unusual with less than 1% of the normative sample estimated to achieve a larger discrepancy. Fortunately, this slowing did not persist into the latter retest sessions (no speed-accuracy trade-off with the RVP_A effect described above). Responses were also lengthened on the RTI_ms after four [$t(98)= 1.40$, $p=.16$] and eight [$t(98)= 1.75$, $p=.08$] weeks CVS, although there was some uncertainty attached to these estimates [four weeks CVS 8.22%: 2.67, 17.42%; eight weeks CVS 4.19%: 1.05, 10.20%].

Contrary to the hypothesis, the number of errors observed on the PAL was significantly higher than predicted across all four retests, including those after four [$t(98)= 3.56$, $p<.001$] and eight [$t(98)= 4.10$, $p<.001$] weeks CVS. Performance on the PAL appeared to decline over the course of the study relative to the pre-CVS baseline, with the largest discrepancy occurring at follow-up. Estimates of abnormality showed that the normative sample would be highly unlikely to exhibit this decline in performance (all retest estimates <3.64%). Participant 06's performance on the DMS was also lower than expected relative to the pre-CVS baseline, after sham stimulation [$t(98)= -2.0$, $p<.05$] and eight weeks CVS, where the effect was stronger [$t(98)= -3.20$, $p<.05$] and more unusual [0.09%: 0.003, 0.46%]. No other changes were present during active CVS (all other estimates of abnormality >10.72%).

Questionnaire responses. Contrary to the hypothesis, no shifts from clinical cut-offs or categories were present during CVS (see Table 3.9). BDI scores fell within the severe category across the study and were highest during CVS. Clinically significant levels of anxiety (BAI) were also present throughout the study, although the severity varied and was most extreme at the initial baseline and after sham stimulation. Participant 06 also

experienced abnormal levels of fatigue (FSS) at the majority of assessment sessions (except from the first baseline and after eight weeks CVS), although he did not report feeling overly sleepy (ESS). Total scores on the DHI also revealed a moderate level of handicap was present across the three assessments.

Additionally, the EQ-5D percentage score declined between the third baseline and after eight weeks CVS, indicating the participant's perceptions of his general health and well-being had deteriorated. As no clinical cut-offs were available for this measure, the clinical significance of this decline is difficult to determine. Importantly, the participant testimonial does not suggest any negative perceptions of the CVS.

"The stimulation has left me feeling more upbeat and more able to remember things".

Table 3.9
Questionnaire Responses at Each Session for Participant 06.

Questionnaire	Baseline1	Baseline3	Sham	4 weeks	8 weeks	Follow-up
BDI	37* (sev)	39* (sev)	37* (sev)	43* (sev)	36* (sev)	34* (sev)
BAI	35* (sev)	15 (mild)	28* (sev)	22* (mod)	23* (mod)	16* (mod)
CDS	69	235	65	65	12	65
FSS	3.56	4.11*	4.44*	4.89*	3.56	5.67*
ESS	3	3	2	5	6	9
EQ-5D (%)	70	70			50	
EQ-5D	21123	11133			12223	
WSAS	10	20			18	
DHI	48*	52*			42*	
PIS	3	3			3	

Note. * indicates a score that falls above the clinical cut-off.

Summary. Descriptive statistics showed that the participant's memory performance remained below normal performance limits over the course of the study, while the attention-based measures showed some progression. Further, inferential analyses revealed that hit-rates on the RVP were improved after eight weeks CVS (and at follow-up) relative to the pre-CVS baseline. However, RTs on the attention based measures (RVP and RTI) were also longer during CVS and there were abnormal declines in performance on the PAL and DMS during CVS relative to the pre-CVS baseline, suggesting cognitive performance did not generally

benefit from the stimulation. Questionnaire responses for the BDI and EQ-5D (%) were worsened during CVS, but no clinically significant shifts were driven by CVS across any of the measures.

Participant 07

Descriptive statistics. Figure 3.13 shows that the majority of participant 07's scores fell within normal limits across the study, with the exception of the SSP where scores were frequently below average. Performance on several tests appeared to improve across the study (i.e. SSP, DMS, and RVP_A). However, these changes had often commenced prior to the onset of CVS and did not appear to be driven by the stimulation. Responses on the RTI_ms (four weeks *z*= -0.2) and RVP_ms (eight weeks *z*= 0.63) were also longer during CVS relative to the other sessions.

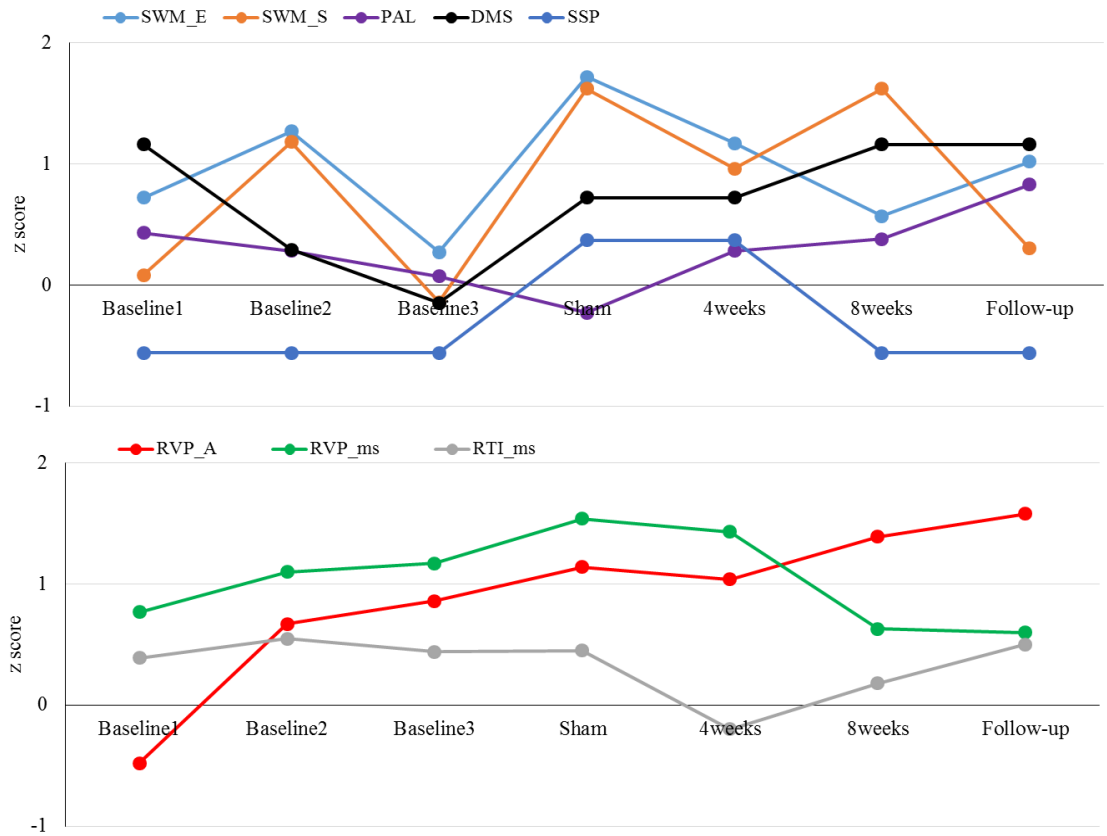


Figure 3.13. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 07.

Inferential statistics. Analyses of reliable change revealed that the majority of participant 07's scores had remained stable between the baseline and retest intervals (see Appendix B). Contrary to the hypothesis, any unusual discrepancies from the pre-CVS baseline occurred after sham stimulation and at follow-up, meaning these cognitive changes were unlikely to be driven by CVS (all estimates of abnormality during active CVS >15.52%).

Questionnaire responses. At study-onset participant 07 complained of a particular dizziness symptom of light headedness and unsteadiness when bending over. Therefore a more specific measure of dizziness symptoms, the Vertigo Symptom Scale (VSS- Yardley et al., 1992), was administered instead of the DHI (which assesses the impact of dizziness on daily functioning) to closely monitor this complaint at baseline and after eight weeks CVS.

Table 3.10 displays participant 07's questionnaire responses. Psychiatric symptoms were minimal (BDI, BAI) or absent (CDS) throughout the study and the participant was not suffering from abnormal levels of sleepiness (ESS), although clinical levels of fatigue (FSS) were present on several sessions but not during CVS. Vertigo symptoms (VSS) did not appear to increase over the course of the study.

Table 3.10
Questionnaire Responses at Each Session for Participant 07.

Questionnaire	**Baseline1**	**Baseline3**	**Sham**	**4 weeks**	**8 weeks**	**Follow-up**
BDI	14 (mild)	9 (min)	19 (mild)	19 (mild)	13 (min)	15 (mild)
BAI	7 (min)	4 (min)	7 (min)	9 (mild)	5 (min)	4 (min)
CDS	110	20	80	68	0	30
FSS	4.22*	3.89	4.44*	3.22	2.11	4*
ESS	4	8	3	5	3	6
EQ-5D (%)	75	85			85	
EQ-5D	11221	21221			11221	
WSAS	13	16			11	
VSS_SA	17	9			7	
VSS_VS	6	1			4	
PIS	2	2.5			2	

Note. * indicates a score that falls above the clinical cut-off.

Summary. Descriptive statistics showed that the CANTAB was largely performed within or above normal limits over the course of the study. Inferential statistics also indicated that cognitive performance was not significantly altered by CVS. Similarly, responses on the questionnaire measures were not shifted across clinical categories during CVS. These findings are echoed in the participant testimonial below, which describes some subtle effects of the CVS alongside some persisting difficulties.

"It is difficult to say how much of an effect the treatment has had on me. I certainly feel calmer and more like my old-self. I enjoyed doing the treatments, they were relaxing. I have noticed some improvements in being able to concentrate and remember things at work, but some things have stayed the same like my ability to taste and smell."

Participant 08

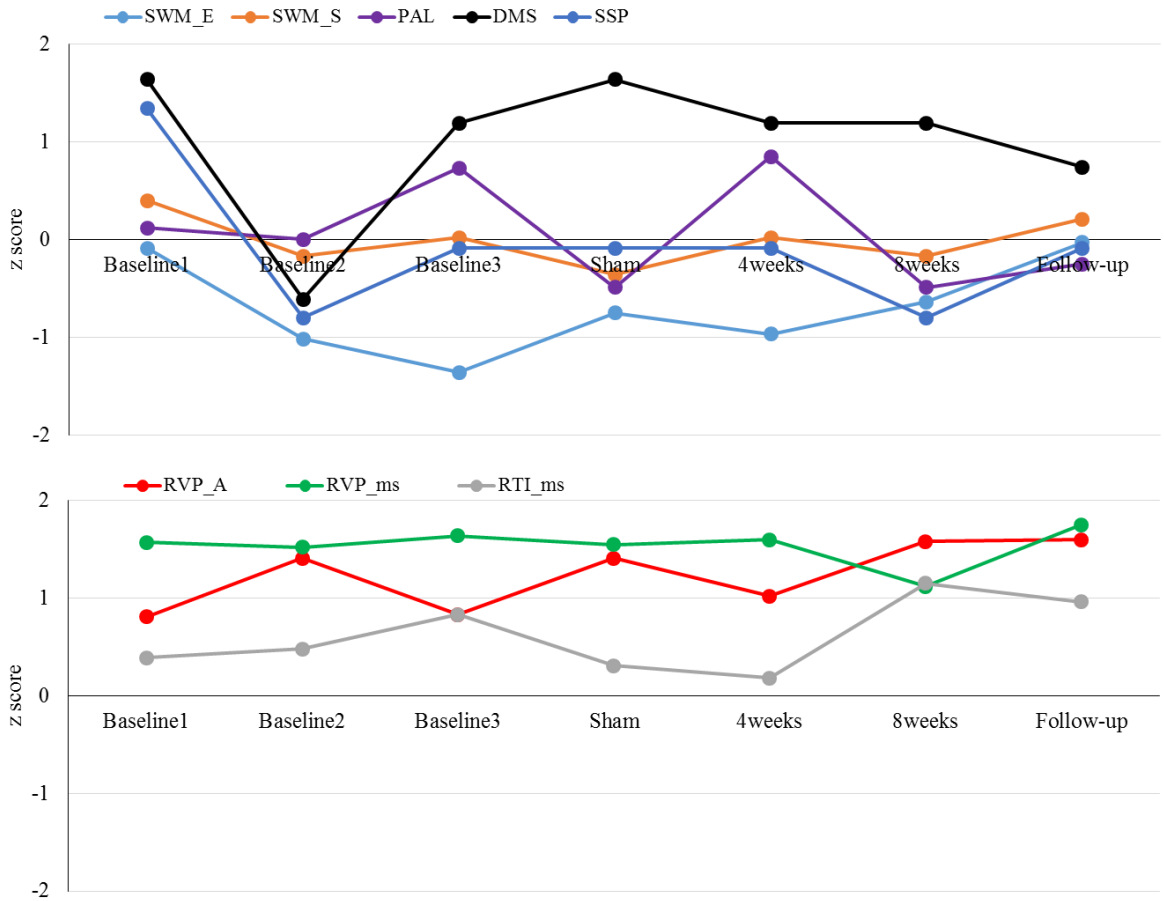


Figure 3.14. Descriptive statistics on the memory (top) and attention-based assessments (bottom) for participant 08.

Descriptive statistics. Figure 3.14 displays participant 08's *z*-scores on the CANTAB, the majority of which fell within normal limits over the course of the study (except the SSP

and SWM). Participant 08's performance on the memory-based tests fluctuated across assessment sessions, but these changes did not appear to relate to CVS. Attentional performance was less variable and response speeds on the RTI appeared to peak after eight weeks of CVS.

Inferential statistics. Contrary to the hypothesis, the majority of the observed and predicted retest scores were similar during active CVS (see Appendix B). Although, an unusual improvement [4.95%: 2.38, 8.64%] was demonstrated on the OTS after eight weeks CVS whereby the number of problems solved was improved relative to the pre-CVS baseline, $t(98)= 1.67$, $p=.09$. The improvement on the RTI_ms that was noted in the descriptive statistics did not reach significance here.

Unexpectedly, the number of errors on the SWM was higher than predicted after four weeks CVS [$t(98)= 1.35$, $p=.18$], with 9.02% [4.55, 15.17%] of the normative sample estimated to show a larger discrepancy. Later, after eight weeks CVS fewer items than expected were remembered on the SSP [$t(98)= -1.51$, $p=.14$], again this discrepancy was estimated to be fairly unusual in the normative sample [6.83%: 3.64, 11.15%]. No other changes were present during active CVS (all estimates of abnormality >13.45%).

Questionnaire responses. These scores were also unaffected by CVS (see Table 3.11). Severe symptoms of depression (BDI) and clinical levels of anxiety (BAI) persisted throughout study, although anxiety symptoms were reduced at follow-up. Some experiences of depersonalisation were also reported (CDS), fortunately these symptoms reduced as the study progressed and were lowest after eight weeks CVS.

Abnormal levels of fatigue (FSS) and sleepiness (ESS) were present during all sessions and remained stable throughout the study. Clinically significant levels of functional impairment (WSAS) and dizziness symptoms (DHI) were also reported across the three

assessments. On a more positive note, general perceptions of health on the EQ-5D (%) were improved after eight weeks CVS (from 45 to 95), suggesting the participant's perceived health status may have been elevated by CVS.

Table 3.11
Questionnaire Responses at Each Session for Participant 08.

Questionnaire	Baseline1	Baseline3	Sham	4 weeks	8 weeks	Follow-up
BDI	36* (sev)	39* (sev)	41* (sev)	37* (sev)	38* (sev)	41* (sev)
BAI	21* (mod)	23* (mod)	32* (sev)	21* (mod)	29* (sev)	16* (mod)
CDS	690	650	575	560	195	460
FSS	7*	7*	7*	7*	7*	7*
ESS	13*	13*	13*	15*	14*	13*
EQ-5D (%)	20	45			95	
EQ-5D	43545	33534			32425	
WSAS	35*	39*			37*	
DHI	82*	80*			80*	
PIS		4			3	

Note. * indicates a score that falls above the clinical cut-off.

Summary. Descriptive statistics indicated that the participants' performance largely fell within normal limits, with some variability across the memory measures. Analyses of reliable change showed that cognitive performance was largely similar following CVS relative to the pre-CVS baseline, with the exception of the OTS where performance was briefly improved, and the SSP and SWM_E where performance was temporarily reduced during CVS. Blocks of CVS may have induced a selective alteration in spatial working memory and problem solving performance that emerged after eight weeks stimulation but ceased at follow-up. Clinically significant shifts on the questionnaires were absent during CVS and the following testimonial from the participant appears to reflect these findings.

"I felt that I was able to concentrate better and for longer periods as the treatment progressed. I still feel as tired as I did at the start of the treatment."

Discussion of Behavioural Outcomes

This chapter described a multiple-single cases, sham-controlled study that was conducted to provide the first investigation into the effects of CVS on the neuropsychiatric

symptoms of TBI. Analyses examined whether any behavioural changes in cognition, mood and fatigue symptomology, as well as general wellbeing coincided with blocks of CVS using regression based statistics and established clinical cut-offs. Descriptive statistics revealed variable patterns of performance, with several participants appearing to improve on the visuospatial memory tests during active CVS relative to the baseline/ sham period. Moreover, although the inferential statistics were largely non-significant, nearly all participants (except 07) improved on at least one cognitive test during CVS relative to pre-CVS baseline period. These improvements were not accompanied by concurrent changes in general well-being, mood and fatigue symptomology which were largely unaffected by CVS. No single descriptive (e.g. age, gender) or clinical feature (e.g. TBI severity, vestibular symptoms) appeared to impact responsiveness to the CVS, though a larger and more tightly controlled sample would need to be tested before any generalised conclusions could be made. A detailed review of the findings is provided below and a general discussion will follow the electrophysiological results presented in the next chapter.

Key Results

Descriptive statistics. Taken together these showed that cognitive performance peaked on at least one test within five participants (02, 03, 04, 05, 08) during active CVS. These effects were most commonly found on the memory-based measures, mainly the PAL, SWM and DMS (all *Ns*= 3), which all test short-term visual memory but differ in their emphasis on spatial and pattern information (SWM: spatial, DMS: pattern, PAL: both). In line with these trends, four out of the six participant testimonials made a specific reference to memory improvements or being able to remember information more easily after completing the CVS treatments. These findings provide some provisional evidence for a CVS-related improvement on the memory-based CANTAB measures and move closer to evidencing a vestibular contribution to memory function.

Descriptive statistics also showed that the PAL, an assessment of visuospatial learning where participants are given multiple attempts to accurately position objects within a display, was the worst performed test in three of the participants. Anecdotally most of the sample also tended to report that they found this task challenging. It could be argued that the task of retaining and combining details of complex visual patterns as well as spatial locations was especially difficult, in comparison to the other memory tasks which place more reliance on either spatial (SSP, SWM) or pattern information (DMS). Visuospatial learning may therefore be a relevant target for future intervention, particularly since there was room for improvement on the test.

Further trends were difficult to come by given the diversity in cognitive performance across the sample as well as within individual participants (see Figures 3.7-3.14). Even before the onset of CVS some individuals performed within or close to normal limits (participants 01, 03, 07, 08), while others attained scores several standard deviations below the normative mean on multiple assessments (participants 02, 04, 05, 06). Descriptive statistics and testing observations also indicated that the participants' cognitive performance had fluctuated across sessions due to a combination of potential factors which were not limited to the CVS (e.g. fatigue, concentration lapses) thus increasing intra-individual variability and limiting conclusions about the effectiveness of CVS.

Inferential statistics. Tables 3.12 and 3.13 provide a summary of the inferential results from the retest sessions taken after four and eight weeks of CVS, according to the significance values found in traditional ($p<.05$) and pilot ($p<.20$) studies (Stallard, 2012). Contrary to the hypothesis, the majority of the inferential *t*-tests revealed a non-significant result, meaning a generic effect of CVS could not be evidenced across the sample. These results indicate that the difference in participants' scores between the combined pre-CVS baseline and after active CVS would not be unusual in a normative sample who had not

received treatment. Nearly all participants showed improved performance on at least one test during CVS relative to their baseline performance, yet the majority of the comparisons were non-significant and some tests also showed a temporary decline. Where improvements were present, these mainly occurred after eight weeks CVS, suggesting repeated sessions of CVS may be important.

Table 3.12
Count of Participants that Declined, Remained Stable, or Improved Based on Standardised Regression-Based Methodology (α= 0.05).

	Four weeks CVS			**Eight weeks CVS**		
	Decline	Stable	Improve	Decline	Stable	Improve
PAL	2	6	0	1	6	1
SWM_S	0	8	0	0	8	0
SWM_E	0	8	0	0	8	0
DMS	0	8	0	3	5	0
SSP	0	8	0	0	8	0
OTS	0	8	0	0	6	2
RTI (ms)	0	8	0	0	7	1
RVP hits	2	6	0	2	5	1
RVP (ms)	1	7	0	0	8	0
Total	5	67	0	6	61	5

Table 3.13
Count of Participants that Declined, Remained Stable, or Improved Based on Standardised Regression-Based Methodology (α= 0.2).

	Four weeks CVS			**Eight weeks CVS**		
	Decline	Stable	Improve	Decline	Stable	Improve
PAL	2	6	0	1	6	1
SWM_S	0	8	0	0	7	1
SWM_E	1	7	0	2	4	2
DMS	1	7	0	3	5	0
SSP	0	7	1	1	7	0
OTS	0	8	0	0	5	3
RTI (ms)	1	6	1	1	5	2
RVP hits	2	5	1	2	5	1
RVP (ms)	1	7	0	0	8	0
Total	8	61	3	10	52	10

Interestingly participants' scores were more changeable on particular tests, mainly the SWM_E, RTI (ms) and RVP_hits. The OTS, a test of executive functioning, yielded the

largest number of performance improvements after eight weeks CVS (two participants at α= 0.05, three participants α= 0.2) and none of the sample declined on this measure after CVS. Repeated sessions of CVS may therefore have improved problem solving abilities in some individuals.

In line with this finding, previous research has also shown that vestibular inputs may be relevant for executive functioning. Tangen, Engedal, Bergland, Moger and Mengshoel (2014) previously tested the association between balance and cognitive function across a sample of adults with various levels of cognitive impairment (subjective, mild, AD). Although the authors used a large battery of assessments, the only test to retain its association with balance function in a final regression model which adjusted for demographic variables was executive function (Trail Making Test-B; Reitan, 1955). Mirelman et al. (2012) also showed that poor performance on tests of executive functioning taken five years earlier then predicted older adults' risk of falling when they were followed-up five years later, with the deterioration of frontal processing resources thought to contribute to these declines.

Altogether, the current and previous findings indicate an association between vestibular signals and the completion of executive functions such as problem solving or set-shifting (tested by the OTS). The vestibulo-thalamo-cortical pathway, which enables projections from vestibular areas (e.g. PIVC) to the frontal lobes (Preuss et al., 2014), may offer an anatomical explanation for these associations. The modulatory effects of CVS within frontal areas of the brain (e.g. the parieto-frontal operculum; Lopez et al., 2012) could therefore underlie the cognitive changes that were present here. This alteration to frontal processing resources could also explain why some participants showed improved working memory performance (01: SSP; 02: SWM_S, SWM_E) alongside the OTS. If executive functions such as planning, volition, purposive action and self-monitoring are facilitated by CVS, then performance on working memory tasks that draw upon these functions are also

likely to be improved. For example, during the SWM participants must plan an efficient search strategy in order to memorise the locations of stimuli and thus any CVS-related effects on executive function may also link to memory.

The analyses also revealed that those participants whose test scores fell below normal limits (according to descriptive statistics) tended to show larger discrepancies from their predicted scores within analyses of reliable change. For example, participants 03, 07 and 08 performed close to or above the normative mean across most tests and had fairly stable retest scores during CVS, whereas participants whose performance fell below the normative mean showed more variability including significant improvements on one or two measures during CVS (02: SWM, OTS; 04: PAL; 05: PAL; and 06: RVP_hits). It could be argued that the severity (and location) of the brain injuries sustained by these four patients caused changes in the brainstem which meant that these individuals were less able to inhibit vestibular signals and thus were more susceptible to CVS (Saj, Honoré & Rousseaux, 2006).

Group Effects.

To help interpret the multiple cognitive effects presented above, a group analysis was also performed. Given the small sample size, the Friedman test was adopted as a non-parametric alternative to the one-way repeated measures ANOVA. This approach was used to explore whether a group-based change in performance was present across the key study sessions entered into the regression analyses above. Since not all participants received sham stimulation (cohort B only), analyses focused on the remaining four sessions (combined pre-CVS baseline, four weeks CVS, eight weeks CVS, follow-up) to avoid reducing the sample size. If a significant main effect was found, Friedman tests could then incorporate the sham session to estimate any placebo effects in the remaining six participants.

Composite scores were first computed from the descriptive *z* scores for the eight CANTAB outcome measures. A Friedman test comparing the four key sessions (N= 8)

revealed a significant group effect $\chi^2(3) = 16.65$, $p<.05$. However, Bonferroni corrected ($p<0.008$) Wilcoxon signed-rank post-hoc testing revealed no significant differences between individual sessions (all *z*s >-2.52; all *p*s> .012). To estimate the effect of sham stimulation, composite scores were then compared across the five sessions ($N= 6$). A significant, albeit weaker, group effect was again present ($\chi^2(4) = 12.93$, $p<.05$), but no post-hoc tests reached significance (all zs> 2.52; all *p*s> .012) according to the Bonferroni criterion ($p<0.005$). Figure 3.15 shows an improvement in composite *z* scores from the pre-CVS baseline onwards, with performance appearing to peak after four weeks CVS, albeit not robustly.

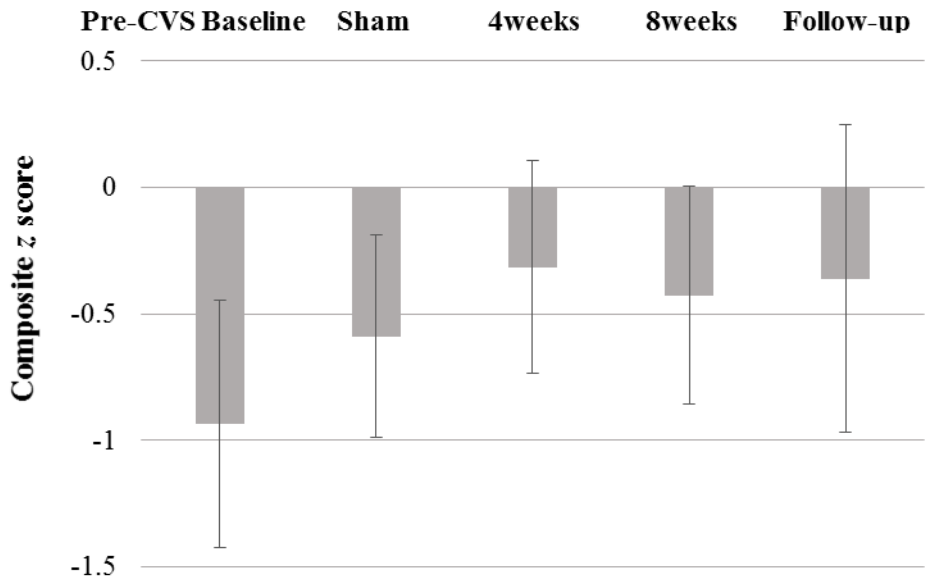


Figure 3.15. Composite group scores across the five key sessions for the CANTAB outcome measures. Negative scores indicate performance below the normative mean.

To explore whether any group-based changes were present for individual cognitive outcomes, group analyses were also completed for each of the key CANTAB measures across the four sessions (see. Table 3.14). Only the RVP_hits measure showed a significant main effect $\chi^2(3) = 12.69$, $p<.05$. Post hoc, Bonferroni-corrected testing ($p<.008$) was therefore conducted on the RVP_hits measure but this failed to support any significant differences between any of the four levels (all *z*>-1.54; all *p*s>.12). To ensure no significant effects were missed from the sham session, four additional post-hoc tests were completed on

the six participants who had completed this session for the RVP_hits measure, but again these did not survive Bonferroni correction (criterion of $p<.005$: all $z>-2.20$; all ps$>.028$). Together the results suggest that CVS had not exerted a group effect on either the composite or individual outcomes.

Table 3.14
Group analysis of CANTAB responses to CVS.

	χ^2	p
Composite *z* score	16.65	.001
Paired Associates Learning	1.79	.62
Spatial Working Memory Strategy	0.12	.99
Spatial Working Memory Errors	6.45	.09
Delayed Match to Sample	6.93	.07
Spatial Span	6.86	.08
One Touch Stockings	5.62	.13
Reaction Time (ms)	1.05	.79
Rapid Visual Processing hits	12.69	.005
Rapid Visual Processing (ms)	3.75	.29

Note. df= 3. Session variable is comprised of four levels: baseline (an average of the three assessments), four weeks CVS, eight weeks CVS, follow-up. The sham session is excluded from the table since the study design meant that it was not completed by all participants.

Questionnaire responses. Contrary to the hypothesis, no shifts from clinical cut-offs or categories appeared to be driven by CVS. Similar to the vestibular cohort tested in Chapter 2, clinically significant symptoms of anxiety (*N*= 3), depression (*N*= 5), fatigue (*N*= 7) and sleepiness (*N*= 5) were again prevalent and tended to persist within this sample across the study. Yet both the questionnaire responses and participant testimonials indicated that CVS had not been effective at targeting psychiatric and fatigue disturbances, and neither had it induced a more generalised impact on wellbeing. The absence of clinical shifts on these questionnaires suggests that any potential effects of CVS on the cognitive symptoms of TBI were not dependent on comorbid changes in psychiatric and fatigue symptomology. The results therefore provide further tentative evidence for a direct vestibular-cognitive pathway, since the vestibular signals themselves appeared to alter cognitive processing rather than any

fluctuations in comorbid symptomology which could influence cognition indirectly (Hanes & McCollum, 2006).

Limitations

The current study could be critiqued for its focus on visuospatial assessments of cognition, which meant that other important verbal impairments that frequently present within TBI samples (e.g. aphasia or verbal memory) could have been neglected. Unfortunately, given the time constraints of this PhD it was not possible to extend the assessment battery. Moreover, by incorporating the CANTAB the current study could continue to investigate the vestibular-cognitive effects on visual processes that were shown to be important in Chapter 2. However, since evidence has demonstrated improved verbal processing in both aphasic patients (word naming; Wilkinson et al., 2013) and healthy adults (word recognition; Bächtold et al., 2001) following right ear CVS, verbal measures may make a useful addition to future assessment batteries. Nevertheless, the CANTAB did highlight several tests which appeared to be susceptible to CVS (OTS and SWM according to inferential statistics; PAL and DMS according to descriptive statistics) and might be the very beginnings of an important CVS-related effect on cognition. Given these effects, it would now be interesting to implement more specific assessments (e.g. Hayling and Brixton Tests, Burgess & Shallice, 1997; Trail Making Test, Reitan, 1955; Corsi block-tapping task, Kessels et al., 2000) to investigate whether further improvements could be elicited within these cognitive domains.

The current assessment battery might also be limited by its reliance on self-report measures as indicators of psychiatric, fatigue and general wellbeing symptomology, since these could be distorted by various factors (e.g. ongoing litigation status, social desirability, lack of insight). These questionnaires were selected on the basis of previous research which

has shown them to be sensitive to alterations in the neuropsychiatric symptomology of TBI, as well as recommendations from the two referring NHS sites where they are routinely implemented. However, researchers might want to consider implementing objective measurements (e.g. polysomnography, multiple sleep latency testing) or carer/ clinician ratings to supplement these questionnaires (e.g. Hamilton Rating Scale for Depression; Hamilton, 1967). The current study aimed to overcome some of these limitations by looking at electrophysiological measures as a neurological indicator of general recovery (see next Chapter).

Another possible shortcoming was the use of the regression-based approach. This analysis was deemed the most suitable since it allows for individual differences at baseline, incorporates the psychometric properties of the test and provides an inferential difference statistic (Crawford & Garthwaite, 2007), all of which are highly relevant to neuropsychological case-studies (Duff, 2012). However, the approach does not eliminate the occurance of false positives which could be problematic here where individualised rather than collective changes were expected within this diverse pilot sample. Moreover, it could be argued that by combining the three baselines together to form a pre-CVS baseline, changes in natural recovery that occurred prior to CVS may have been missed. Nonetheless, by averaging the data in this way initial practice gains during the first and second test repetition were accounted for (Collie et al., 2003), and a more reliable baseline was obtained by testing the participants on three separate occasions.

It could also be argued that the published data used to build the equation would have been more informative if it were based on a TBI sample (Heaton et al., 2001). While the data used to build this equation cannot determine whether any performance changes from test to retest were unusual for patients with TBI, they did provide useful inferences about participants' performance on seven of the eight tests relative to a larger healthy sample and

over a similar retest interval. Overall this was deemed to provide a closer estimate of reliable change than building the equation from multiple different TBI studies that had only administered one or two CANTAB tests to smaller sample over a shorter retest interval (e.g. Salmond et al., 2005; Silver et al., 2009; Mehta et al., 2001; Wäljas et al., 2014). If a registered psychologist was available, then future research could consider administering more widely-recognised neuropsychological assessments (e.g. Weschler Memory Scale-Revised; Weschler, 1987 or the Rivermead Behavioural Memory Test; Wilson, Cockburn, & Baddeley, 1985), since published data within TBI samples (administered at similar multiple retest intervals) is likely to be more readily available.

Behavioural Data Summary

The current sample demonstrated considerable heterogeneity in their cognitive performance both at baseline, as well as in response to CVS. Participants 02 (SWM), 04 (PAL), 05 (PAL) achieved their highest test score during CVS which also corresponded to a significant improvement from the pre-CVS baseline within the analyses of reliable change. However, the inferential statistics generally tended to show that participant's scores had remained stable during CVS relative to the pre-CVS baseline. At the group-level, a composite measure of cognitive performance was significantly altered across the study sessions. However, post-hocs did not reveal any significant changes during active CVS after corrections for multiple comparisons. Similarly, shifts from clinical categories on the questionnaires were largely absent during CVS. Overall the current study was able to demonstrate isolated CVS-related cognitive improvements which included but were not limited to memory processes or dependent on concurrent changes in psychiatric or fatigue symptomology.

The next chapter aimed to explore the neurological mechanisms that might underpin the above effects using EEG and ERP (event-related potential) techniques. A discussion

section will then bring together and interpret the behavioural and electrophysiological results and consider more general limitations of the protocol.

Chapter 4
Electrophysiological Outcomes in Individuals with Traumatic Brain Injury Following Caloric Vestibular Stimulation.

This chapter discusses the electrophysiological measures that were collected with the behavioural assessments reported in the previous chapter. Recall that behavioural responses to repeated sessions of CVS varied amongst the TBI sample. Some participants showed short-lived visuospatial memory and problem solving improvements, but these were not replicated across the group and varied from person to person. Electrophysiological techniques were also included in this study to detect any subtle changes in symptomology which could potentially have been missed or distorted (i.e. malingering) by the behavioural assessment battery.

Historically, EEG was the first neuroimaging technique to assess whether brain functions had been altered by a TBI (Slobounov, Sebastianelli & Hallet, 2012). Since then, EEG has proved a useful tool for investigating online brain activity which is not phase-locked to a specific event (Luck & Kappenham, 2012). Previous research indicates that EEG may be particularly useful for profiling the effects of TBI because it is sensitive to covert neurological abnormalities that might be missed by a neurological or neuropsychological examination (Koufen & Dichgans, 1978), as well as subtle physiological effects caused by cortical atrophy or thinning that may not manifest on an MRI (Rapp et al., 2015).

A number of studies have also evidenced changes in brain activity following a TBI by measuring ERPs. ERPs represent the averaged EEG signal time-locked to the onset of a given stimulus and are defined by their latency, polarity, distribution and relation to experimental stimuli. The voltage deflections comprising the ERP can be used to study the processing of incoming sensory information, as well as higher level cognitive processes including attention, memory, and comprehension (Dockree & Robertson, 2011; Duncan et al., 2009). Because ERPs are non-invasive and offer excellent temporal resolution, the technique has provided

important insights into cognitive processing in both healthy and TBI samples (Duncan et al., 2009).

This chapter aims to investigate whether several neural substrates (as measured by EEG and ERP) can be modulated by CVS in a way that they might start to resemble that of the healthy population over the course of the study. As such, it provides the first interrogation into the neural mechanisms of CVS in TBI patients. The chapter begins by introducing the measurements and markers of the EEG and ERP techniques employed, and then describes how the electrophysiological response typically presents within healthy and TBI samples. Relevant evidence of electrophysiological modulation in response to NSM, particularly vestibular stimulation, will then be reviewed and the hypotheses outlined. Resting-state EEG and ERPs are described separately below, since the former was used to form a profile of impairment and the latter was used to provide a more direct test of cognitive function. To give an overview, resting state EEG was altered across the sample during CVS, with four out of the eight participants showing some effects which were in accordance with a shift towards a healthy topography. However, there was little convergence and most participants' also demonstrated EEG effects which contrasted with the normalisation hypothesis. ERPs tended to fluctuate across the study and were largely unaffected by CVS, with the exception of one participant. Overall, everyone showed at least one favourable electrophysiological change providing suggestive evidence of a beneficial effect of vestibular inputs on the targeted electrophysiological outcomes. These changes mainly manifested within the EEG power data as opposed to the ERPs indicating CVS may have induced broad scale changes in arousal and wakefulness as opposed to a specific cognitive process within this TBI sample.

EEG

Power spectrum. The EEG power spectrum is one of the standard methods used to quantify the EEG signal in TBI populations (Dressler, Schneider, Stockmanns & Kochs, 2004; Rapp et al., 2015). The spectrum describes the distribution of signal power over five different frequency bands, reflecting different speeds of neural oscillations (see Figure 4.1): Delta (≤4Hz), Theta (4-8Hz), Alpha (8-12Hz), Beta (12-30Hz) and Gamma (>32Hz) (the precise ranges can differ slightly across studies).

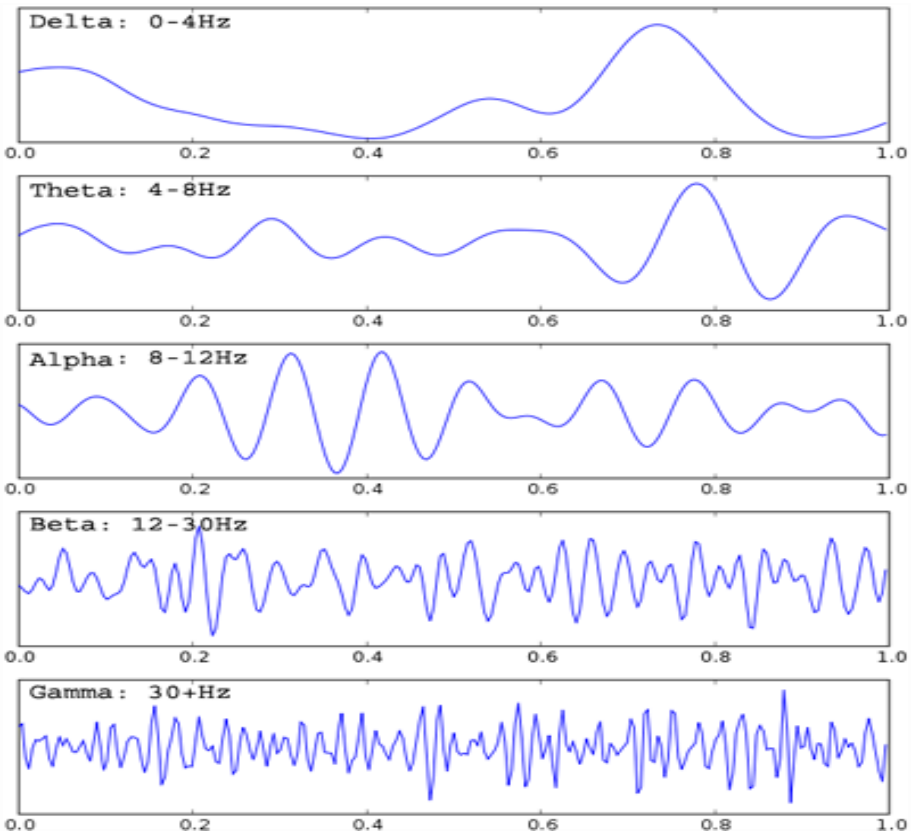


Figure 4.1. EEG frequency bands plotted across a one second interval. Reprinted from Electroencephalography (EEG). Retrieved December 08, 2015, from http://www.wearablesensing.com/images/EEG.png.

Each band has been associated with specific cognitive and regulatory functions. Delta wave activity can often be found in healthy adults during sleep, theta activity has also been identified during periods of drowsiness but can also emerge during some mental tasks (Westmoreland, 2009). Alpha activity is observed during relaxed periods of wakefulness and

forms the predominant background activity within healthy adults, particularly over the posterior brain region (Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Martin & Dominguez-Morales, 2009). Beta activity is also highly prevalent within healthy adults and is usually most marked within the fronto-central regions. Beta activity often responds to alerting stimuli and during cognitive tasks (Kellaway, 2003). Finally gamma has been observed during multiple sensory functions and during cognitive processes such as working memory and attention (Jia & Kohn, 2011).

The current study measured the power spectrum of the filtered EEG signal over the delta, theta and alpha bands (μV^2). Beta and gamma power were excluded from the analysis since the general functional role, as well as the effects of TBI on these bands are less well understood (see Craig, Tran, Wijesuriya & Nguyen, 2012, further detail is also provided below). Additionally, gamma activity can be distortdetted by line noise which is difficult to isolate in participants' homes (e.g. from lights, fans, washing machines; Luck, 2014). The objective was to identify whether CVS could normalise (according to the trends described above and the next section) the pattern of EEG activity within TBI patients. Some of the more common abnormalities amongst TBI survivors are outlined below.

Power spectrum in TBI. Although previous EEG research with TBI samples has produced variable findings, amongst the most consistent effects are a slowing of the EEG signal indexed by greater activity in the delta and theta bands (slower waveforms), and a reduction in the faster waveforms (particularly alpha) (Leon-Carrion et al., 2009). Tebano et al. (1988) observed a reduction in faster activity at both the alpha, and beta bands in a TBI sample assessed three to ten days after their trauma. Alvarez et al. (2008) also demonstrated greater delta and theta activity and reduced alpha activity in patients who had sustained their TBI within a longer two year window. Gosselin et al. (2009) and Tomkins et al. (2011) also

showed that individuals who had suffered both mild and severe TBIs respectively had significantly more delta activity and less alpha activity, relative to matched controls.

One explanation for these trends is that the structural pathology of TBI causes diffuse axonal injury involving the white matter tracts (which pass sensory input between different areas of the cerebral cortex and the central nervous system), and a simplification of the dendritic connections in cortical grey matter (Rapp et al., 2015). This interruption to the nerve cells has a knock-on effect on the firing rate and synchronisation of neurons causing inappropriate synaptic plasticity and irregular oscillatory interactions (Pevzner, Izadi, Lee, Shahlaie & Gurkoff, 2016). As a result, EEG power spectra can be seen to slow such that activity is increased at the delta and theta bands and reduced over the faster bands.

However, it is important to note that no clear EEG markers have yet been identified as unique to TBI or characteristic of recovery (Nuwer, Hovda, Schrader & Vespa, 2005). Rapp et al. (2015) recently reviewed fifteen relevant studies which measured spectral power within TBI samples and found that most had identified statistically significant alterations in at least one frequency band in TBI patients relative to control groups. While some generalisations could be made between the studies (decreased alpha activity and increased delta, theta and beta activity), heterogeneities amongst the populations sampled (e.g. injury severity, lesion location and recovery-phase) as well as variations in experimental procedures (e.g. performed during a task or at rest, within versus between subjects design, sub-bands) both increased the variability of the reported effects and limited the inferences that could be drawn about spectral power in TBI (Arciniegas, 2011; Haneef, Levin, Frost & Mizrahi, 2013; Pevzner et al., 2016).

Of particular relevance to this study is whether the observed abnormalities tend to resolve after the acute stages, or persist into the chronic stages where the current sample were placed. Although the majority of acute EEG abnormalities appeared to be transient,

particularly after a mild TBI, residual irregularities have been identified (see Haneef et al., 2013 for a review). For example, Korn, Golan, Pascual-Marqui and Friedman (2005) revealed a significant increase in delta alongside a reduction in alpha power that persisted for at least six months in 11 out of 17 participants with post-concussion syndrome relative to controls. Further, Lewine et al. (2007) used magnetoencephalography (MEG) to study 30 patients with persistent neuropsychiatric symptoms (> one year after injury) and identified high levels of slow-wave activity during rest within 63% of the sample. Taken together these studies suggest that residual spectral abnormalities may be present within the current TBI sample, providing a therapeutic target for modulation by CVS.

Neurostimulation and the power spectrum. At present little is known about the influence of CVS on spectral power. However, general insights into how CVS affects brain activity have been gathered from tools such as fMRI and positron emission topography (PET). A meta-analysis by Lopez et al. (2012) showed that CVS produces widespread projections to the parietal, temporal, frontal and insular cortices. Amongst these projections is a connection with subcortical nuclei that supply the reticular activating system, a crucial element of the brain's core arousal system (Bense, Stephan, Yousry, Brandt & Dieterich, 2001). If vestibular inputs make a significant contribution to arousal, then power could be expected to increase in those bands associated with wakefulness and engaged activity during CVS (Wilkinson, Ferguson & Worley, 2012).

The present study is amongst the first investigations, to my knowledge, to examine how CVS influences ongoing resting-EEG activity. It is therefore useful to consider how research has been conducted using other neurostimulation techniques. For example, Griškova, Rukšėnas, Dapšys, Herpertz, & Höppner (2007) examined the effects of sham and real-TMS on spectral power pre and post stimulation. The authors demonstrated an increase in delta power in response to TMS over the left dorsolateral prefrontal cortex, relative to a

sham condition in all 18 healthy subjects that were tested. However, the effects of TMS on the alpha, beta and theta bands varied between participants. Given that this study shared some similarities with the present research in terms of the aims (elicit changes in resting EEG power in response to neurostimulation), design (crossover of active versus sham blocks) and recording procedures (several minutes of resting activity), the analysis approach employed by Griškova et al. was used to inform the preparation and statistical analysis of the current EEG data.

Two studies have also looked at changes in power spectra during coincident GVS within healthy participant samples. Wilkinson et al. (2012) measured spectral power during a face processing task (alongside ERP measures), and demonstrated a stepwise increase in delta (posterior temporal) and theta (temporal-occipital) power as the amplitude of stimulation increased. The results indicated that GVS had modulated neurological components linked to face processing as well as inducing potentially broader cortical changes in arousal. Kim et al. (2013) also showed that noisy GVS had a direct impact on resting EEG activity while participants kept their eyes open. Spectral power was consistently increased across all bands (theta, alpha, beta, and gamma) over the frontal-parietal electrodes shortly after the stimulation had ended. The authors suggested that noisy GVS could be a potentially useful tool for the neuromodulation of distributed functional brain networks. However, since the studies above recorded EEG while participants were either receiving stimulation or immediately after their stimulation had ceased, the longer-lasting effects of vestibular stimulation could not be determined. As this is a key goal of neurorehabilitation, the current study aimed to advance upon existing research by looking at the offline effects of CVS on EEG activity (CVS delivered >one hour prior to the recording).

Hypothesis (i). In light of the above discussion, five minutes of resting state EEG were recorded across four sessions placed at important stages of the protocol (see Figure 3.3

in Chapter 3). Based on the research described above which has identified an impaired neural profile characterised by slow-wave dominance following TBI, this study aimed to normalise the spectral power of TBI patients using CVS. More specifically, the study tested whether the recordings taken during active CVS would begin to reflect the normative topography whereby slow-wave activity in the delta and theta bands would be significantly reduced and faster-wave activity in the alpha band increased, compared to those recordings taken pre-CVS (baseline and sham stimulation).

ERP

Continuous EEG reflects a wide-range of sensory and cognitive processes and thus provides a useful index of a patient's overall neural profile. However, because the EEG signal reflects multiple co-occurring self-regulation functions it can be difficult to separate the contribution of these higher and lower processes. By contrast, ERPs reflect brain responses to specific stimuli or events and can thus provide a clearer window into cognitive functioning (Key, Dove & Maguire, 2005). Here ERPs were captured to determine whether CVS impacts the way that visuospatial stimuli are evaluated.

The P300 ERP component. This study measured the classic P300 component which has been well characterised (relative to other ERP components) in terms of eliciting stimuli, recording and quantification procedures, and the cognitive processes which it reflects (Duncan et al., 2009). The P300 is a positive component which typically peaks around 300ms after the onset of a rare novel stimulus and is formed of subcomponents including the P3a and P3b (see Figure 4.2). The P3a originates from fronto-central activity associated with the processing of infrequent task-irrelevant stimuli, whereas P3b originates from temporo-parietal activity and is driven by infrequent task-relevant target stimuli (Polich, 2007). The component is thought to indicate the categorisation of incoming information (P3a-novelty, P3b target stimuli) and has also been linked with updating the context of working memory

(P3b) (Donchin & Coles, 1988; Duncan-Johnson & Donchin, 1977; Luck, 2014). Here the P3b was studied (referred to as the P300), given its association with attention and memory processes.

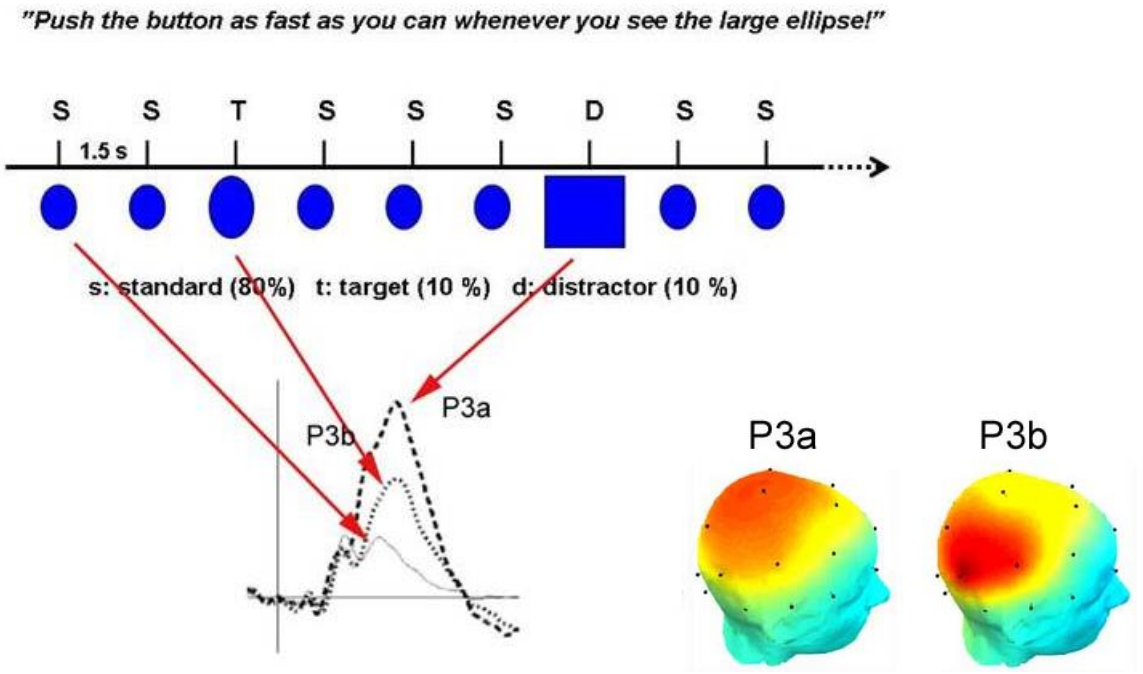


Figure 4.2. A waveform and topography elicited by the P3a and P3b subcomponents in response to targets (P3b) and distractors (P3a). Reprinted from Ferguson, H. J. (2016). *An Introduction to ERP* [PowerPoint slides]. Retrieved from http://www.moodle.kent.ac.uk/.

P300 in TBI. The P300 (P3b) is typically studied in TBI survivors using oddball paradigms, whereby participants must identify and respond to infrequent target stimuli amongst more frequent non-targets. In healthy adults, the P300 amplitude tends to increase when the target presentation becomes less frequent or more salient, and this response is thought to indicate greater attentional resources being deployed to stimulus processing. Finding a reduced P300 amongst TBI samples could therefore indicate that fewer cognitive resources are available for allocation to stimulus categorisation (Duncan, Kosmidis & Mirsky, 2005). P300 latencies can also be studied to infer whether TBI induces slowed processing and categorisation of stimuli, and if this slowing occurs at a particular stage of processing (i.e. when used in conjunction with RTs, stimulus processing can be isolated from response production; Lew, Gray, & Poole, 2009).

Several researchers have investigated whether the aforementioned P300 abnormalities are present within TBI samples. Duncan et al. (2005) reviewed 16 experiments which studied the visual P300 (elicited by visual stimuli) and found that P300 amplitudes were reduced relative to healthy controls in approximately half of the studies. Moreover, in those studies where a significant attenuation was not present, visual P300 amplitudes still appeared to be reduced when compared with healthy controls. Auditory P300 amplitudes (elicited by auditory stimuli) were more commonly studied, with over half of the 39 studies reviewed showing a significantly attenuated amplitude. However, the authors noted that the task conditions (for both sensory modalities) needed to be sufficiently challenging in order to tax attention processes, and therefore attenuate P300 amplitudes. Delays in P300 latencies were also observed across both sensory modalities. These findings suggest that the availability of attentional resources is reduced following a TBI, as a consequence there is a delay in the categorisation of stimuli, and an impairment to the working memory comparisons that ascertain whether or not the current stimulus is the same as the previous/ target stimulus (Duncan et al., 2005; Duncan et al., 2009; Polich, 2012).

Similar to the literature on spectral power, there are consistencies (described above) as well as discrepancies regarding the reported impact of TBI on the P300. As with most research with TBI survivors, differences in the characteristics of the individuals sampled are likely to contribute to this variability (Folmer Billings, Diedesch-Rouse, Gallan & Lew, 2011). For example, several studies have demonstrated that P300 abnormalities (reduced P300 amplitudes and longer latencies) were more apparent amongst individuals with severe as opposed to mild injuries (Lew et al., 2009; Spikman, van der Naalt, van Weerden & van Zomeren, 2004). Abnormalities were also more prevalent during the acute stages of injury (Keren, Ben-Dror, Stern, Goldberg & Groswasser, 1998; Onofrj et al., 1991), but could still emerge during the latter stages of recovery (as sampled in this study) (Ledwidge & Molfese,

2016; Müller et al., 2002). Changes to the experimental parameters have also influenced findings, with variations in the eliciting stimuli, response format, and task difficulty (Duncan, Kosmidis & Mirsky, 2003; Duncan et al., 2005; Lew et al., 2002) all restricting the conclusions that can be drawn across studies.

Nevertheless, several researchers have advocated the use of ERPs to assess and monitor the progress of TBI patients during recovery and in response to rehabilitative interventions (Dockree & Robertson, 2011; Folmer et al., 2011). An experiment was thus devised whereby ERPs were recorded alongside behavioural measures (accuracy and RT) before and after CVS. A working memory task was chosen to further explore vestibular contributions to short-term visuospatial memory.

N-back tasks and working memory. The P300 has been widely studied across both healthy and clinical populations using the n-back task. The task requires participants to monitor a sequence of stimuli, and to identify a stimulus as a target, if it matches a pre-specified infrequent stimulus presented 'n' trials previously ('n' is varied across studies, usually between 0-3). By systematically varying working memory load (without any other task modifications), this experimental paradigm can be used to determine how high the task demands must be for the detection of cognitive impairment. Changes in this threshold can therefore be recorded during the recovery process, or in response to an intervention.

During the task, information must be continuously registered, updated and stored, therefore placing substantial demands on information processing resources. This challenging task was selected since many studies have successfully applied the paradigm to elicit a P300 response in healthy individuals (Brouwer et al., 2012), and after previous research conducted with TBI survivors and healthy controls highlighted that the eliciting task must be sufficiently difficult for P300 abnormalities to emerge (Bernstein, 1999; Duncan et al., 2005). This was

also necessary in the current study to prevent participants from reaching ceiling levels of behavioural performance once the task has been repeated across several sessions.

In healthy participants, n-back paradigms tend to elicit an inverse relationship between working memory load and P300 amplitude, as the load increases (i.e. from 0 to 3-back) P300 amplitude decreases. This inverse relationship is thought to reflect dual-task demands between the attentional resources required for the matching of stimuli to a mental representation of a target, and the increasing memory demands required at the higher load levels (Gaspar et al., 2011; Ozen, Itier, Preston & Fernandes, 2013). Given that attention (particularly divided attention) and working memory problems are prevalent amongst TBI patients, the n-back task seemed an especially relevant way of eliciting the P300 (Asloun et al., 2008).

Although several experiments have studied the performance of TBI survivors on the n-back using behavioural outcome measures and fMRI (e.g. Asloun et al., 2008; Dettwiler et al., 2014; Dymowski, Owens, Ponsford & Willmott, 2015; Perlstein et al., 2004), few have used ERP measures. In one study Ozen et al., (2013) looked at the performance of 17 mild-TBI patients (at least one year post-injury) on a visual-letter n-back task. In line with previous n-back research, both patients and controls showed significantly smaller P300 amplitudes in response to non-targets, and for higher rather than lower working memory loads (the effect was greatest between the 0 and 3-back loads). Moreover, the patients also had significantly smaller P300 peak amplitudes in response to target stimuli compared to a control sample, at all n-back loads of working memory (i.e. group- control/ TBI did not interact with Load). This occurred in the absence of any behavioural performance deficits on the task or any delays in P300 latency (Gaspar et al. 2011 also provided a similar demonstration in a psychiatric sample). The authors concluded that the attenuated P300 amplitudes reflected long-term inefficiencies in the resources available for target classification, and also in the

ability to allocate resources (from the primary oddball matching task to the working memory sub-task) during attention and memory tasks.

Findings from other neuroimaging studies completed with acute mild TBI patients have provided similar demonstrations of differential brain activity in patients relative to controls in the absence of behavioural performance deficits on the n-back (McAllister et al., 1999, 2001). However, Perlstein et al. (2004) did evidence a significant group difference in accuracy (but not RTs) on their visual-letter n-back task between TBI and control samples. More specifically, while the patients with milder injuries showed normal behavioural performance on the task, those patients with moderate or severe injuries exhibited behavioural deficits during the higher memory loads only (2 and 3-back).

Taken together, the evidence above has mostly shown the accompanying n-back behavioural responses to be unaffected by TBI, therefore the current analyses focused on electrophysiological measures but also considered behavioural responses to characterise any potential electrophysiological changes in working memory. Moreover, as the present sample had all sustained moderate to severe TBIs, behavioural changes might also be expected if working memory impairments were present at baseline (as in Perlstein et al., 2004).

Vestibular stimulation and the P300. Since vestibular-cognitive effects have reportedly been strongest for visuospatial aspects of perception and memory (Hanes & McCollum, 2006; Smith et al., 2010), a visuospatial n-back task was implemented to exploit this connection. The task required participants to respond to a target stimulus that was presented in the same location as a stimulus shown ‘n’ trials previously (i.e. the visual target is a spatial location). Performance was monitored using behavioural and electrophysiological measures which were compared pre-CVS and after blocks of active CVS with the aim of increasing participants’ attentional capacity, and in turn facilitating working memory.

Previous research has already demonstrated that ERPs can be modulated by vestibular stimulation, however these studies have focused on non-spatial tasks and/ or other ERP components. For example, Wilkinson et al. (2012) reported an increase in the amplitude of the N170 component (a marker associated with early visual structural encoding), during concurrent GVS relative to sham stimulation, while participants completed a face processing task. Wang et al. (2004) also reported that the P300 was quicker to peak when participants were stimulated using chair rotations (constant 10°/s) relative to control and angular acceleration conditions, while they completed an auditory go/no-go task. Perhaps of most relevance to the present study are the results from Schmidt-Kassow, Wilkinson, Denby and Ferguson (2016), who studied the effects of concurrent vestibular-stimulation on the P300. Participants completed an auditory oddball task which required them to silently count deviant tones that appeared within strings of standard tones while receiving either sub-sensory active or sham GVS. Results showed that the P300 effect to deviant oddball stimuli was increased during GVS relative to sham, but only when the temporal frequency of the alternating current matched that at which the tones were played (1Hz). This indicates that vestibular stimulation can significantly impact cognitive processes involved in stimulus categorisation, as indexed by the P300.

Here the effects of CVS on the P300 ERP component were assessed (offline) in a TBI sample. The widespread boost in brain activity elicited by the stimulation (Suzuki et al., 2001) means that it is particularly suited to remediate TBI where the diffuse damage sustained to multiple neural connections from the brain stem to the forebrain (Folmer et al., 2011) may have diminished the contribution of subcortical P300 generators including the fronto-parietal networks and the ACC, thus resulting in P300 abnormalities (Linden, 2005). Since these generator regions are amongst the main clusters activated during CVS (Lopez et al., 2012), the P300 may provide a useful rehabilitation target.

Hypothesis (ii). Based on the research above which has identified P300 abnormalities following TBI (reduced amplitudes, slowed latencies), this study aimed to 'normalise' the P300 of TBI patients using CVS. More specifically, it was anticipated that P300 amplitudes would increase after active CVS (irrespective of memory load) as participants became more accurate at stimulus categorisation, potentially with the improved availability of attentional resources. P300 latencies were also expected to reduce as another indication of facilitated stimulus classification. Similar increases in accuracy and reductions in behavioural RTs were also anticipated in response to CVS, as it was assumed that the moderate/ severe TBIs sustained by this sample would be likely to result in a behavioural working memory impairment (that could be remediated by CVS). Participants were also expected to show an overall effect of load, whereby performance was worsened (reduced amplitude/ accuracy and increased latencies/ RTs) with increased working memory demands, as observed within healthy and brain injured individuals. However, specific interactions between load and CVS were not specified after previous research showed that TBI participants respond to different working memory loads in a similar way to controls, irrespective of any impairment or intervention (Ozen, et al., 2013; Perlstein et al., 2004- mild TBI, lower loads). If supported, the findings would provide the first electrophysiological evidence for improved attentional and working memory processes following CVS in TBI and would also help to clarify which memory processes interact with the vestibular system.

The following sections will describe the recording and analysis procedures for the electrophysiological data, along with any resulting changes in response to CVS. Overall CVS modulated EEG power in at least one band in most participants. However contrary to the hypothesis, power generally tended to decrease across all the bands (delta: four, theta: three, alpha: five participants). Data from the ERP measures (P300 amplitudes and latencies) and the accompanying behavioural responses were largely unaffected by CVS.

Method

ERP Experimental Paradigm

The task included four load conditions (0 to 3-back), with identical encoding and response demands, but with increasing levels of working memory load. Participants were sat in front of a 1920 x 1200 pixel laptop screen. The stimuli comprised a small black square (175 x 175 pixels) presented in one of four locations within a white box (600 x 600 pixels) (see Figure 4.3). Participants observed the black square stimulus and responded to its location using the keyboard. In the 0-back condition, participants responded to a single pre-specified target location (the first location to appear during the trial block). In the 1-back condition, the target location was any position which was identical to the immediately preceding trial. In the 2-back and 3-back conditions, the target was the location that the square was presented in two or three trials back, respectively (see Figure 4.3).

Each trial started with the presentation of a fixation cross which acted as the inter-stimulus interval (ISI) and lasted between 1000 and 2000ms (200ms intervals randomly sampled). The ISI length was varied to account for the fact that P300 amplitudes and latencies are affected by the interval between two targets within a stimulus array (smaller P300 amplitude when a target is preceded by another target; Polich, 2012). This was followed by the black square stimulus which was shown alongside a central fixation cross (included to minimise unnecessary eye movements) for 2500ms or until participants responded. Participants used a keyboard to respond to each stimulus with their dominant hand, the 'N' key was pressed for targets and the 'M' key for non-targets. E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA) was used to present the visual stimuli and record accuracy and RTs.

N-back loads were blocked and completed sequentially (0 to 3-back) for consistency and to familiarise participants with the task before more difficult loads were attempted. Each

load condition consisted of 130 trials: 30 practice then 100 experimental trials. Half of the trials contained target stimuli (15 practice, 50 experimental), and the other half non-target stimuli, these were presented in a randomised order. Verbal and computerised instructions were given at the beginning of each trial block and accuracy feedback was provided at the end of each practice block. The entire n-back task typically took participants 30 minutes to complete, plus breaks varying in length between load conditions/ practice blocks.

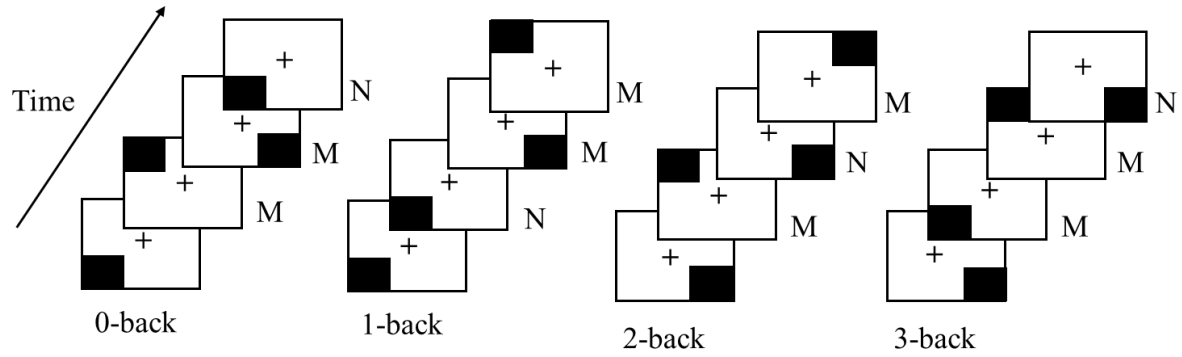


Figure 4.3. Schematic representation of the different n-back loads (increased from 0 to 3-back). The letters N (target) and M (non-target) show the correct button press for each trial.

Electrophysiological Recording

All EEGs were carried out in a quiet room within the participant's home, and efforts were made to reduce potential distractions to a minimum. Participants kept their eyes open (to minimise drowsiness) and focused on a central fixation cross displayed on a computer screen for the duration of the recording. Five minutes of resting-state EEG were first taken before participants moved onto the n-back task, the recording procedures were the same for both.

The Brain Products portable BrainAmp amplifier with an EasyCap electrode cap was used for continuous recording of EEG activity from 19 scalp electrodes. Electrodes were placed according to the 10-20 system, with the ground placed at AFz. HEOG activity (horizontal eye movements) was recorded from electrodes placed at the outer canthus of the left and right eyes. VEOG activity (vertical eye movements) was recorded from an electrode

placed underneath the right eye. During EEG recording, all electrodes were sampled at 500Hz and electrode impedances were reduced below 10 kΩ at the start of the session. Efforts were made to keep impedances below 20kΩ during the recording. All channels were referenced online to electrodes placed over the left and right mastoids.

Offline Analysis

Brain Vision Analyzer version 2.1 was used to prepare the EEG and ERP data prior to statistical analysis, the procedures for both are discussed separately below.

EEG power. First the data was filtered using a 0.1Hz high pass and a 40Hz low pass filter with a notch filter at 50Hz to prevent electrical noise from the environment distorting the EEG data. Data containing blinks or eye movements was then corrected using ocular correction Independent Components Analysis (ICA). EEG data from the first four minutes of the recording was then segmented into consecutive 2s epochs. A semi-automatic procedure identified and rejected any segments that contained nuisance artifacts (e.g. muscle movements, channel blockage etc.). The minimum number of artifact-free segments per session was 104, and the average was 117. An exception was made for patient 05 where all recording sessions were limited to 75 segments, due to the patient wanting to discontinue one of the EEG recording sessions (more detail given below). Fast Fourier Transformation, with a 10% Hanning window, was applied to the segmented EEG data, and the resulting power was averaged across segments in three brain regions: frontal (Fz, F3, F4), central (Cz, C3, C4), and parietal (Pz, P3, P4), as in Griškova et al. (2007). Power was analysed in three frequency bands: delta (1- 4Hz), theta (4- 8Hz) and alpha (8- 12Hz).

ERP. Data were filtered using a 0.1Hz high pass and a 30Hz low pass filter, with a 50Hz notch filter. Eye artifacts (e.g. blinks, eye-movements) were again corrected using ocular correction ICA. EEG data from target trials where participants made a correct response

was segmented at each n-back load (maximum of 50 trials per load level, see Table 4.1 for average number of segments) into epochs that began 200ms before, and continued 1500ms post-stimulus onset. A semi-automatic procedure identified and rejected any segments containing nuisance artifacts. All segments were then baseline corrected (-200 to 0ms). The MovingAverage procedure was then used to smooth the temporal structure of the data by averaging EEG activity over a 100ms window at the parietal midline electrode Pz. The MinMax Markers procedure was subsequently used to identify the peak amplitude in each segment during a specified window between 250 and 500ms post-stimulus onset (as in Polich, 2012). Peak amplitude and latency values were then exported for further analysis. Finally, segments were averaged separately for each load level and session for display purposes.

Challenges of Patient Research

Conducting these electrophysiological assessments with clinical populations involved unique challenges above and beyond the general issues that are faced with healthy research participants (Kappenman & Luck, 2016). For example, although EEG recordings are generally well tolerated by patients (more so than PET and fMRI), it was still necessary to modify the recording procedures (i.e. reduced set-up time, recording time/ number of experimental trials) to avoid participants becoming uncomfortable, tired or disengaged.

To further ease convenience, all assessments took place in participants' homes. This meant that these meetings could be fitted around daily commitments and participants' symptoms could be better managed during testing. However, this also resulted in less control over the experimental settings. Additionally there were incidents where the EEG data was distorted by technical faults (see results for participants 02 and 06) which were difficult to resolve without technical support or back-up equipment. Nevertheless, because of the

investment made by the research team as well the participants to collect this unique data, efforts were made to utilise as much of the data as possible unless omission was unavoidable (i.e. nuisance artifacts in EEG segment, no correct target n-back trials, the participant could not be encouraged to continue the test) as a result there are three instances where the statistical analysis deviates from the approaches detailed below.

Statistical Analysis

Four electrophysiological recordings were gathered at key stages in the protocol (baseline, second baseline/ sham stimulation, four weeks CVS, eight weeks CVS). A multiple-single case analysis approach was again adopted for both the EEG and ERP data to better address the heterogeneity of TBI given the small sample size. The analysis procedures for the EEG and ERP data are discussed separately below.

EEG power. A repeated measures ANOVA was performed separately for each participant and frequency band, with total power as the dependent variable. The within-subjects factors were as follows: "Stimulation" (pre-CVS *versus* active CVS); "Session" (first *versus* second recording within each Stimulation block); "Region" (frontal *versus* central *versus* parietal). Although there are multiple ways that these data could have been analysed, this particular design was selected to address the key question of interest: does CVS modulate spectral power? Power was expected to increase within the higher frequency band (alpha) and to decrease within the lower frequency bands (theta, delta) during active CVS, compared to those recordings taken pre-CVS. By including the Session variable the two pre-CVS recordings could be combined and compared to the two active CVS recordings, which increased the number of data points, reduced variance, and provided more power to detect an effect of Stimulation on spectral power.

In keeping with the key question, the analyses focused on significant main effects and interactions involving the Stimulation variable. Therefore, main effects of Region were only discussed in terms of the standard power topographies mentioned above (see EEG power spectrum section). Further, the Session variable was only considered when it interacted with the Stimulation variable. Where a three-way interaction was present, post-hoc analyses then compared the effects of Stimulation and Session within each Region (i.e. does the EEG signal change across sessions in response to CVS, within each Region). If a three-way interaction was absent, two-way interactions involving the Stimulation variable were examined and post-hoc tests completed.

Figure 4.4a illustrates the hypothesised pattern of results for the slower (top) and faster (bottom) power bands. A main effect of Stimulation was predicted whereby the pre-CVS recordings differed from the active CVS recordings (overall across all regions and sessions). Stimulation and Session interactions were also expected to reveal significant differences between the Stimulation conditions at both Session one (baseline *versus* four weeks CVS) and Session two (baseline two/ sham *versus* eight weeks CVS). Additionally, the two pre-CVS recordings (baseline, baseline two/ sham) were not expected to differ from one another, while a cumulative effect of CVS was predicted between the recordings taken after four and eight weeks CVS (when a main effect of Stimulation was present). This follows demonstrations of promoted recovery from neurological conditions with repeated, rather than single sessions of vestibular stimulation (Johannsen, Ackermann & Karnath, 2003; Ohn et al., 2008; Wilkinson et al., 2014).

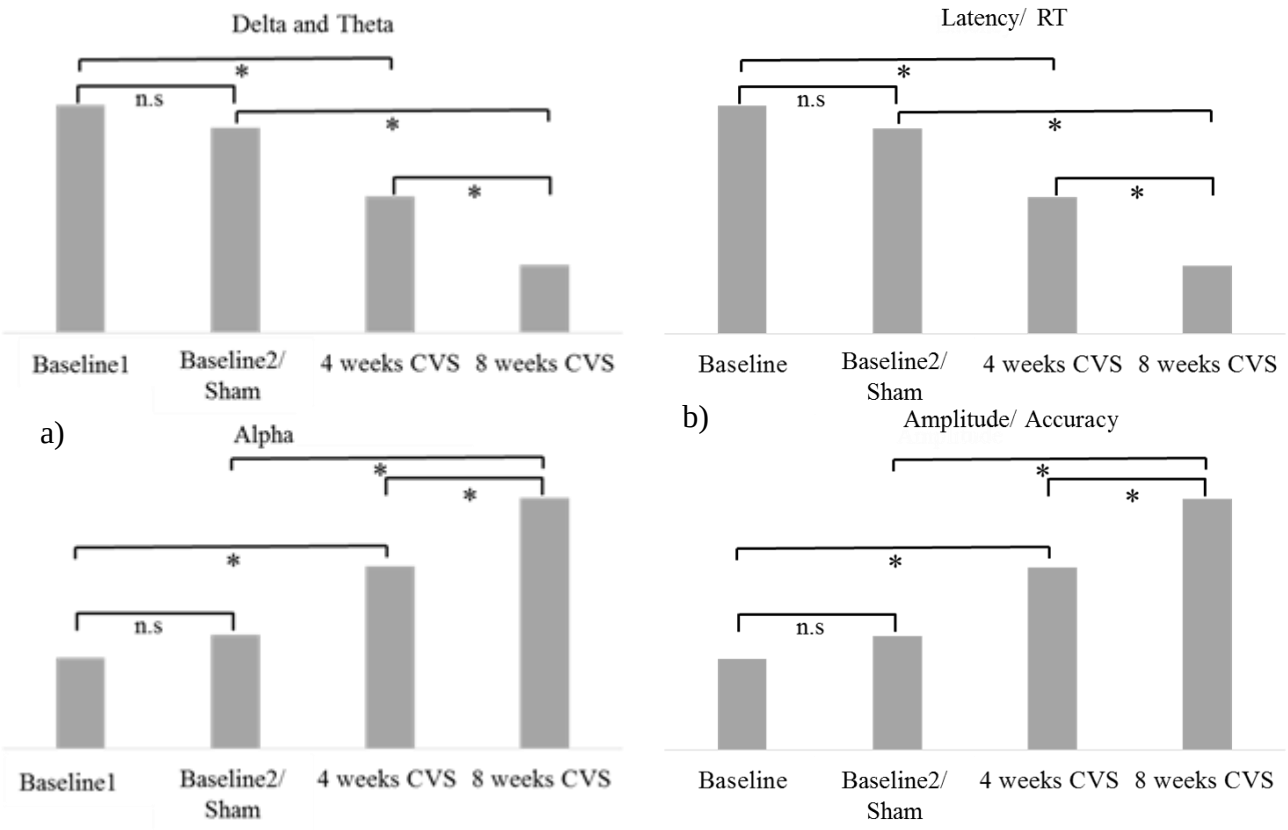


Figure 4.4. Illustration of hypothesised Stimulation and Session effects for EEG spectral power (a) and the ERP outcome measures (b) if CVS were to exert a normalising influence.

ERP. This analysis adopted a between-subjects design to more effectively examine the effects of Session and Load within each participant, since it allowed for unequal segment numbers in each condition. In contrast, a within-subjects design would have reduced the number of segments to the minimum number of correct-responses during one Session or n-back Load. Table 4.1 displays the average and minimum number of segments across all participants for those sessions and trial blocks which were completed without any technical or participant difficulties. As can be seen from the table, the number of included segments could be very small for the most difficult n-back loads and would thus be insufficient for ERP analysis in a within-subjects design. Implementing a between subjects design involved applying a more conservative approach to significance, but meant that the maximum number of trials could be retained in each condition.

P300 peak amplitude, P300 latency, accuracy and correct *z*-score filtered[3] RTs were submitted to separate three-way ANOVAs with "Stimulation"; "Session" and n-back "Load" (0, 1, 2, 3) as factors. This analysis (Stimulation, Session) was similar to the design applied to the EEG data and was selected so that the two pre-CVS and active CVS recordings could be combined and compared with more power. This was especially valuable in participants where few correct n-back trials were available for the analysis.

Table 4.1
Average and Minimum Number of Correct-Responses Included for Analysis at Each n-back Load for Target Trials.

Load	Minimum segment number	Average segment number
0	14	45
1	25	46
2	13	38
3	6	29

Note. Two recordings (participant 05 eight weeks CVS, participant 06 baseline) and one trial block (participant 02 sham recording for the 0-back) have been omitted from this table due to faults which are described further in the results section.

To address the key question, the analyses focused on the presence of significant main effects and interactions involving the Stimulation variable. Main effects of Load were also discussed in terms of the inverse trends observed within normative samples (reduced amplitudes/ accuracy and longer latencies/ RTs for higher n-back loads). Lastly, main effects of Session were only considered within the behavioural data to determine whether any practice effects had occurred between consecutive testing sessions (no practice-effects were expected within the electrophysiological data).

[3] Outliers were removed using a *z*-score correction whereby a grand mean RT was calculated (across all sessions completed by the participant) and then subtracted from every individual trial RT, before being divided by a grand standard deviation ($Z= \frac{X-\mu}{\sigma}$). Any resulting *z*-scores that were greater than 2.5 (and therefore an outlier of less than $p<0.001$) were removed from the data.

Where a Stimulation x Load x Session interaction was present, post-hoc analyses then compared the effects of Stimulation and Session within each Load (i.e. does performance change across sessions in response to CVS, within each n-back Load). This decision was made on the basis of previous research which has employed various oddball paradigms (Duncan et al., 2005) and shown that the widespread cortical and subcortical damage induced by TBI leads to memory and attention deficits, resulting in a systematically reduced P300 amplitude that takes longer to peak. Therefore, the present analyses examined amplitude/ latency changes (and behavioural responses) within each n-back Load to determine whether the aforementioned abnormities (if present) could be remediated with CVS. The interaction was not broken down by Stimulation x Load (within each Session) given that previous research has often failed to show an interaction between groups (patient versus control) and working memory load (Ozen et al., 2013; Dymowski et al., 2015). Thus the study focused on examining the overall P300 (and behavioural responses) to CVS irrespective of Load. If a three-way interaction was absent, two-way interactions involving the Stimulation variable were examined and post-hoc tests completed. Bonferroni corrections were again adopted for all post-hoc tests.

The analysis design described above was applied to both the ERP and behavioural data. However, based on the results of previous n-back studies which have demonstrated electrophysiological abnormalities in TBI without any behavioural effects and given the word length constraint of the thesis, the results section focusses on the ERP responses (amplitude and latency). Short summaries of the most important behavioural effects are provided below to characterise any P300 effects, while the full reports of any CVS-related behavioural effects can be found in Appendix C.

Figure 4.4b illustrates the hypothesised pattern of results for the positively (top: accuracy and P300 amplitude) and negatively (bottom: RT and P300 latency) indicated

outcome measures. Based on previous research which has demonstrated impaired attention and memory functioning after TBI (Ozen et al., 2013; Perlstein et al., 2004), a main effect of Stimulation was predicted whereby the two pre-CVS recordings differed from the active CVS recordings (overall across all regions and sessions). The main effect was expected to reveal an overall increase in P300 amplitudes/ accuracy and a decrease in P300 latencies/ RTs during the active CVS phase of the protocol (in line with a normalisation effect), relative to the pre-CVS recordings. Stimulation and Session interactions were also expected to reveal significant differences between the Stimulation conditions at both Session one (baseline *versus* four weeks CVS) and Session two (baseline two/ sham *versus* eight weeks CVS) within each Load. Importantly, P300 amplitudes/ accuracy and latencies/ RTS were not expected to differ between the two pre-CVS recordings (baseline, baseline two/ sham), however a cumulative effect of CVS should result in an increase in P300 amplitudes/ accuracy and a decrease in P300 latencies/ RTs between the two active CVS recordings at each Load.

Some variability in responsiveness was predicted across all the electrophysiological measures given the heterogeneous nature of TBI. The statistical analyses described above resulted in 24 ANOVAs for the EEG power data (eight participants x three bands) and 28 ANOVAs for the ERP data (seven participants x four dependent variables). Thus in the interest of brevity, only those analyses where the underlying effects were driven by Stimulation (either via a main effect or interaction) are described. For those analyses where the electrophysiological changes were not driven by Stimulation and hence do not relate to the key question of interest (does CVS modulate electrophysiological activity?), the underlying effects are summarised. All post-hoc tests were Bonferroni corrected to account for multiple comparisons and to try to reduce the occurance of false positives. A corrective

epsilon was not applied to the degrees of freedom since all ANOVA effects remained robust without this.

Results

Participant 01

EEG power.

Table 4.2
Statistical Analysis of EEG power (μV²) in Participant 01.

	ANOVA			
Frequency Band	***df***	***F***	***p* value**	η_p^2
Delta				
Stimulation	1, 117	104.42	<.001***	.47
Session	1, 117	3.92	.05	.03
Region	2, 234	9.23	<.001***	.07
Stimulation*Session	1,117	1.31	.26	.01
Stimulation*Region	2, 234	19.68	<.001***	.14
Session*Region	2, 234	39.62	<.001***	.25
Stimulation*Session*Region	2, 234	22.60	<.001***	.16
Theta				
Stimulation	1, 117	109.25	<.001***	.48
Session	1, 117	1.78	.19	.02
Region	2, 234	117.43	<.001***	.50
Stimulation*Session	1, 117	45.09	<.001***	.28
Stimulation*Region	2, 234	5.99	.003**	.05
Session*Region	2, 234	11.55	<.001***	.09
Stimulation*Session*Region	2, 234	30.74	<.001***	.21
Alpha				
Stimulation	1, 117	0.88	.35	.01
Session	1, 117	9.62	.002**	.08
Region	2, 234	90.00	<.001***	.44
Stimulation*Session	1, 117	58.68	<.001***	.33
Stimulation*Region	2, 234	2.44	.09	.02
Session*Region	2, 234	15.37	<.001***	.12
Stimulation*Session*Region	2, 234	43.99	<.001***	.27

Note. Significant at *0.05, **0.01, ***0.001

Delta (1- 4Hz). A main effect of Stimulation emerged at the delta band. Contrary to the hypothesis, activity was significantly increased during active CVS relative to the pre-CVS recordings (see Table 4.2). A main effect of Region was also present, such that delta activity was highest over the central electrodes and reduced over the parietal electrodes. Since a

significant Stimulation x Session x Region interaction was also present (see Table 4.2), planned comparisons were next completed to investigate Stimulation x Session relationships within each Region.

Only the frontal electrodes showed a significant Stimulation x Session interaction [$F(1, 117)= 10.42$, $p<.05$, $\eta_p^2 = .08$] (all other ps>.44). Comparisons between the Stimulation conditions (within each Session) revealed an unexpected increase in frontal delta activity between the first baseline ($M = 5.11\mu V^2$) and the recording taken after four weeks CVS ($M = 8.68\mu V^2$) [$t(117)= -7.93$ $p<.001$], as well as between the second baseline ($M= 6.32\ \mu V^2$) and the recording taken after eight weeks CVS ($M= 7.64\ \mu V^2$) [$t(117)= -2.80$, $p<.05$], although to a lesser extent (see Figure 4.5). Post-hoc tests of Session showed that frontal delta had already begun to increase between the first ($M= 5.11\mu V^2$) and second ($M= 6.32\mu V^2$) baselines, $t(117)= -3.40$ $p<.001$. Delta activity then remained stable between the two stimulation recordings ($p=.08$). In summary, frontal delta activity was increased during active CVS relative to the baseline recordings which contrasted with the hypothesis.

Theta (4- 8Hz). Analyses showed a significant main effect of Stimulation on theta wave activity. Contrary to the hypothesis, activity was significantly increased during active CVS relative to the pre-CVS recordings. A main effect of Region also emerged, which reflected an increase in theta activity over the frontal electrodes, and a reduction over the parietal electrodes. A significant Stimulation x Session x Region interaction was also present (see Table 4.2) and was followed up with separate two-way ANOVAs for each Region.

The Stimulation x Session interaction was significant over frontal [$F(1, 117)= 57.99$, $p<.001$, $\eta_p^2= .33$], central [$F(1, 117)$ 38.98, $p<.001$, $\eta_p^2 = .25$] and parietal electrodes [$F(1,117)= 18.47$, $p<.001$, $\eta_p^2 = .14$], reflecting the same underlying patterns. Comparisons first examined whether any differences between the Stimulation conditions were present in

each Session. Contrary to the hypothesis, theta activity was increased between the first baseline (frontal M= 5.99μV²; central M= 5.48μV²; parietal M= 5.16μV²) and after four weeks CVS (frontal M=12.47μV²; central M= 11.69μV²; parietal M= 9.45μV²) across all regions (frontal $t(117)$= -11.30 p<.001; central $t(117)$= -11.41, p<.001; parietal $t(117)$= -8.89, p<.001). Theta activity was also increased between the second baseline (central M = 9.01μV²; parietal M= 6.66μV²) and after eight weeks CVS (central M= 10.40μV²; parietal M= 8.31μV²) over the central [$t(117)$= -2.66, p<.001] and parietal electrodes [$t(117)$= -4.21, p<.001] (frontal p=.72). Post-hoc tests of Session showed that theta activity was unexpectedly increased from the first (frontal M= 5.99μV²; central M= 5.48μV²; parietal M= 5.16μV²) to the second baseline (frontal M= 9.33μV²; central M= 9.01μV²; parietal M= 6.66μV²) across all regions (frontal $t(117)$ =-7.24 p<.001; central $t(117)$= -8.62, p<.001; parietal $t(117)$= -4.60, p<.001). Theta activity was then decreased between the recordings taken after four (frontal M=12.47μV²; central M = 11.69μV²; parietal M= 9.45μV²) and eight weeks CVS (frontal M= 9.13μV²; central M = 10.40μV²; parietal M= 8.31μV²) (frontal $t(117)$= 4.90 p<.001; central $t(117)$= 2.02, p<.05; parietal $t(117)$= 2.19, p<.05). Contrary to the hypothesis, theta activity was largely increased during active CVS and was greatest after four weeks of stimulation (see Figure 4.5).

Alpha (8- 12Hz). ANOVA testing showed that alpha activity fluctuated over the course of the study. However, since these changes were not driven by the Stimulation variable (see Figure 4.5) the analyses will not be described further.

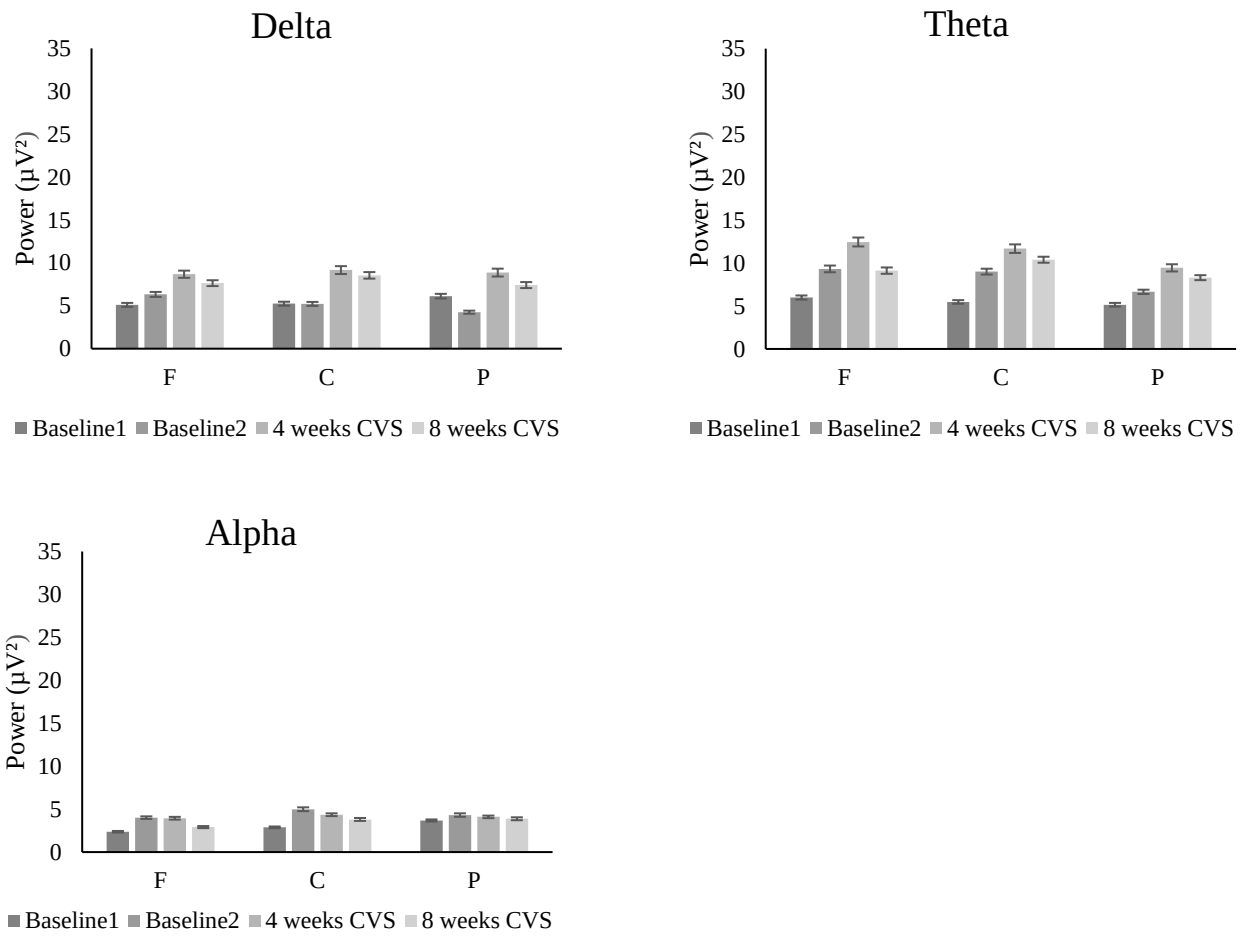


Figure 4.5. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 01.

ERP.

Behavioural data summary. In line with the hypothesis, a Stimulation x Load interaction revealed that accuracy on the higher n-back loads was improved after active CVS. Response times showed a main effect of Load only, such that RTs were shorter during the lower n-back loads.

Peak amplitude. Contrary to the hypothesis, P300 peak amplitudes were unaffected by main effects of Stimulation or Load (see Table 4.3 and Figure 4.6). Since a three-way interaction was also absent, post-hoc analyses interrogated significant two-way interactions involving the Stimulation variable.

A significant Stimulation x Load interaction was present and comparisons first examined whether any significant amplitude differences were present between the Stimulation conditions. P300 peak amplitudes were significantly increased during the active CVS recordings (M= 16.23μV) relative to the pre-CVS recordings (M= 13.66μV) under the 0-back, $t(195)= -2.47$, $p<.05$. No other differences were present between the Stimulation conditions (all ps>.19). Effects of Load were then examined within each Stimulation condition. Participants did not show any effects of Load during the pre-CVS recordings (all ps>.05). However during the stimulation recordings, P300 peak amplitudes were decreased during the 2 (M= 13.26μV) [$t(191)= 2.83$, $p<.05$] and 3-back (M= 13.37μV) [$t(174)= 2.73$, $p<.05$] loads, relative to the 0-back condition (M= 16.23μV) (see Figure 4.6). These effects suggest that CVS may have normalised the ERP response such that P300 amplitudes were reduced for higher n-back loads (relative to lower n-back loads) as observed within healthy samples.

A significant Stimulation x Session interaction was also observed. Post-hoc testing revealed that P300 peak amplitudes varied across the study, however since these changes were not driven by Stimulation-related effects the interaction will not be described further. No other significant main effects or interactions were present (all ps>.11).

Peak latency. ANOVA testing revealed that P300 latencies were unaffected by the Stimulation variable over the course of the study (see Table 4.3). A significant main effect of Load was present, such that latencies were unexpectedly shorter for the 2 (M= 371ms) [$t(357)= 2.82$, $p<.05$] and 3-back (M= 370ms) [$t(331)= 3.17$, $p<.05$] conditions, relative to the 1-back load (M= 402ms). No other significant main effects or interactions were present (all ps>.13).

Table 4.3
Statistical Analysis of the P300 Component in Participant 01.

		ANOVA		
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Stimulation	1, 685	0.05	.82	<.01
Session	1, 685	0.72	.40	<.01
Load	3, 685	1.30	.27	<.01
Stimulation*Session	1, 685	13.45	<.001***	.02
Stimulation*Load	3, 685	3.04	.03*	.01
Session*Load	3, 685	1.32	.27	<.01
Stimulation *Session*Load	3, 685	2.00	.11	<.01
P300 peak latency (ms)				
Stimulation	1, 685	1.80	.18	<.01
Session	1, 685	0.04	.85	<.01
Load	3, 685	4.27	.01**	.02
Stimulation*Session	1, 685	1.89	.17	<.01
Stimulation*Load	3, 685	1.90	.13	<.01
Session*Load	3, 685	1.03	.38	<.01
Stimulation *Session*Load	3, 685	1.20	.31	<.01

Note. Significant at *0.05, **0.01, *0.001.

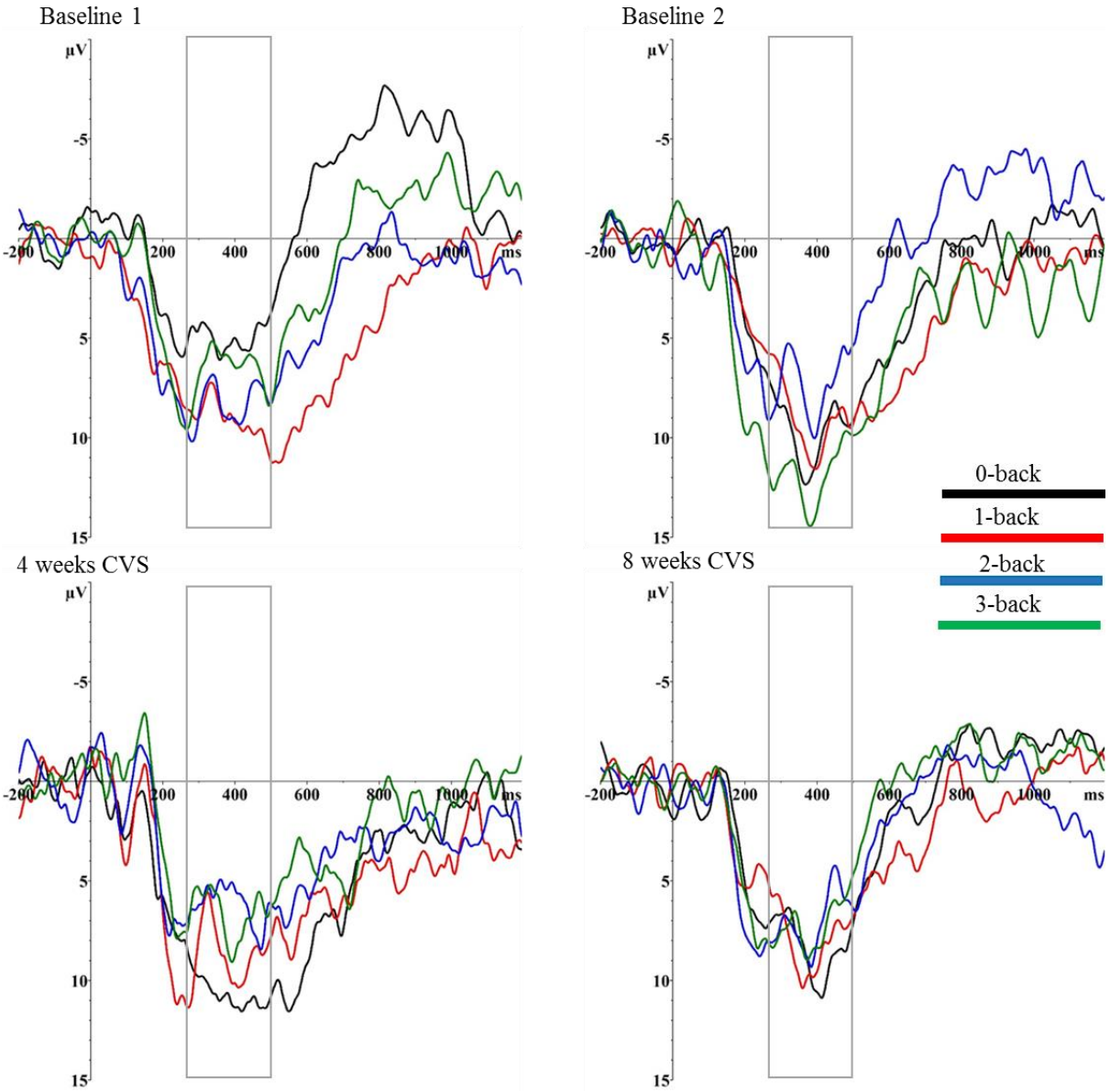


Figure 4.6. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the four EEG recordings, at the Pz electrode in participant 01.

Participant 02

EEG power.

Delta (1- 4Hz). Although several comparisons in this analysis reached significance (see Table 4.4), together these showed that frontal and parietal delta activity were highest at baseline and began to decline thereafter, rather than in response to CVS (see Figure 4.7), thus this band will not be described further.

Table 4.4
Statistical Analysis of EEG Power (μV²) in Participant 02.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_p^2
Delta				
Stimulation	1, 103	10.75	.001***	.09
Session	1, 103	7.51	.007*	.07
Region	2, 206	54.24	<.001***	.35
Stimulation*Session	1, 103	2.89	.09	.03
Stimulation*Region	2, 206	3.28	.04*	.03
Session*Region	2, 206	11.64	<.001***	.10
Stimulation *Session*Region	2, 206	5.18	.006*	.05
Theta				
Stimulation	1, 103	80.61	<.001***	.44
Session	1, 103	140.10	<.001***	.58
Region	2, 206	55.56	<.001***	.35
Stimulation*Session	1, 103	53.57	<.001***	.34
Stimulation*Region	2, 206	8.67	<.001***	.08
Session*Region	2, 206	9.16	<.001***	.08
Stimulation *Session*Region	2, 206	29.25	<.001***	.22
Alpha				
Stimulation	1, 103	19.03	<.001***	.16
Session	1, 103	0.21	.89	<.01
Region	2, 206	62.81	<.001***	.38
Stimulation*Session	1, 103	34.24	<.001***	.25
Stimulation*Region	2, 206	1.30	.28	.01
Session*Region	2, 206	32.63	<.001***	.24
Stimulation *Session*Region	2, 206	1.62	.20	.02

Note. Significant at *0.05, **0.01, *0.001.

Theta (4- 8Hz). A main effect of Stimulation also emerged at the theta band. In line with the hypothesis, activity was decreased during active CVS compared to the pre-CVS recordings. A main effect of Region was also present such that, activity was highest centrally, and lowest at the parietal site (see Figure 4.7). Since a significant Stimulation x Session x Region interaction was present (see Table 4.4), post-hoc tests were next completed to follow-up these associations.

A significant Stimulation x Session interaction was revealed over the frontal [$F(1, 103)= 66.66$, $p<.001$, $\eta_p^2= .39$], central [$F(1, 103)$ 56.34, $p<.001$, $\eta_p^2=.35$] and parietal regions

[$F(1, 103)= 17.76$, $p<.001$, $\eta_p^2= .15$], reflecting the same underlying patterns. Comparisons between the Stimulation conditions revealed that theta wave activity had decreased as predicted between the baseline (frontal $M= 5.51\mu V^2$; central $M= 5.59\mu V^2$; parietal $M= 4.41\mu V^2$) and after four weeks CVS (frontal $M= 3.08\mu V^2$; central $M = 3.17\mu V^2$; parietal $M= 2.97\mu V^2$) (frontal $t(103)= 9.59$, $p<.001$; central $t(103)= 9.91$, $p<.001$; parietal $t(103)= 7.21$, $p<.001$). Theta activity remained stable between the recordings taken after sham stimulation and eight weeks CVS over the frontal and central electrodes (all ps>.18), but was decreased between the sham recording ($M= 2.62\mu V^2$) and after eight weeks CVS ($M= 2.23\mu V^2$) over the parietal electrodes [$t(103)= 2.96$, $p<.05$]. Contrary to the predictions, post-hoc tests between Sessions showed that theta activity had already begun to decrease between the baseline (frontal $M= 5.51\mu V^2$; central $M= 5.59\mu V^2$; parietal $M= 4.41\mu V^2$) and sham recordings (frontal $M= 2.67\mu V^2$; central $M= 2.90\mu V^2$; parietal $M= 2.62\mu V^2$) (frontal $t(103)= 11.31$, $p<.001$; central $t(103)= 10.92$, $p<.001$; parietal $t(103)= 9.64$, $p<.001$) (see Figure 4.7). Theta activity was also reduced between recordings taken after four (frontal $M= 3.08\mu V^2$; central $M= 3.17\mu V^2$; parietal $M= 2.97\mu V^2$) and eight weeks CVS (frontal $M= 2.59\mu V^2$; central $M= 2.66\mu V^2$; parietal $M= 2.23\mu V^2$) where it was lowest (frontal $t(103)= 3.11$, $p<.05$; central $t(103)= 3.15$, $p<.05$; parietal $t(103)= 4.94$, $p<.001$). In sum, theta activity was highest at baseline and began to decline thereafter, with the lowest level of activity occurring after eight weeks CVS. Theta activity at the parietal site was significantly reduced during active CVS relative to the pre-CVS recordings across both sessions indicating a Stimulation-related reduction may have occurred over at least some electrodes.

Alpha (8- 12Hz). Similar to the delta band, although several comparisons reached significance (see Table 4.4), Stimulation did not appear to modulate these effects. Instead, comparisons appeared to show that alpha activity was highest at the baseline and was not surpassed during CVS (see Figure 4.7), thus this band will not be described further.

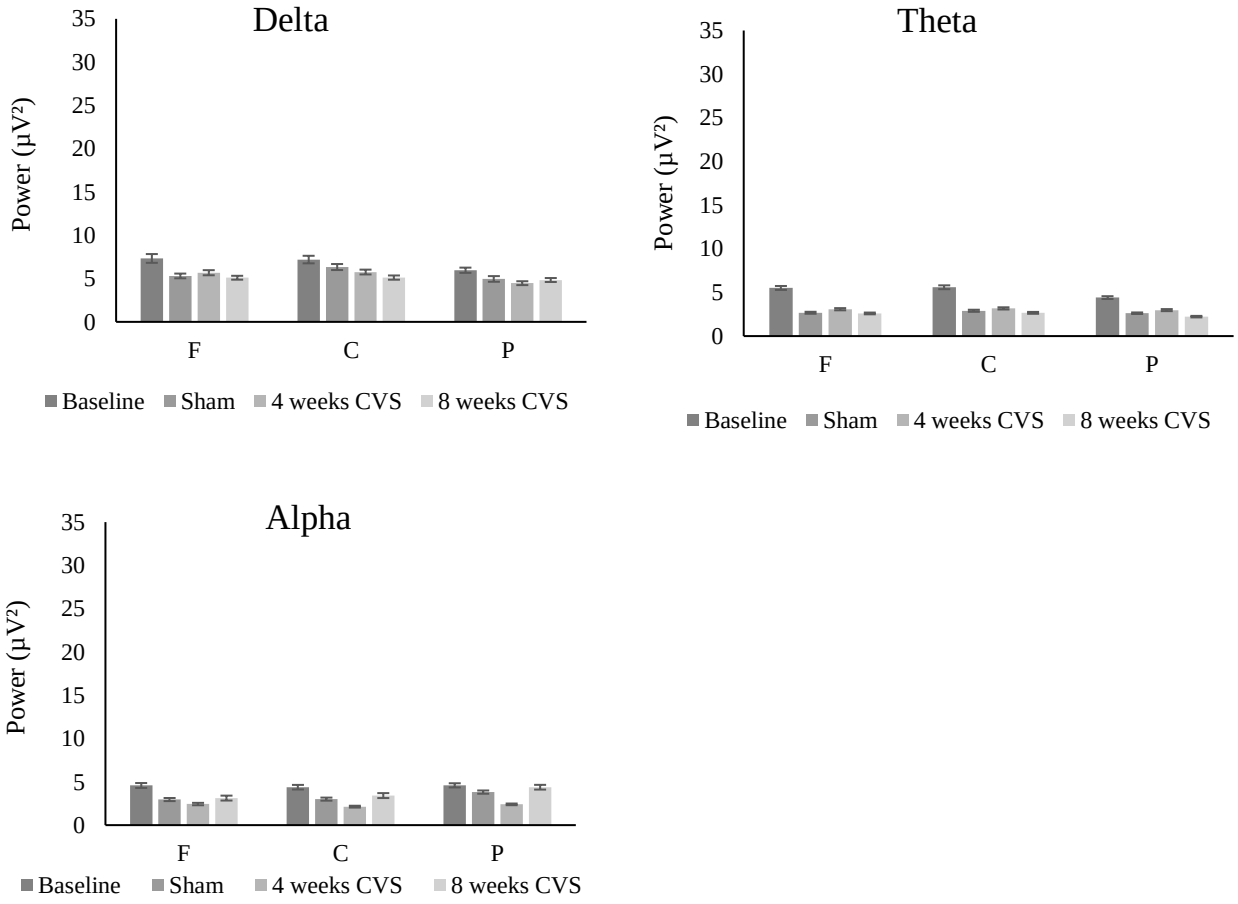


Figure 4.7. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 02.

ERP.

Behavioural data summary. Data logging for the 0-back Load was disrupted during the sham recording due to a technical fault with the keyboard which meant that the participant's behavioural responses were not registered. Therefore, statistical analyses for the behavioural data were conducted using a 2 (Stimulation) x 2 (Session) x 3 (1, 2 and 3-back Load) ANOVA to examine the remaining Loads, and a separate one-way ANOVA for

responses to the 0-back Load across the remaining three sessions (baseline, four weeks CVS, eight weeks CVS).

Accuracy responses entered into the 2 x 2 x 3 ANOVA revealed a Stimulation x Load interaction whereby accuracy was lower for the higher n-back Load levels, irrespective of whether active CVS was being delivered. Response times were also influenced by a Stimulation x Load interaction such that RTs were shorter during the active CVS recordings for the 3-back Load. Neither the accuracy nor the RT analyses upon the 0-back Load appeared to be affected by CVS.

After interrogating the behavioural responses from participant 02 it was concluded that it would be justified to analyse the ERP data for the 0-back from the sham recording by assuming that all trials were answered correctly. This is because the 0-back Load was performed with consistently high levels of accuracy across the other sessions (M = 0.98). The electrophysiological data was therefore analysed using the 2 (Stimulation) x 2 (Session) x 4 (Load) ANOVA described previously.

Peak amplitude. In line with the hypothesis, P300 amplitudes showed a significant main effect of Stimulation such that participant 02 had significantly higher peak amplitudes during the active CVS recordings (M= 4.52µV), relative to the pre-CVS recordings (M= 3.38µV) (see Table 4.5 and Figure 4.8). A main effect of Load was also present, which reflected a decline in P300 peak amplitudes between the 0 (M= 4.65µV) and 2-back (M= 2.81µV) loads, $t(283)= 3.44$, $p<.001$. No other comparisons reached significance (all ps>.05).

Table 4.5
Statistical Analysis of the P300 Component in Participant 02.

		ANOVA		
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Stimulation	1, 510	8.39	.004**	.02
Session	1, 510	33.72	<.001***	.06
Load	3, 510	3.02	.03*	.02
Stimulation*Session	1, 510	2.81	.09	<.01
Stimulation*Load	3, 510	2.38	.07	.01
Session*Load	3, 510	0.83	.48	<.01
Stimulation *Session*Load	3, 510	0.12	.95	<.01
P300 peak latency (ms)				
Stimulation	1, 510	6.11	.01**	.01
Session	1, 510	3.64	.06	<.01
Load	3, 510	2.16	.09	.01
Stimulation*Session	1, 510	5.10	.02*	.01
Stimulation*Load	3, 510	0.16	.92	<.01
Session*Load	3, 510	0.97	.41	<.01
Stimulation *Session*Load	3, 510	0.08	.97	<.01

Note. Significant at *0.05, **0.01, ***0.001.

Peak latency. Contrary to the hypothesis, a significant main effect of Stimulation revealed that the P300 took longer to peak during the active CVS recordings, relative to the pre-CVS recordings. The main effect of Load and the three-way interaction were absent from the latency data. However, a significant Stimulation x Session interaction was observed (see Table 4.5).

Comparisons completed to interrogate this interaction first examined differences between the Stimulation conditions within each Session. P300 latencies remained stable between the baseline and the recording taken after four weeks CVS (p=.87) and were unexpectedly increased between the recordings taken after sham stimulation (M= 380ms) and eight weeks CVS (M= 423ms), $t(249)$= -3.81, p<.05. Post-hoc tests also examined whether any Session effects were present within each Stimulation condition. P300 latencies remained stable between the baseline and sham recordings as predicted (p=.81), and were then

unexpectedly increased between the recordings after four (*M*= 386ms) and eight of CVS (*M*= 423ms), *t*(259)= -3.16, *p*<.05. Contrary to the hypothesis, these effects suggest that P300 latencies took longer to peak after eight weeks. No other significant interactions were present (all *p*s>.06).

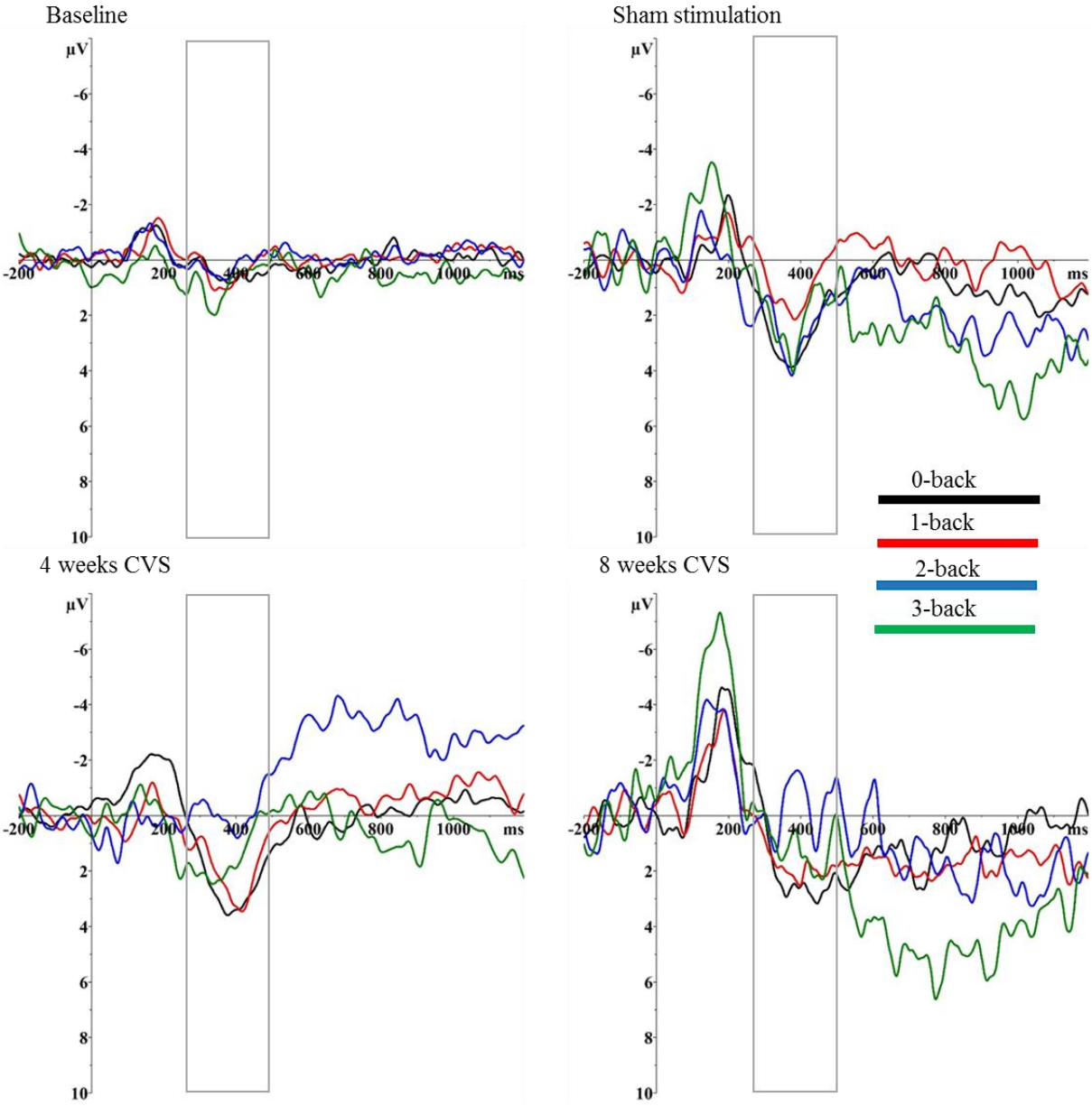


Figure 4.8. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the four EEG recordings, at the Pz electrode in participant 02.

Participant 03

EEG power.

Table 4.6
Statistical Analysis of EEG Power (μV²) in Participant 03.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_{p^2}
Delta				
Stimulation	1, 119	38.66	<.001***	.25
Session	1, 119	7.12	<.001***	.06
Region	2, 238	47.61	<.001***	.29
Stimulation*Session	1, 119	25.49	<.001***	.18
Stimulation*Region	2, 238	14.96	<.001***	.11
Session*Region	2, 238	17.75	<.001***	.13
Stimulation*Session*Region	2, 238	1.57	.21	.01
Theta				
Stimulation	1, 119	0.12	.73	<.01
Session	1, 119	27.69	<.001***	.19
Region	2, 238	11.17	<.001***	.09
Stimulation*Session	1, 119	105.00	<.001***	.47
Stimulation*Region	2, 238	3.09	.05	.03
Session*Region	2, 238	2.15	.12	.02
Stimulation*Session*Region	2, 238	8.19	<.001***	.06
Alpha				
Stimulation	1, 119	37.98	<.001***	.24
Session	1, 119	0.92	.34	.01
Region	2, 238	31.00	<.001***	.72
Stimulation*Session	1, 119	75.5	<.001***	.39
Stimulation*Region	2, 238	19.26	<.001***	.14
Session*Region	2, 238	1.64	.18	.01
Stimulation*Session*Region	2, 238	39.30	<.001***	.25

Note. Significant at *0.05, **0.01, ***<0.001.

Delta (1- 4Hz). A significant main effect of Stimulation emerged at the delta band. In line with the hypothesis, delta activity was greater during the pre-CVS recordings. A significant main effect of Region was also revealed, which reflected decreased delta wave activity over the parietal region. Since a three-way interaction was absent (see Table 4.6), significant two-way interactions involving the Stimulation variable were next interrogated.

A significant Stimulation x Session interaction was revealed. However, comparisons showed that the interaction was being driven by the elevated levels of delta activity during the baseline relative to the other recordings (see Figure 4.9) rather than in response to Stimulation and thus this effect will not be described further.

A Stimulation x Region interaction also emerged at the delta band. Comparisons first examined whether activity differed between the Stimulation conditions (within each Region). As predicted, delta wave activity was consistently lower during the active CVS recordings, relative to the pre-CVS recordings (all *p*s<.001). The effect was greatest at the central region (pre-CVS *M*= 9.05μV²; active CVS *M*= 6.51μV²), *t*(119)= 7.46, *p*<.001. Post-hoc tests also compared delta activity across the three regions (within each Stimulation condition), all comparisons were significant (all *p*s<.01). During the pre-CVS recordings the largest discrepancy occurred between the central (*M*= 9.05μV²) and parietal electrodes (*M*= 7.37μV²), *t*(119)= 11.58, *p*<.001. Whereas during active CVS the effect was greatest between the frontal (*M*= 7.17μV²) and parietal electrodes (*M*= 5.88μV²), *t*(119)= 6.04, *p*<.001. Taken together, these interactions suggest that although delta activity was reduced during active CVS (across all regions), this decline may have begun during sham stimulation.

Theta (4- 8Hz). ANOVA testing showed that changes in theta activity were driven by a decline in power between the pre-CVS recordings rather than a CVS-related effect, thus this band will not be described further (see Figure 4.9).

Alpha (8- 12Hz). ANOVA testing showed a significant main effect of Stimulation whereby alpha wave activity was increased during active CVS as predicted. In line with the normative topography, a main effect of Region also revealed that alpha activity was greatest over the parietal electrodes. A significant Stimulation x Region x Session interaction was also

present (see Table 4.6) and post-hoc tests were next completed to interrogate Stimulation x Session effects within each Region.

A significant Stimulation x Session interaction emerged over the frontal site, $F(1, 119)= 56.15$, $p<.001$, $\eta_{p^2}=.32$. However, comparisons revealed that the interaction was driven by the reduction in frontal alpha activity during the sham recording rather than in response to CVS and thus the effect will not be described further (see Figure 4.9).

Stimulation x Session interactions were also present over the central ($F(1, 119)= 87.29$, $p<.001$, $\eta_{p^2}= .42$) and parietal electrodes ($F(1, 119)= 55.85$, $p<.001$, $\eta_{p^2}= .32$) which appeared to reflect the same underlying trend. Pairwise comparisons examining the effects of Stimulation failed to reveal any differences in alpha activity between the recordings taken at baseline and after four weeks of CVS (all *p*s>.06). In line with the hypothesis, activity was increased between the sham recording (central $M= 4.40\mu V^2$; parietal $M= 10.53\mu V^2$) and after eight weeks of CVS (central $M= 12.53\mu V^2$; parietal $M= 29.69\mu V^2$) (central $t(119)= -11.59$, $p<.001$; parietal $t(119)= -8.47$, $p<.001$). Comparisons between the recording sessions revealed that alpha activity was unexpectedly reduced between the baseline (central $M= 8.98\mu V^2$; parietal $M=21.83\mu V^2$) and sham recordings (central $M= 4.40\mu V^2$; parietal $M= 10.53\mu V^2$) across both regions (central $t(119)=10.45$ $p<.001$; parietal $t(119)= 6.14$, $p<.001$), and then accumulated as predicted between the recordings taken after four (central $M= 8.81\mu V^2$; parietal $M= 17.97\mu V^2$,) and eight (central $M= 12.53\mu V^2$; parietal $M= 29.69\mu V^2$) weeks of CVS (central $t(119)= -4.45$, $p<.001$; parietal $t(119)= -4.88$, $p<.001$). Importantly, central and parietal alpha activity was highest once eight weeks of CVS had been delivered (see Figure 4.9), suggesting alpha power had increased in response to CVS over most sites.

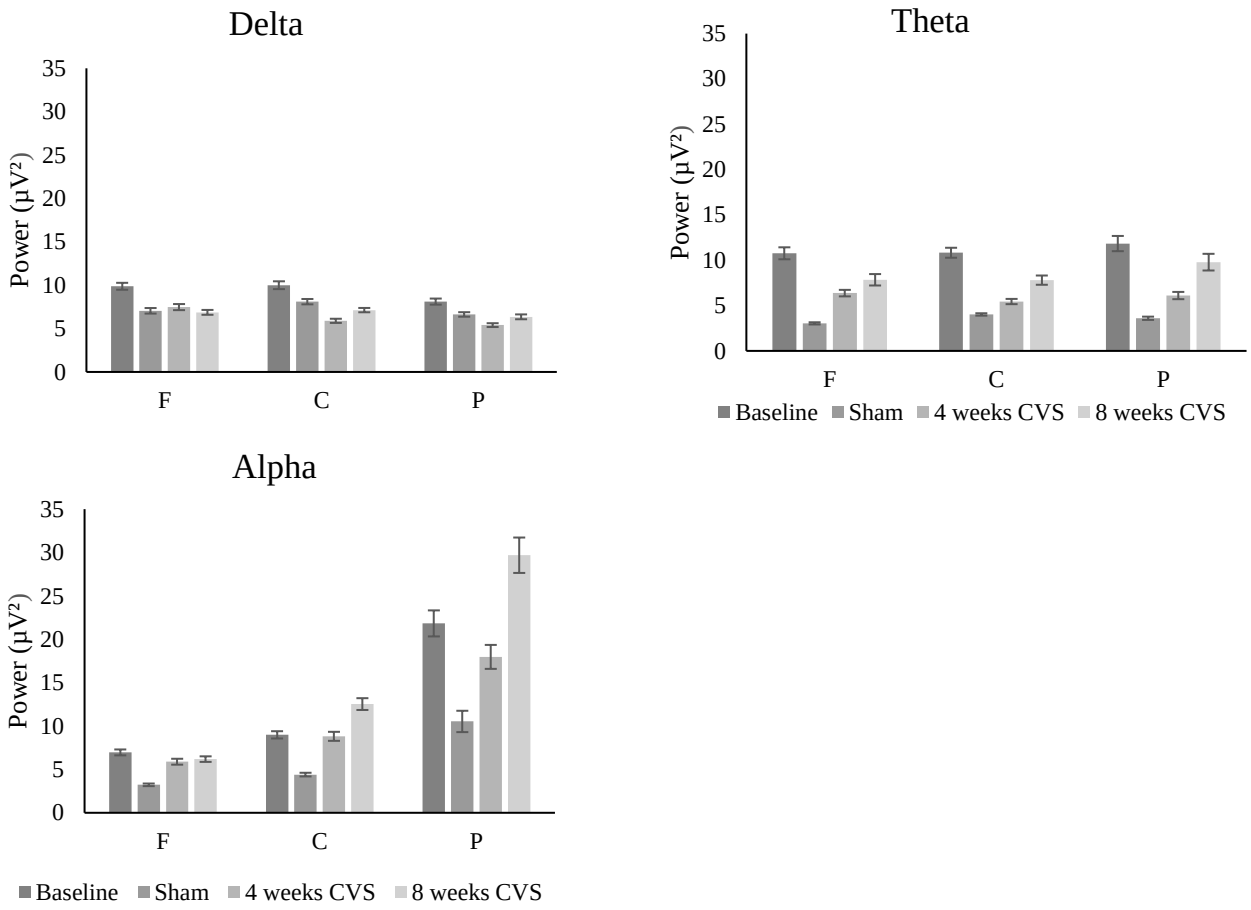


Figure 4.9. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 03.

ERP.

Behavioural data summary. Within the RT data, significant main effects revealed that responses were shorter during the active CVS recordings relative to the pre-CVS recordings and also during the lower n-back loads as predicted. However, a Stimulation x Load interaction showed that RTs were not consistently decreased during CVS, such that RTs were longer during active CVS at the 2-back Load relative to the pre-CVS recordings. This variability on the 2-back therefore reduces the likelihood that CVS has induced a beneficial effect on RTs.

Accuracy responses also revealed a Stimulation x Load interaction, whereby performance on the 3-back Load was less accurate relative to the other loads (across both

Stimulation conditions) and did not improve in response to CVS indicating the participant found this Load more challenging.

Peak amplitude. ANOVA testing showed that although peak P300 amplitudes were increased during active CVS (see Table 4.7) this was because of a decline in peak amplitude during the sham recording relative to the other sessions (Stimulation x Session interaction). Since CVS did not modulate peak amplitudes (see Figure 4.10), this analysis will not be described further.

Peak latency. Contrary to the hypothesis, a main effect of Stimulation was absent from this analysis (see Table 4.7). However, a main effect of Load was present, such that P300 latencies unexpectedly became shorter as n-back Load increased. Since a significant three-way interaction was observed (see Table 4.7), post-hoc analyses were completed to follow-up Stimulation x Session interactions within each n-back Load.

The Stimulation x Session interaction was only present for the 0-back Load, $F(1, 196)= 11.27$, $p<.05$, $\eta_{p^2}= .05$ (all other ps>.14). Comparisons first examined Stimulation effects within each Session. In line with the hypothesis, analyses showed that the P300 was quicker to peak after four weeks CVS (M= 384ms), relative to the baseline (M= 448ms), $t(98)= 4.03$, $p<.001$. Conversely, P300 latencies remained stable between the sham recording and after eight weeks CVS (p=.32). Post-hoc tests between Sessions revealed that P300 latencies had remained stable between the baseline and sham recordings as predicted (p=.95). Latencies for the 0-back then fluctuated between the active CVS recordings and were unexpectedly increased between the recordings taken after four (M= 384ms) and eight weeks CVS (M= 464ms) [$t(98)= -4.84$, $p<.001$], contrasting with the accumulative effect that was predicted. Taken together, these effects suggest a temporary CVS-related facilitation whereby the P300 was quicker to peak after four weeks at the 0-back. However, since this effect was

not sustained after eight weeks CVS and did not extend to the other loads the robustness of the effect is unclear. No other significant effects were present (all *p*s >.37).

Table 4.7
Statistical Analysis of the P300 Component in Participant 03.

	ANOVA			
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Stimulation	1, 653	9.94	.002**	.02
Session	1, 653	15.86	<.001***	.02
Load	3, 653	2.19	.09	.01
Stimulation*Session	1, 653	24.60	<.001***	.04
Stimulation*Load	3, 653	2.08	.10	.01
Session*Load	3, 653	2.00	.11	.01
Stimulation *Session*Load	3, 653	0.58	.63	<.01
P300 peak latency (ms)				
Stimulation	1, 653	<0.01	.96	<.01
Session	1, 653	13.38	<.001***	.02
Load	3, 653	8.07	<.001***	.04
Stimulation*Session	1, 653	0.80	.37	<.01
Stimulation*Load	3, 653	4.32	.005**	.02
Session*Load	3, 653	0.46	.71	<.01
Stimulation *Session*Load	3, 653	3.74	.01**	.02

Note. Significant at *0.05, **0.01, ***0.001.

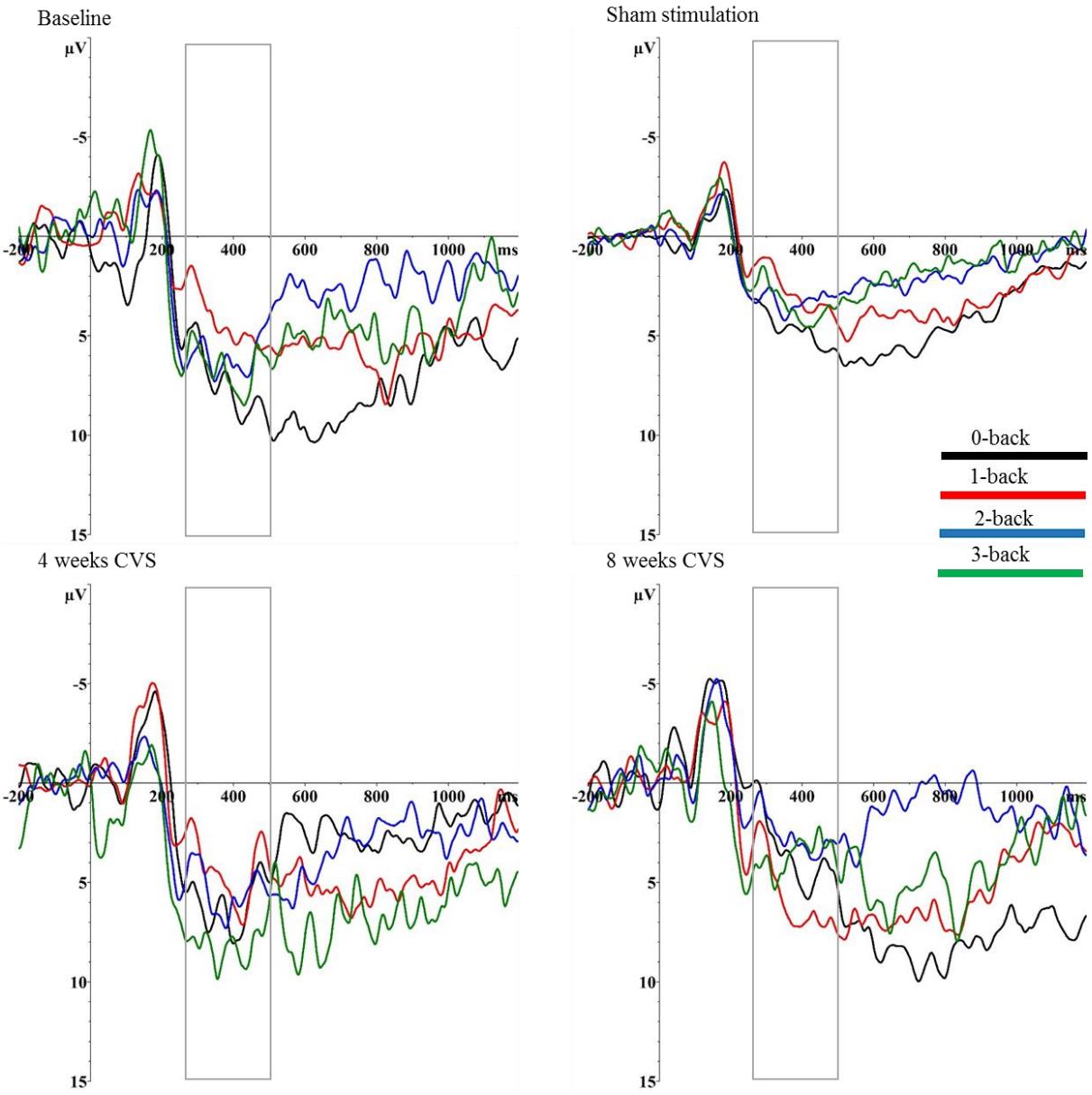


Figure 4.10. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the four EEG recordings, at the Pz electrode in participant 03.

Participant 04

The protocol was amended for participant 04 such that only resting EEG was completed. This was necessary to accommodate for the participant's information processing (stimuli moved quickly on the screen) and mobility (restricted movement of fingers) impairments.

EEG power.

Table 4.8
Statistical Analysis of EEG Power (μV²) in Participant 04.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_p^2
Delta				
Stimulation	1, 74	58.98	<.001***	.44
Session	1, 74	85.35	<.001***	.54
Region	2, 148	49.99	<.001***	.40
Stimulation*Session	1, 74	58.05	<.001***	.44
Stimulation*Region	2, 148	19.99	<.001***	.21
Session*Region	2, 148	34.59	<.001***	.32
Stimulation *Session*Region	2, 148	31.96	<.001***	.30
Theta				
Stimulation	1, 74	28.80	<.001***	.28
Session	1, 74	42.90	<.001***	.37
Region	2, 148	77.40	<.001***	.51
Stimulation*Session	1, 74	51.57	<.001***	.41
Stimulation*Region	2, 148	49.88	<.001***	.40
Session*Region	2, 148	23.91	<.001***	.24
Stimulation *Session*Region	2, 148	50.67	<.001***	.41
Alpha				
Stimulation	1, 74	12.00	.001***	.14
Session	1, 74	2.55	.12	.03
Region	2, 148	130.80	<.001***	.64
Stimulation*Session	1, 74	27.67	<.001***	.27
Stimulation*Region	2, 148	35.73	<.001***	.33
Session*Region	2, 148	15.91	<.001***	.18
Stimulation *Session*Region	2, 148	5.75	.004	.07

Note. Significant at *0.05, **0.01, ***0.001.

Delta (1- 4Hz). ANOVA testing revealed a significant main effect of Stimulation (see Table 4.8) whereby delta activity was unexpectedly increased during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present such that delta activity was elevated over the central electrodes, and lowest at the parietal electrodes. Since a significant Stimulation x Session x Region was present (see Table 4.8), post-hoc analyses were completed to follow-up the effects of Stimulation and Session within each Region.

Significant Stimulation x Session interactions were present over the frontal [$F(1, 74)= 26.11$, $p<.001$, $\eta_p^2= .26$], central [$F(1, 74)= 53.20$, $p<.001$, $\eta_p^2=.42$] and parietal regions [$F(1, 74)= 75.19$, $p<.001$, $\eta_p^2= .50$], reflecting the same underlying patterns. Comparisons first examined whether any differences between the Stimulation conditions were present in each Session. Contrary to the hypothesis, delta activity remained stable between the first baseline and after four weeks CVS (all *ps*>.19), and was increased between the second baseline (frontal $M= 11.86\mu V^2$; central $M= 12.20\mu V^2$; parietal $M= 9.80\mu V^2$) and after eight weeks CVS (frontal $M= 19.83\mu V^2$; central $M= 23.24\mu V^2$; parietal $M= 24.33\mu V^2$) across all regions (frontal $t(74)= -1.32$, $p<.001$; central $t(74)= -8.11$, $p<.001$; parietal $t(74)= -9.22$, $p<.001$). Post-hoc tests examining the effects of Session showed that delta activity remained stable across the two baselines over the frontal and central electrodes (all *ps*>.06), and was increased between the first ($M= 8.24\ \mu V^2$) and second baseline ($M= 9.80\mu V^2$) over the parietal electrodes [$t(74)=-2.17$, $p<.05$]. Unexpectedly, delta activity was significantly increased between the recordings taken after four weeks (frontal $M= 11.24\mu V^2$; central $M= 11.38\mu V^2$; parietal $M= 8.16\mu V^2$) and eight weeks CVS (frontal $M= 19.83\mu V^2$; central $M= 23.24\mu V^2$; parietal $M= 24.33\mu V^2$) across all regions (frontal $t(74)= -7.56$, $p<.001$; central $t(74)= -9.21$, $p<.001$; parietal $t(74)= -10.81$, $p<.001$). In sum delta activity was highest after eight weeks CVS across all regions therefore contrasting with the hypothesis (see Figure 4.11).

Theta (4- 8Hz). A significant main effect of Stimulation emerged at the theta band (see Table 4.8). Unexpectedly, theta activity was significantly increased during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present (see Table 4.8), such that theta activity was highest over the central electrodes and lowest over the parietal site. Since a significant three-way interaction was also revealed (see Table 4.8), post-

hoc analyses were completed to follow-up the effects of Stimulation and Session within each Region.

A significant Stimulation x Session interaction was present over the frontal [$F(1, 74)= 14.37$, $p<.001$, $\eta_p^2= .16$], central [$F(1, 74)= 63.48$, $p<.001$, $\eta_p^2= .46$] and parietal electrodes [$F(1, 74)= 68.02$, $p<.001$, $\eta_p^2= .48$], reflecting the same underlying patterns. Comparisons between the Stimulation conditions showed that theta activity was reduced from the first baseline ($M= 8.84\mu V^2$) to the recording after four weeks CVS ($M= 7.08\mu V^2$) over the central electrodes [$t(74)= 2.70$, $p<.05$] as anticipated, but remained stable over the frontal and parietal electrodes (all $ps> .10$). Theta activity was also significantly increased between the second baseline (frontal $M= 8.20\mu V^2$; central $M= 7.78\mu V^2$; parietal $M= 6.00\mu V^2$) and after eight weeks of CVS (frontal $M= 10.82\mu V^2$; central $M= 14.21\mu V^2$; parietal $M= 13.71\mu V^2$) across all regions (frontal $t(74)= -4.05$, $p<.001$; central $t(74)= -8.09$, $p<.001$; parietal $t(74)= -9.45$, $p<.001$). Comparisons between sessions (within each Stimulation condition) revealed that theta activity had remained stable between the first and second baselines (all $ps> .07$), and was then significantly increased between the recordings taken after four (frontal $M= 6.82\mu V^2$; central $M= 7.08\ \mu V^2$; parietal $M= 5.56\mu V^2$) and eight weeks of CVS (frontal $M= 10.82\mu V^2$; central $M= 14.21\mu V^2$; parietal $M= 13.71\mu V^2$) across all regions (frontal $t(74)= -5.39$, $p<.001$; central $t(74)= -7.60$, $p<.001$; parietal $t(74)= -9.49$, $p<.001$). Similar to the delta band, theta activity was highest after eight weeks CVS across all regions (see Figure 4.11), contrasting with the CVS-related decreases in theta activity that were hypothesised.

Alpha (8- 12Hz). A significant main effect of Stimulation (see Table 4.8) showed that alpha activity was increased during active CVS relative to the pre-CVS recordings, as predicted. A significant main effect of Region was also present, in line with the normative topography activity was elevated over the parietal site. Since a significant Stimulation x

Session x Region interaction was observed (see Table 4.8), post-hoc tests were next completed to follow-up the interaction.

ANOVA testing revealed similar Stimulation x Session interactions over the frontal [$F(1, 74)= 34.89$, $p<.001$ $\eta_p^2= .32$], central [$F(1, 74)= 24.77$, $p<.001$, $\eta_p^2= .25$] and parietal electrodes [$F(1, 74)= 22.02$, $p<.001$, $\eta_p^2= .23$]. Comparisons between the Stimulation conditions showed that alpha activity was unexpectedly decreased between the first baseline ($M= 9.05\mu V^2$) and after four weeks CVS ($M= 6.47\mu V^2$) over the frontal region [$t(74)= 4.0$, $p<.001$], but remained stable over the central and parietal electrodes (all $ps>.11$). Alpha activity was then increased as predicted between the second baseline (frontal $M= 6.32\mu V^2$; central $M= 7.62\mu V^2$; parietal $M= 10.72\ \mu V^2$) and after eight weeks CVS (frontal $M= 9.18\mu V^2$; central $M= 13.28\mu V^2$; parietal $M= 17.72\ \mu V^2$) across all regions (frontal $t(74)= -4.71$, $p<.001$; central $t(74)= -6.04$, $p<.001$; parietal $t(74)= -6.42$, $p<.001$). Post-hoc tests of Session showed that alpha activity was unexpectedly reduced between the first (frontal $M= 9.05\mu V^2$; central $M= 11.06\mu V^2$) and second baseline (frontal $M= 6.32\mu V^2$; central $M= 7.62\mu V^2$) over the frontal [$t(74)= 5.73$, $p<.001$] and central electrodes [$t(74)=4.81$, $p<.001$] (parietal $p=.06$). Similar to the delta and theta bands, alpha activity was subsequently increased between the recordings taken after four (frontal $M= 6.47\mu V^2$; central $M= 9.36\mu V^2$; parietal $M= 10.72\mu V^2$) and eight weeks of CVS (frontal $M= 9.18\mu V^2$; central $M= 13.28\mu V^2$; parietal $M= 17.72\ \mu V^2$) across all regions (frontal $t(74)= 3.87$, $p<.001$; central $t(74)= -3.30$, $p<.05$; parietal $t(74)= -6.42$, $p<.001$). In line with the hypothesis, alpha activity was highest after eight weeks CVS. While a clear elevation in alpha activity was present over the central and parietal sites after eight weeks CVS, the frontal electrodes reached a similar magnitude at baseline one (see Figure 4.11).

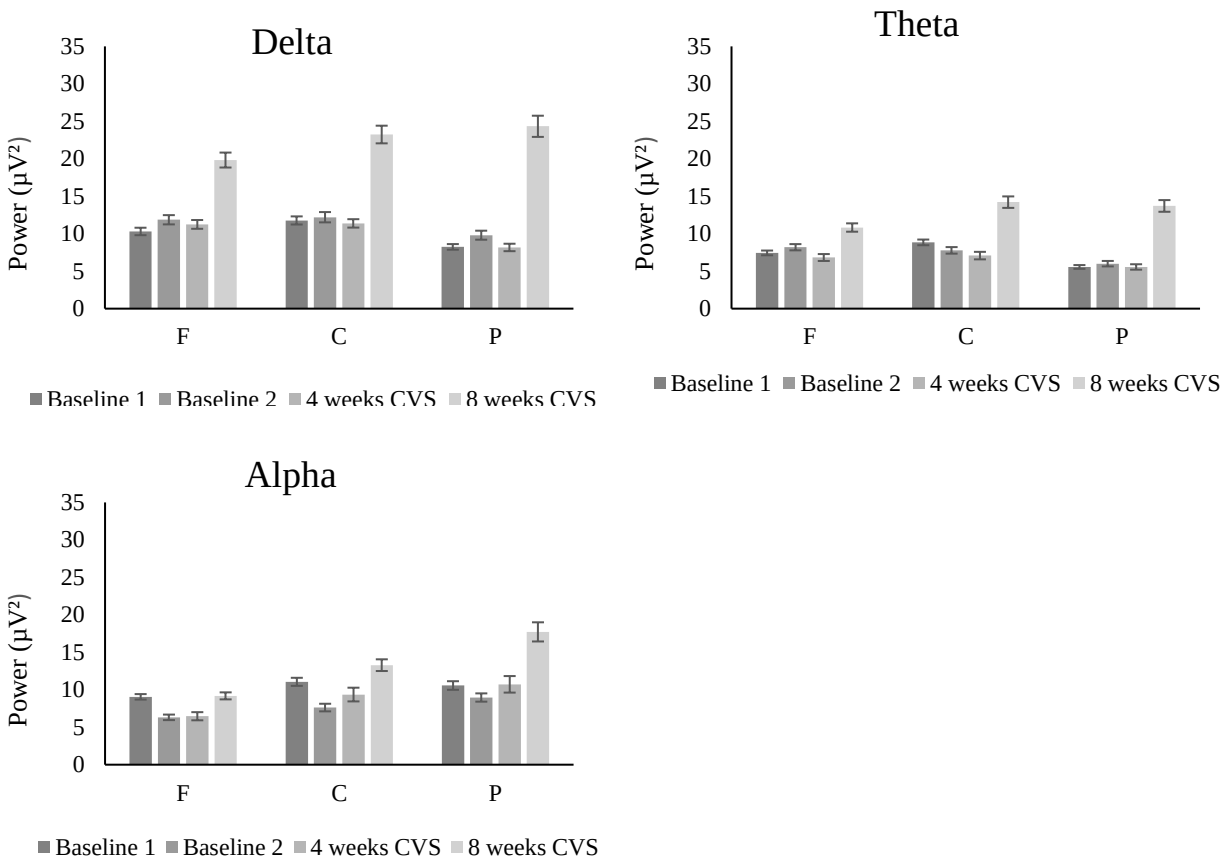


Figure 4.11. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 04.

Participant 05

EEG Power.

Table 4.9
Statistical Analysis of EEG power (μV²) in Participant 05.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_{p^2}
Delta				
Stimulation	1, 118	119.60	<.001***	.50
Session	1, 118	6.19	.014*	.05
Region	2, 236	94.86	<.001***	.45
Stimulation*Session	1, 118	0.11	.74	<.01
Stimulation*Region	2, 236	6.79	<.001***	.05
Session*Region	2, 236	0.96	.35	.01
Stimulation*Session*Region	2, 236	0.71	.49	.01
Theta				
Stimulation	1, 118	109.24	<.001***	.48
Session	1, 118	25.58	<.001***	.18
Region	2, 236	114.84	<.001***	.49
Stimulation*Session	1, 118	9.06	.003**	.07
Stimulation*Region	2, 236	17.00	<.001***	.13
Session*Region	2, 236	12.57	<.001***	.10
Stimulation*Session*Region	2, 236	17.82	<.001***	.13
Alpha				
Stimulation	1, 118	16.12	<.001***	.12
Session	1, 118	2.70	.10	.02
Region	2, 236	503.71	<.001***	.81
Stimulation*Session	1, 118	1.87	.17	.02
Stimulation*Region	2, 236	5.53	.005**	.05
Session*Region	2, 236	1.59	.21	.01
Stimulation*Session*Region	2, 236	1.19	.31	.01

Note. Significant at *0.05, **0.01, ***<.001.

Delta (1- 4Hz). The ANOVA revealed a significant main effect of Stimulation. Consistent with the hypothesis, delta activity was significantly lowered during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present such that activity was elevated over the parietal site and decreased over the frontal electrodes. Since a Stimulation x Region x Session interaction was absent (see Table 4.9), analyses focused on any significant two-way interactions that concerned the Stimulation variable.

Stimulation did not interact with Session, but was related to Region (see Table 4.9). Post-hoc tests first examined differences between the Stimulation conditions at each Region. In line with the hypothesis, delta activity was significantly lowered during active CVS (frontal *M*= 11.46μV², central *M*= 13.11μV², parietal *M*= 15.03μV²) relative to the pre-CVS recordings (frontal *M*= 17.33μV², central *M*= 19.97μV², parietal *M*= 23.71μV²). The effect was similar over the frontal [*t*(118)= 9.78, *p*<.001], central [*t*(118)= 8.97, *p*<.001] and parietal regions [*t*(118)= 8.98, *p*<.001]. Comparisons also examined whether delta activity differed between the three regions within each Stimulation condition. All comparisons were significant across both Stimulation conditions, with the largest differences occurring between the frontal (pre-CVS *M*= 17.33μV²; active CVS *M*= 11.46μV²) and parietal (pre-CVS *M*= 23.71μV²; active CVS *M*= 15.03μV²) regions in both the pre-CVS [*t*(118)= -7.81, *p*<.001] and active CVS recordings [*t*(118)= -7.35, *p*<.001]. Overall delta activity was reduced during the active CVS recordings across all three regions, as predicted (see Figure 4.12).

Theta (4- 8Hz). Theta wave activity also showed a significant main effect of Stimulation (see Table 4.9). In line with the hypothesis, theta activity was significantly reduced during active CVS relative to the pre-CVS recordings. A main effect of Region was also present (see Table 4.9) which reflected elevated activity over the parietal site, and decreased activity over the frontal electrodes. Since a significant three-way interaction was also revealed (see Table 4.9), separate Stimulation x Session ANOVAs were completed for each Region.

The Stimulation x Session interaction was significant over the central [*F*(1, 118)= 4.61, *p*<.05, η_{p^2} =.04.] and parietal electrodes [*F*(1, 118)= 16.85, *p*<.001, η_{p^2}= .13], reflecting the same underlying patterns (frontal *p*=.29). Comparisons first examined differences between the Stimulation conditions. In line with the hypothesis, theta activity was decreased between the baseline (central *M*= 17.98μV²; parietal *M*= 20.91μV²) and after four weeks of

CVS (central *M*= 12.42μV²; *M*= 15.62 μV²) across both regions (central *t*(118)= 6.00, *p*<.001; parietal *t*(118)= 4.75, *p*<.001). Theta activity was also reduced between the sham recording (central *M*= 23.05μV²; parietal *M*= 33.47μV²) and after eight weeks of CVS (central *M*= 13.59μV²; parietal *M* = 17.11μV²), where the effects were greater (central *t*(118)= 6.82, *p*<.001; parietal *t*(118)= 7.16, *p*<.001). Post-hoc tests examining the effects of Session showed an unexpected increase in theta activity between the baseline (central *M*= 17.98μV²; parietal *M*= 20.91μV²) and sham (central *M*= 23.05μV²; parietal *M*= 33.47μV²) recordings (central *t*(118)= -3.52, *p*<.001; parietal *t*(118)= -5.32, *p*<.001), where theta levels were highest (see Figure 4.12). Theta activity remained stable between the recordings taken after four and eight weeks CVS (all *p*s>.25), the only effects not to reach significance in the analyses. In summary, theta activity appeared to show the predicted decline in response to CVS over the central and parietal regions (see Figure 4.12).

Alpha (8- 12Hz). A significant main effect of Stimulation emerged at the alpha band (see Table 4.9). Contrary to the hypothesis, alpha was decreased during active CVS relative to the pre-CVS recordings. However, it should be noted that alpha activity was very high prior to CVS, particularly over the parietal electrodes (see Figure 4.12). A significant main effect of Region was also present, in line with the normative topography alpha levels were elevated over the parietal site. Since a three-way interaction was not present between the variables (see Table 4.9), analyses focused on any significant two-way interactions involving the Stimulation variable.

Alpha wave activity was influenced by a Stimulation x Region interaction (see Table 4.9). Comparisons between the Stimulation conditions (within each Region) showed that alpha activity was consistently lower during active CVS relative to the pre-CVS recordings across all regions (all *p*s<.05). The effect was greatest over the central electrodes (pre-CVS *M*= 53.58μV²; active CVS *M*= 40.91μV²), *t*(118)= 5.83, *p*<.001. Post-hoc tests examining the

effects of Region within each Stimulation condition were also all significant (all *p*s<.001). The largest effects occurred between the frontal (pre-CVS *M*= 28.11μV²; active CVS *M*= 22.87μV²) and central regions (pre-CVS *M*= 53.59μV²; active CVS *M*= 40.91μV²) during both the pre-CVS [*t*(118)= -18.22, *p*<.001] and active CVS recordings [*t*(118)= -18.77, *p*<.001], comparisons involving the frontal and parietal regions were also strong (all *t*s>13.35, all *p*s<.001). Contrary to the hypothesis alpha activity was significantly reduced during the active CVS recordings relative to the pre CVS recordings (across all regions). Since the participant displayed high levels of alpha prior to the onset of CVS (see Figure 4.12), this reduction may have been beneficial (this issue will be returned to in the discussion).

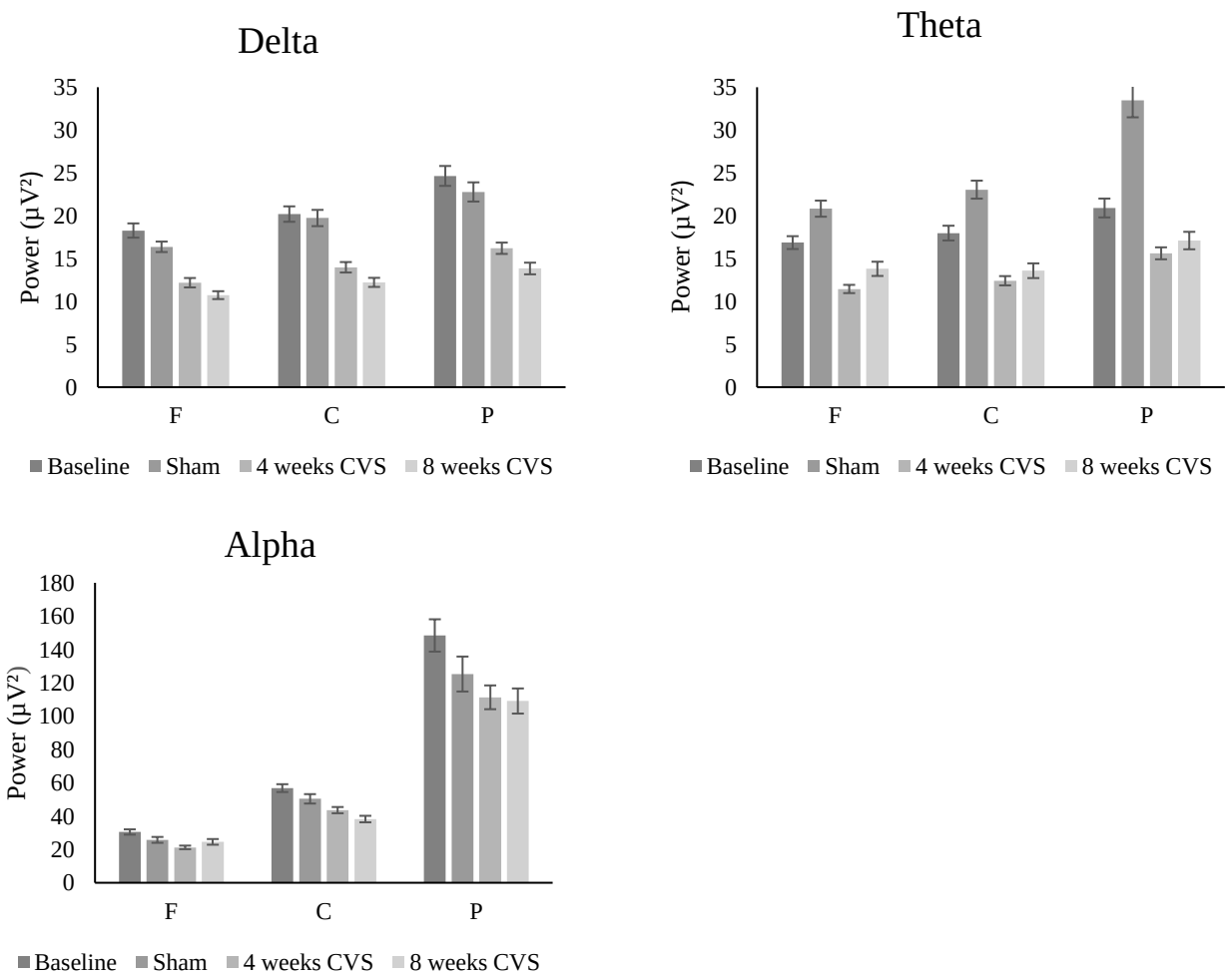


Figure 4.12. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 05. Note the different scaling for the alpha band.

ERP.

Behavioural data summary. Accuracy fluctuated across the study but did not appear to be driven by Stimulation or a potential practice effect (across sessions). A Stimulation x Region x Session interaction revealed that accuracy on the 0-back was reduced subsequent to the baseline, accuracy for the 1-back also steeply declined after eight weeks CVS relative to the remaining sessions where performance was stable. Within the RT data, a Stimulation x Load interaction showed that RTs were longer during the lower loads relative to the higher loads across both Stimulation conditions, contrasting with previous research in healthy samples.

The behavioural data demonstrated that this participant's performance was very inconsistent. Of particular relevance to the ERP analyses was the extremely low level of accuracy on the 1-back condition after eight weeks CVS (i.e. only two trials out of 50 answered correctly). Since two segments are insufficient for ERP analysis (Luck, 2005), this session was removed from statistical analyses. Therefore, electrophysiological data for this patient was analysed using a 3 (Session: baseline, sham, four weeks CVS) x 4 (Load: 0, 1, 2, 3) ANOVA.

Peak amplitude and peak latency. Table 4.10 shows that no significant main effects or interactions were present in this participant's data (all *p*s>.14)[4].

[4] For comparison, if only two trials were accepted for the 1-back load after eight weeks of CVS, the 2 x 2 x 4 ANOVA showed a significant Stimulation x Load interaction [$F(1, 303)= 3.07$, $p<.05$, $\eta_{p^2}= .03$]; all other *p*s>.28. This interaction reflected a reduced P300 amplitude during the active CVS recordings ($M= 16.26\mu V$) relative to the pre-CVS recordings ($M= 23.25\mu V$) for the 3-back only ($p<.05$, all other *p*s>.054). No differences were present between Loads within each Stimulation conditions (all *p*s>.16). No significant effects were revealed within the P300 latency data using this analysis (all *p*s>.18).

Table 4.10
Statistical Analysis of the P300 Component in Participant 05.

		ANOVA		
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (μV)				
Session	2, 236	1.42	.24	.01
Load	3, 236	1.57	.20	.02
Session*Load	6, 236	1.63	.14	.04
P300 peak latency (ms)				
Session	2, 236	0.08	.93	<.01
Load	3, 236	1.47	.22	.02
Session*Load	6, 236	0.97	.45	.02

Participant 06

EEG power.

Delta (1- 4Hz). Delta activity was influenced by a significant main effect of Stimulation (see Table 4.11), as predicted delta levels were lower during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present such that delta wave activity was highest over the frontal site and lowest over the parietal electrodes. Since a three-way interaction was also observed (see Table 4.11), separate Stimulation x Session ANOVAs were next completed for each Region.

The Stimulation x Session interaction was significant over the frontal [F (1, 117)= 40.18, p<.001, η_{p^2} = .26], central [F(1, 117)= 33.53, p<.001, η_{p^2}= .22] and parietal electrodes [F(1, 117)= 20.50, p<.001, η_{p^2} = .15], reflecting similar trends. Comparisons between the Stimulation conditions revealed an unexpected increase in delta activity from the baseline (M= 14.65μV²), to the recording taken after four weeks CVS (M= 19.76μV²) over the frontal electrodes [t(117)= -5.04, p<.001]. Conversely, delta activity was reduced from the baseline (M= 8.66μV²) to the recording after four weeks CVS (M= 7.25μV²) as expected over the parietal electrodes [t(117)= 2.55, p<.05] (central p=.99). In line with the hypothesis, delta activity was then decreased between the recordings taken after sham stimulation (frontal M=

21.49μV²; central *M*= 18.86μV²; parietal *M*= 13.58μV²) and eight weeks CVS (frontal *M*=15.91μV²; central *M*= 10.83μV²; parietal *M*= 6.55μV²) across all regions (frontal $t(117) = 4.21$, $p<.001$; central $t(117)= 6.42$, $p<.001$; parietal $t(117)= 6.16$, $p<.001$). Post-hoc tests examining the effects of Session also revealed a significant increase in delta activity between the baseline (frontal *M*= 14.65μV²; central *M*= 10.21μV²; parietal *M*= 8.66μV²) and sham recordings (frontal *M*= 21.49μV²; central *M*= 18.86μV²; parietal *M*= 13.58μV²) (frontal $t(117) = -5.09$, $p<.001$; central $t(117)= -6.85$, $p<.001$; parietal $t(117) = -4.55$, $p<.001$). Delta activity was then decreased between the recordings taken after four (*M*= 19.76μV²) and eight weeks CVS (*M*=15.91μV²) over the frontal electrodes [$t(117) = 3.62$, $p<.001$] (central and parietal all *p*s>.35). In line with the hypothesis, delta activity was highest during the sham recording and declined thereafter during active CVS across all regions (see Figure 4.13). However, since only the parietal electrodes showed a reduction which fell below the baseline magnitude, these effects were unlikely to be driven by CVS alone.

Theta (4- 8Hz). A significant main effect of Stimulation also emerged at the theta band (see Table 4.11). As predicted, theta activity was lower during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present (see Table 4.11) such that, theta power was elevated over the frontal electrodes and lowest at the parietal site. A Stimulation x Session x Region interaction was not present (see Table 4.11), therefore the two-way interactions involving the Stimulation variable were next interrogated.

A significant Stimulation x Region interaction was revealed and comparisons first examined whether any differences had emerged between the Stimulation conditions within each Region. In line with the hypothesis, central and parietal theta activity had decreased between the pre-CVS (central *M*= 14.13μV²; parietal *M*= 10.80μV²) and active CVS recordings (central *M*= 12.07μV²; parietal *M*= 6.93μV²) (central $t(117)= 2.82$, $p<.05$; parietal $t(117)= 7.40$, $p<.001$; frontal $p=.79$). Comparisons of Region were then completed for each

Stimulation condition. All three regions differed significantly from each other across both Stimulation conditions (all *p*s<.05). The largest effects appeared to result from the reduction in theta activity over the parietal electrodes (pre-CVS *M*= 10.80μV²; active CVS *M*= 6.93μV²) relative to the frontal electrodes (pre-CVS *M*= 15.05μV²; active CVS *M*= 15.22μV²) across both the pre-CVS [*t*(117)= 11.26, *p*<.001] and active CVS recordings [*t*(117)= 20.59, *p*<.001]. In line with the hypothesis, theta activity was lowered during active CVS relative to the pre-CVS recordings over the central and parietal electrodes (see Figure 4.13). No other significant main effects or interactions involving the Stimulation variable were present (all *p*s>.05).

Alpha (8- 12Hz). ANOVA testing showed alpha activity at the central and parietal sites was elevated during the baseline recording and declined thereafter (see Figure 4.13) rather than increasing in response to Stimulation as predicted. Since CVS did not modulate alpha activity, this band will not be described further

Table 4.11
Statistical Analysis of EEG Power (μV²) in Participant 06.

	ANOVA			
Frequency Band	***df***	***F***	***p* value**	η_{p^2}
Delta				
Stimulation	1, 117	18.85	<.001***	.14
Session	1, 117	17.35	<.001***	.13
Region	2, 234	522.37	<.001***	.82
Stimulation*Session	1, 117	38.52	<.001***	.25
Stimulation*Region	2, 234	29.60	<.001***	.20
Session*Region	2, 234	16.41	<.001***	.12
Stimulation *Session*Region	2, 234	10.86	<.001***	.09
Theta				
Stimulation	1, 117	11.50	.001***	.09
Session	1, 117	6.21	.014*	.05
Region	2, 234	409.16	<.001***	.78
Stimulation*Session	1, 117	3.83	.05	.03
Stimulation*Region	2, 234	32.89	<.001***	.22
Session*Region	2, 234	22.30	<.001***	.16
	2, 234	1.82	.16	.02

Stimulation *Session*Region				
Alpha				
Stimulation	1, 117	1.68	.20	.01
Session	1, 117	0.81	.37	.01
Region	2, 234	139.50	<.001***	.54
Stimulation*Session	1, 117	31.83	<.001***	.21
Stimulation*Region	2, 234	40.43	<.001***	.26
Session*Region	2, 234	18.70	<.001***	.14
Stimulation *Session*Region	2, 234	27.71	<.001***	.19

Note. Significant at *0.05, **0.01, ***0.001.

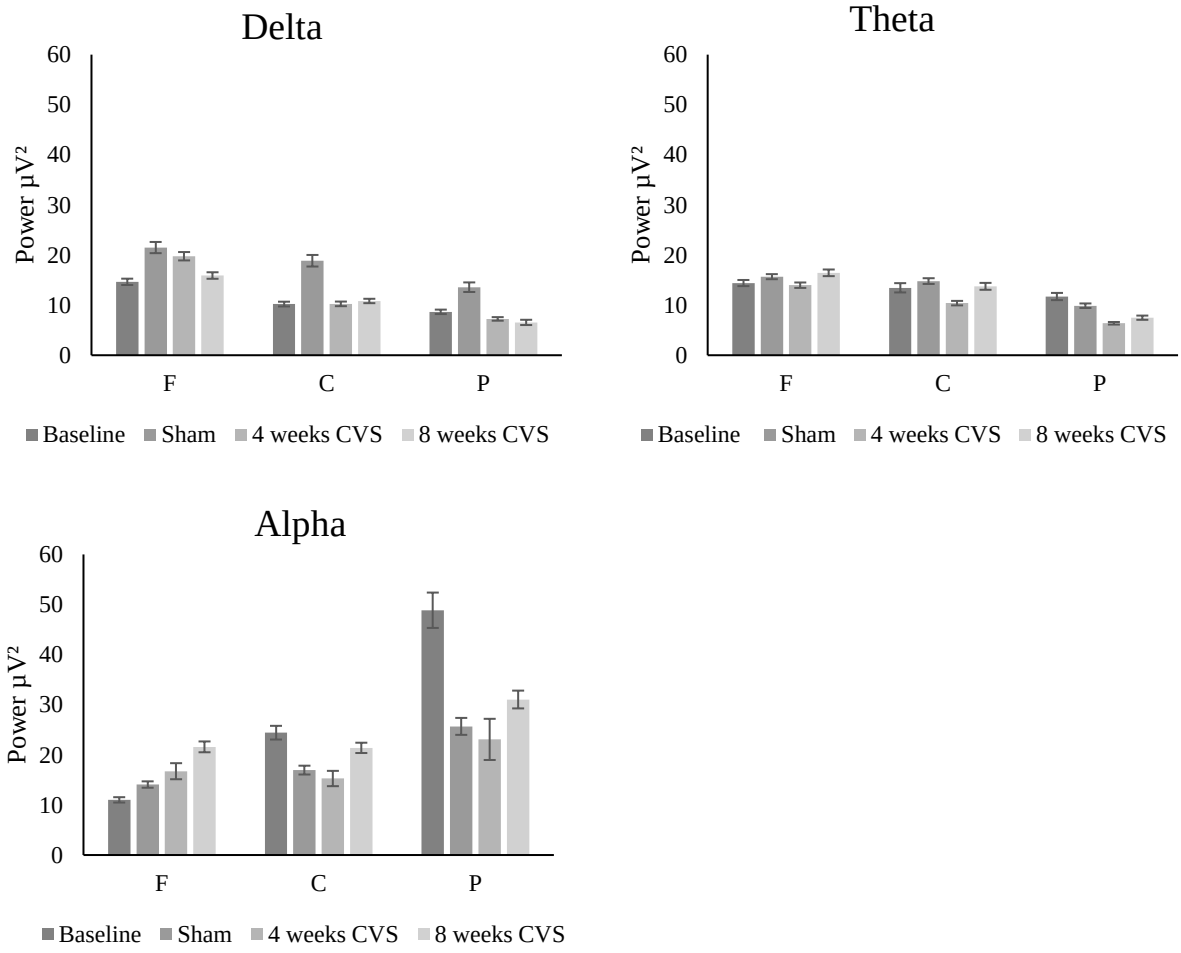


Figure 4.13. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 06.

ERP.

Behavioural data summary. Accuracy responses were influenced by a three-way interaction; post-hoc comparisons revealed that accuracy on the 2-back Load was improved due to practice-effects between the baseline and sham recordings and remained stable

thereafter. Response times also showed a significant three-way interaction. Post-hoc analyses at each Load revealed that RTs were shorter during one of the active CVS sessions relative to one of the pre-CVS sessions at the 2 and 3-back loads. However, the effect on the 3-back appeared to onset during sham stimulation thus limiting the likelihood of CVS-related benefit.

During the baseline EEG recording there were some technical difficulties with the cable that connected the EEG amplifier to the E-prime laptop. This meant that no triggers were sent to record stimuli and response onset times, though additional random (nuisance) triggers were sent, thus preventing the offline matching of stimuli and their associated electrophysiological response. To address this technical fault, the ERP data from the baseline recording was omitted from statistical analysis and a 3 (Session: sham, four weeks CVS, eight weeks CVS) x 4 (Load: 0, 1, 2, 3) ANOVA was conducted on the remaining ERP data.

Peak amplitude and peak latency. Table 4.12 show that no significant main effects or interactions were present in this participant's data (all *p*s>.08).

Table 4.12
Statistical Analysis of the P300 Component in Participant 06.

		ANOVA		
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Session	2, 543	2.93	.05	.01
Load	3, 543	1.19	.32	<.01
Session*Load	6, 543	0.97	.45	.01
P300 peak latency (ms)				
Session	2, 543	1.42	.24	<.01
Load	3, 543	2.23	.08	.01
Session*Load	3, 543	0.66	.69	<.01

Note. Significant at *0.05, **0.01, ***0.001.

Participant 07

EEG power.

Delta (1- 4Hz). ANOVA testing revealed that central delta activity fluctuated across the study. However, since these changes were not driven by Stimulation (see Figure 4.14 and Table 4.13), this band will not be described further.

Table 4.13
Statistical Analysis of Resting EEG Power (μV²) in Participant 07.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_{p^2}
Delta				
Stimulation	1, 118	0.34	.56	<.01
Session	1, 118	71.65	<.001***	.38
Region	2, 236	98.75	<.001***	.46
Stimulation*Session	1, 236	0.86	.36	<.01
Stimulation*Region	2, 236	6.76	<.001***	.05
Session*Region	2, 236	7.12	<.001***	.06
Stimulation *Session*Region	2, 236	4.41	.01**	.04
Theta				
Stimulation	1, 118	1.67	.20	.01
Session	1, 118	175.87	<.001***	.60
Region	2, 236	55.35	<.001***	.32
Stimulation*Session	1, 118	0.53	.47	<.01
Stimulation*Region	2, 236	16.44	<.001***	.12
Session*Region	2, 236	2.37	.10	.02
Stimulation *Session*Region	2, 236	7.47	<.001***	.06
Alpha				
Stimulation	1, 118	45.07	<.001***	.28
Session	1, 118	50.48	<.001***	.30
Region	2, 236	219.64	<.001***	.65
Stimulation*Session	1, 118	6.26	.01**	.05
Stimulation*Region	2, 236	18.61	<.001***	.14
Session*Region	2, 236	1.71	.18	.01
Stimulation *Session*Region	2, 236	19.36	<.001***	.14

Note. Significant at *0.05, **0.01, ***<0.001.

Theta (4- 8Hz). Similar to the delta band, ANOVA testing showed that central theta activity was altered across the study. However, since post-hoc comparisons revealed that

these changes were not related to the Stimulation variable (see Figure 4.14 and Table 4.13), these effects will not be elaborated upon.

Alpha (8- 12Hz). Several comparisons within this ANOVA reached significance (see Table 4.13). However, post-hoc testing revealed that these effects were driven by a decrease in frontal and central alpha activity subsequent to the baseline (Figure 4.14), rather than in response to Stimulation and thus this band will not be described further.

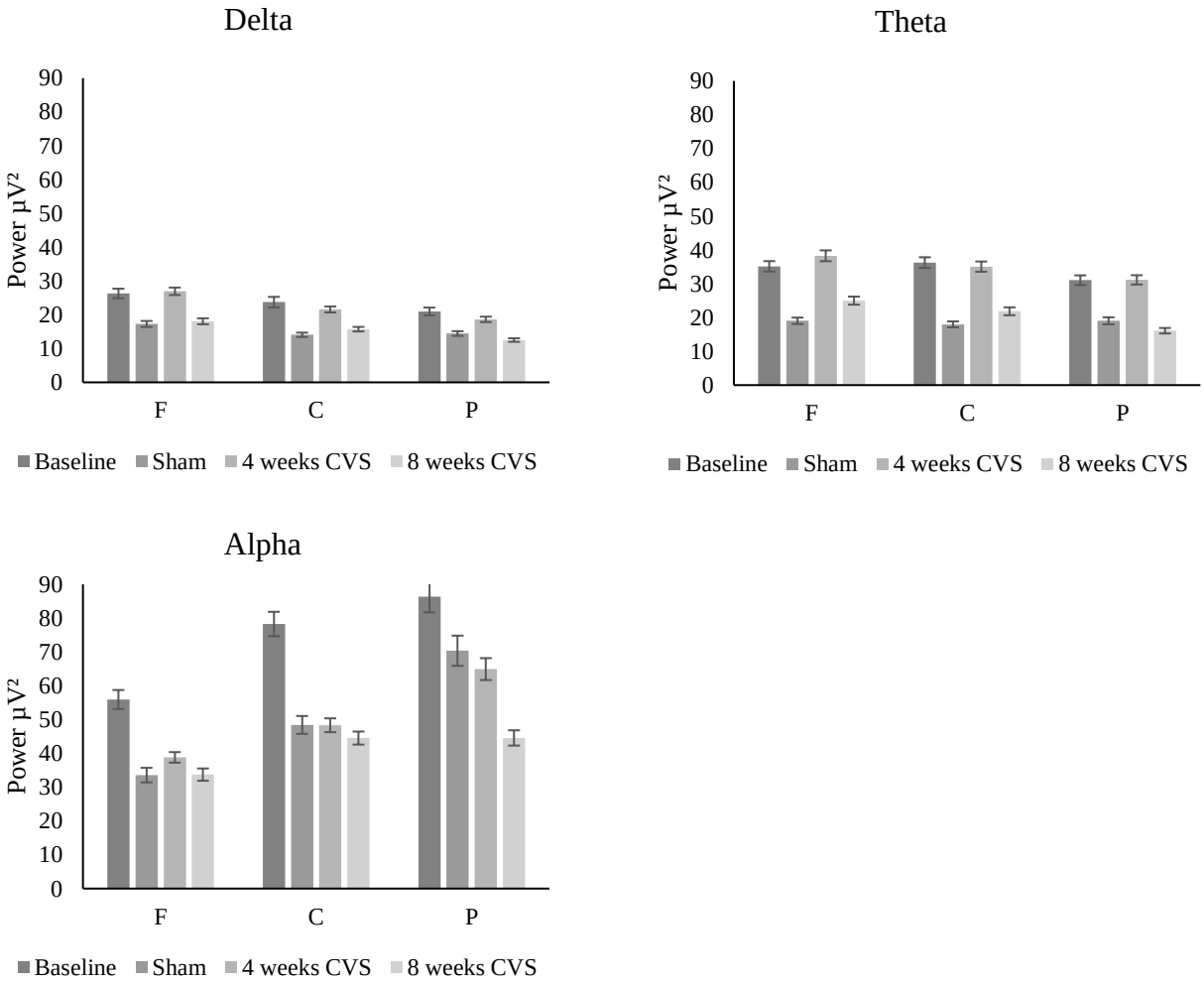


Figure 4.14. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 07.

ERP.

Behavioural data summary. ANVOA testing revealed that changes in accuracy were driven by a significant Stimulation x Session interaction at the 3-back Load, whereby

accuracy continued to improve due to practice and then stabilised after eight weeks CVS. Response times showed a significant Stimulation x Load interaction such that RTs were longer during the higher n-back loads across both Stimulation conditions**.**

Peak amplitude. Contrary to the hypothesis, main effects of Stimulation and Load were absent from the P300 peak amplitude data (see Table 4.14 and Figure 4.15). However, there was a significant three-way interaction which was followed-up with separate Stimulation x Session ANOVAs for each n-back Load.

The Stimulation x Session interaction was only present under the 0-back Load, $F(1, 195)= 5.18$, $p<.05$, $\eta_{p^2}= 0.3$ (all other loads *p*s>.09). However, P300 peak amplitudes did not differ between Stimulation conditions at either Session for the 0-back targets (all *p*s>.09). Comparisons between the Sessions showed that P300 amplitudes for the 0-back initially remained stable between the baseline ($M= 15.01\mu V$) and sham ($M= 15.55\mu V$) recordings ($p=.72$), as predicted. However, P300 amplitudes were then decreased between the recordings taken after four ($M= 17.26\mu V$) and eight ($M= 13.05\mu V$) weeks CVS [$t(98)= 2.63$, $p<.05$]. This result appeared to drive the interaction and contrasted with the cumulative increase in P300 amplitudes that was predicted to occur in response to CVS.

Peak latency. Significant main effects of Stimulation and Load, as well as a three-way interaction were absent from the P300 latencies. Since a significant Stimulation x Session interaction was present (see Table 4.14), post-hoc tests were completed to investigate this interaction.

Comparisons first examined whether any Stimulation effects were present within each Session. P300 latencies were significantly shorter after four weeks CVS ($M= 359$ms) relative to the baseline recording ($M= 382$ms), $t(335)= 1.93$, $p<05$. However, no differences were observed between the recordings taken after sham and eight weeks CVS ($p= .54$). Post-hoc

tests of Session revealed that P300 latencies had remained stable between the pre-CVS recordings (p=.57) and were then unexpectedly increased between the active CVS recordings taken after four (M= 359ms) and eight weeks of CVS (M= 393ms), $t(355)$= -3.89, p<.001. These effects suggest that although the P300 was quicker to peak after four weeks CVS relative to the baseline as predicted, this facilitation may not be robust since it was not sustained after eight weeks CVS (see Figure 4.15). No other significant effects or interactions were present (see Table 4.14).

Table 4.14
Statistical Analysis of the P300 Component in Participant 07.

		ANOVA		
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Stimulation	1, 675	1.94	.16	<.01
Session	1, 675	30.72	<.001***	.04
Load	3, 675	1.82	.14	<.01
Stimulation*Session	1, 675	<0.01	.97	<.01
Stimulation*Load	3, 675	0.62	.61	<.01
Session*Load	3, 675	0.85	.47	<.01
Stimulation *Session*Load	3, 675	2.81	.04*	.01
P300 peak latency (ms)				
Stimulation	1, 675	1.94	.16	<.01
Session	1, 675	9.29	.002**	.01
Load	3, 675	0.04	.99	<.01
Stimulation*Session	1, 675	4.78	.03*	<.01
Stimulation*Load	3, 675	1.62	.18	<.01
Session*Load	3, 675	1.32	.27	<.01
Stimulation *Session*Load	3, 675	2.13	.10	<.01

Note. Significant at *0.05, **0.01, ***0.001.

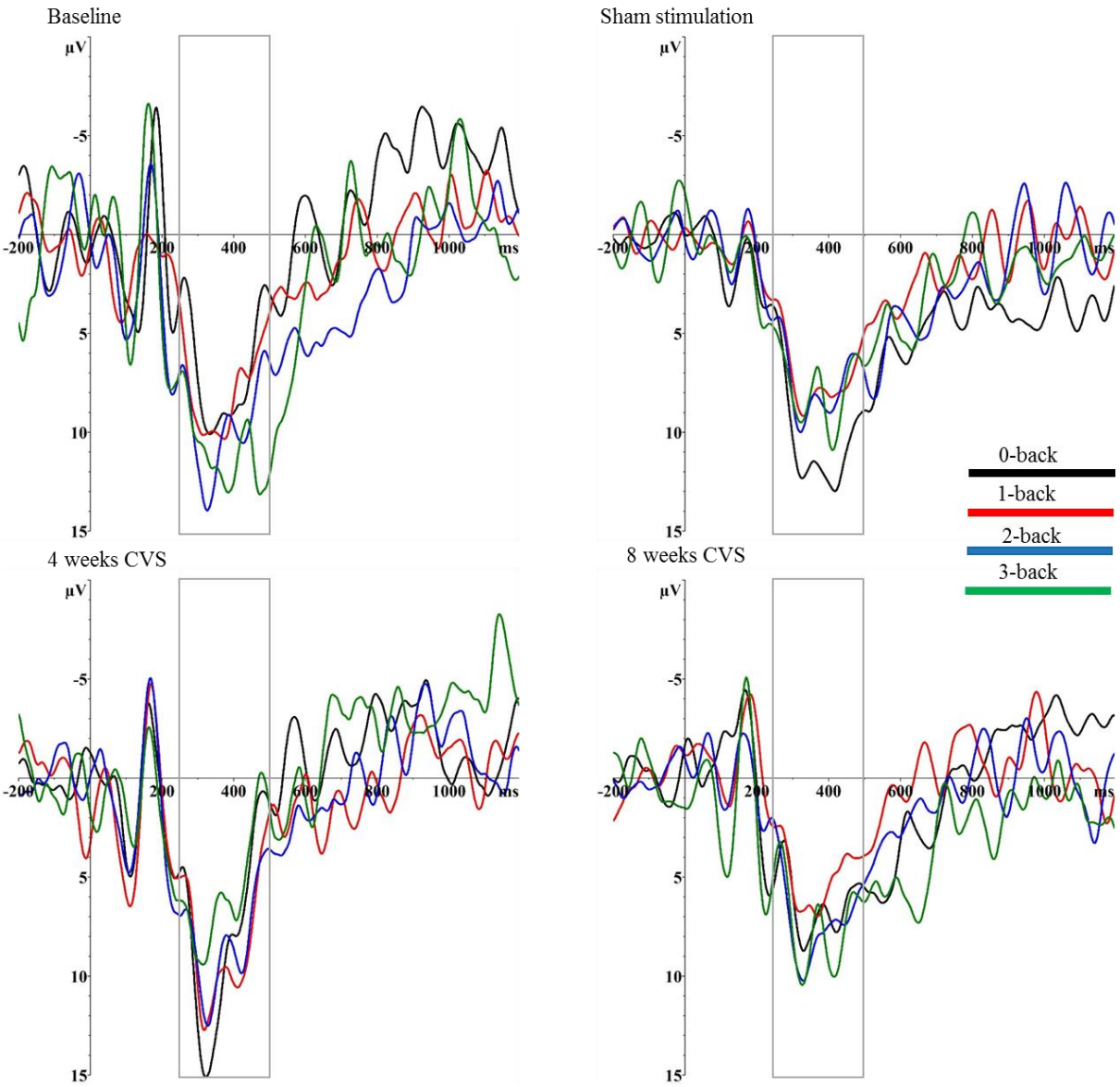


Figure 4.15. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the four EEG recordings, at the Pz electrode in participant 07.

Participant 08

EEG power.

Delta (1- 4Hz). Contrary to the hypothesis, a significant main effect of Stimulation showed that delta activity was increased during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also present, such that delta activity was elevated over the frontal electrodes. Since a three-way interaction was also present (see Table 4.15), separate Stimulation x Session ANOVAs were next completed for each Region to follow-up the interaction.

Significant Stimulation x Session interactions were revealed over the frontal [$F(1, 118)= 135.18$, $p<.001$, $\eta_{p^2}= .16$] and central electrodes [$F(1, 118)= 4.80$, $p<.05$, $\eta_{p^2}= .04$] (parietal electrodes $p=.12$), which reflected the same underlying trends. Comparisons first examined whether any differences were present between the Stimulation conditions during each Session. Frontal delta activity was highest during the baseline recording ($M= 24.59\mu V^2$) and was then significantly reduced after four weeks CVS ($M= 18.07\mu V^2$) [$t(118)= 3.27$, $p<.05$], while central delta remained stable between the two recordings ($p=.08$). Unexpectedly, delta levels were increased between the sham recording (frontal $M= 12.76\mu V^2$; central $M= 8.52\mu V^2$) and after eight weeks CVS (frontal $M= 16.26\mu V^2$; central $M= 14.27\mu V^2$) across both regions (frontal $t(118)= -3.17$, $p<.05$; central $t(188)= -6.38$, $p<.001$). Comparisons between Sessions also showed an unexpected decrease in delta activity (see Figure 4.16) between the baseline (frontal $M= 24.59\mu V^2$; central $M= 14.73\mu V^2$) and sham recordings (frontal $M= 12.76\mu V^2$; central $M= 8.52\mu V^2$) across both regions (frontal $t(118)= 7.56$, $p<.001$; central $t(118)= 5.95$, $p<.001$). Frontal and central delta activity remained stable during the active CVS recordings (all $ps>.22$). Contrary to the hypothesis, frontal and central delta activity was lowered during the sham recording (see Figure 4.16) and subsequently increased during CVS (where power remained stable).

Theta (4- 8Hz). A main effect of Stimulation emerged at the theta band (see Table 4.15). Unexpectedly, theta wave activity was again increased during active CVS relative to the pre-CVS recordings. A significant main effect of Region was also revealed, which reflected elevated theta activity over the frontal site. Since a significant Stimulation x Session x Region interaction was also present, post-hoc tests were next completed to interrogate the interaction within each Region.

The ANOVA over the frontal electrodes revealed a significant Stimulation x Session interaction, $F(1, 118)= 17.13$, $p<.001$, $\eta_p^2= .13$. Comparisons showed that the interaction

reflected elevated levels of frontal theta activity during the baseline recording relative to the subsequent recordings (see Figure 4.16). Since the effect was not driven by CVS it will not be described further.

Central theta activity also showed a significant Stimulation x Session interaction, $F(1, 118)= 5.33$, $p<.05$, $\eta_{p^2=}$ .04. In contrast with the hypothesis, central theta activity was significantly increased from the baseline ($M= 12.81\mu V^2$) to the recording taken after four weeks CVS ($M= 14.48\mu V^2$), $t(118)= -2.14$, $p<.05$. This trend continued between the recordings taken after sham ($M= 10.24\mu V^2$) and eight weeks CVS ($M= 14.28\mu V^2$), where it was stronger, $t(118)= -6.00$, $p<.001$. An unexpected decrease in central theta activity was again present between the baseline ($M= 12.81\mu V^2$) and sham recordings ($M= 10.24\mu V^2$) [$t(118)= 3.46$, $p<.001$], while activity remained stable between the stimulation recordings ($p=.80$). Contrary to the hypothesis, central theta activity was elevated during active CVS relative to the pre-CVS recordings (see Figure 4.16). The two-way interaction was absent over the parietal electrodes ($p=.27$).

Alpha (8- 12Hz). Although several comparisons within this ANOVA reached significance (see Table 4.21), post-hoc testing revealed that this was because alpha wave activity was significantly elevated during the baseline recording (across all regions) relative to the subsequent sessions (see Figure 4.16). Since activity within this band was not driven by the Stimulation variable it will not be described further.

Table 4.15
Statistical Analysis of EEG Power (μV²) in Participant 08.

		ANOVA		
Frequency Band	***df***	***F***	***p* value**	η_{p^2}
Delta				
Stimulation	1, 118	7.14	.009**	.06
Session	1, 118	36.85	<.001***	.24
Region	2, 236	120.11	<.001***	.50
Stimulation*Session	1, 118	4.68	.03*	.04
Stimulation*Region	2, 236	60.54	<.001***	.34
Session*Region	2, 236	9.04	<.001***	.07
Stimulation *Session*Region	2, 236	49.13	<.001***	.29
Theta				
Stimulation	1, 118	12.20	.001**	.09
Session	1, 118	8.24	.005**	.07
Region	2, 236	464.93	<.001***	.80
Stimulation*Session	1, 118	8.66	.004**	.07
Stimulation*Region	2, 236	108.74	<.001***	.48
Session*Region	2, 236	13.23	<.001***	.10
Stimulation *Session*Region	2, 236	19.33	<.001***	.14
Alpha				
Stimulation	1, 118	48.23	<.001***	.29
Session	1, 118	37.56	<.001***	.24
Region	2, 236	306.10	<.001***	.72
Stimulation*Session	1, 118	92.23	<.001***	.44
Stimulation*Region	2, 236	222.46	<.001***	.65
Session*Region	2, 236	46.10	<.001***	.28
Stimulation *Session*Region	2, 236	72.14	<.001***	.38

Note. Significant at *0.05, **0.01, ***<.001.

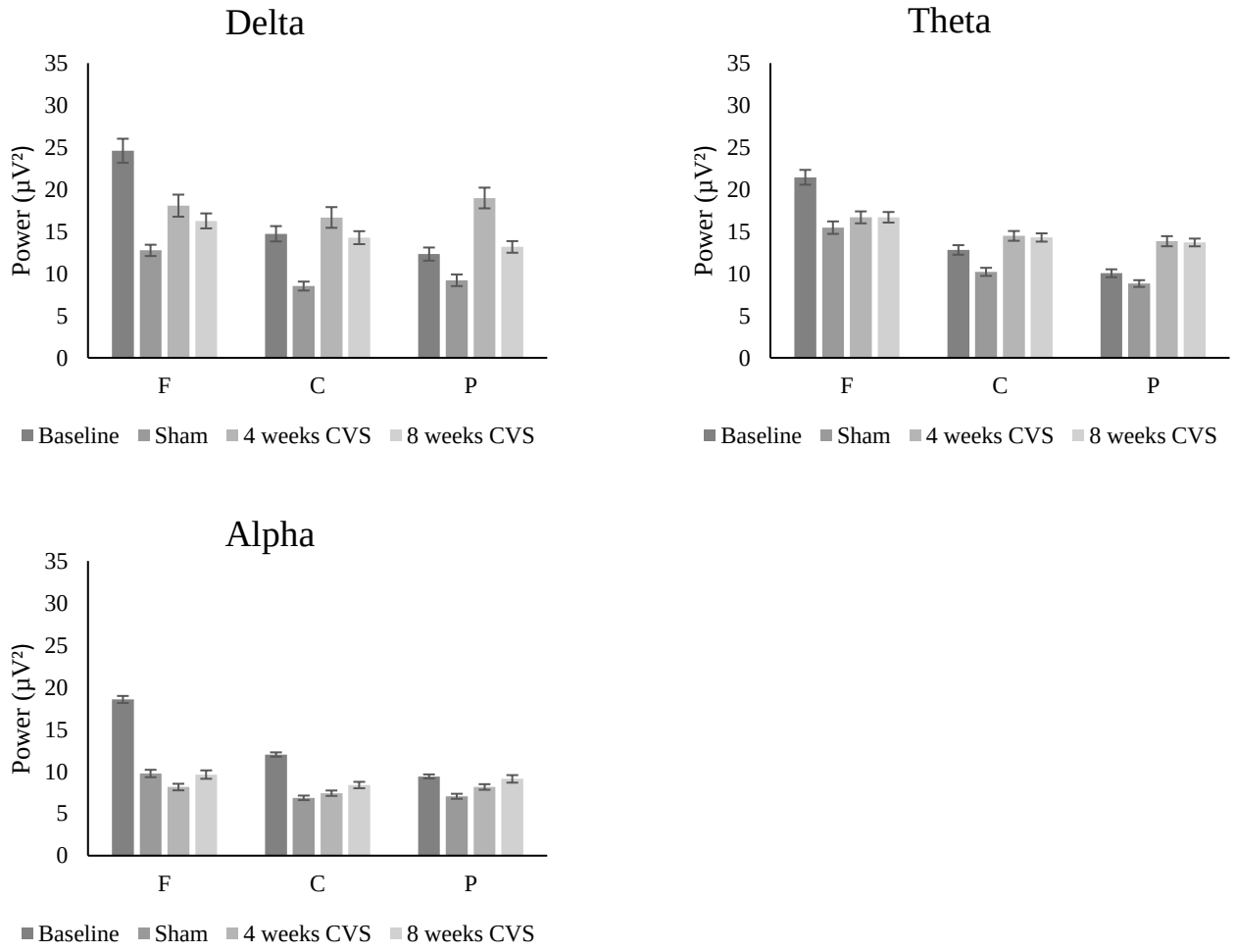


Figure 4.16. Mean levels of power over the frontal, central and parietal regions during the four EEG recordings in participant 08.

ERP.

Behavioural data summary. Accuracy responses showed a main effect of Load only, as predicted accuracy was reduced with increased n-back Load. In line with the hypothesis, response times were affected by a Stimulation x Session interaction whereby RTs were shorter during the active CVS recordings across both Sessions.

Peak amplitude. P300 peak amplitudes were influenced by a significant main effect of Stimulation. As predicted, P300 peak amplitudes were increased during active CVS relative to the pre-CVS recordings. A main effect of Load was also present, such that amplitudes were elevated during the lower loads relative to the higher loads as anticipated

(see Figure 4.17). Since a three-way interaction was absent, analyses focused on the significant Stimulation x Load interaction (see Table 4.16).

Comparisons first examined whether there were differences between the Stimulation conditions within each n-back Load. In line with hypothesis, P300 amplitudes were significantly increased during the active CVS recordings (0-back *M*= 11.75µV; 1-back *M*= 9.78µV) relative to the pre-CVS recordings (0-back *M*= 5.67µV; 1-back *M*= 5.93µV), for the 0 [$t(196)= -4.15$, $p<.05$] and 1-back loads [$t(183)= -3.00$, $p<.05$]. However, no differences were present at the higher n-back loads (all *p*s>.36). P300 peak amplitudes were also compared across the four loads within each Stimulation condition. During the active CVS recordings P300 peak amplitudes for the 0-back condition (*M*= 11.75µV) were significantly increased (see Figure 4.17), relative to the 2 (*M*= 6.70µV) [$t(191)= 3.73$, $p<.05$], and 3-back (*M*= 6.90µV) conditions [$t(159)$ 3.07, $p<.05$] (all other *p*s>.11). Conversely, amplitude was unaffected by Load during the pre-CVS recordings (all *p*s>.05). These effects partially support the increases in P300 amplitudes that were predicted to occur in response to CVS over the lower n-back loads where working memory demands were reduced. The results also indicate that CVS may have normalised the brain response elicited by increased n-back loads whereby P300 amplitudes reduce with increased working memory Load. No other effects reached significance (all *p*s>.05).

Peak latency. A significant main effect of Stimulation (see Table 4.16) showed that latencies were shorter during active CVS (*M*= 348ms), relative to the pre-CVS recordings (*M*= 365ms) as predicted. No other main effects or interactions reached significance (all *p*s>.07).

Table 4.16
Statistical Analysis of the P300 Component in Participant 08.

	ANOVA			
	df	***F***	***p* value**	η_{p^2}
P300 peak amplitude (µV)				
Stimulation	1, 670	18.32	<.001***	.03
Session	1, 670	9.86	.002**	.02
Load	3, 670	3.22	.02*	.01
Stimulation*Session	1, 670	0.25	.62	<.01
Stimulation*Load	3, 670	3.20	.02*	.01
Session*Load	3, 670	2.65	.05	.01
Stimulation *Session*Load	3, 670	1.44	.23	.01
P300 peak latency (ms)				
Stimulation	1, 670	4.60	.03*	<.01
Session	1, 670	2.82	.09	<.01
Load	3, 670	2.02	.11	<.01
Stimulation*Session	1, 670	0.81	.34	<.01
Stimulation*Load	3, 670	0.71	.55	<.01
Session*Load	3, 670	2.38	.07	.01
Stimulation *Session*Load	3, 670	1.03	.38	<.01

Note. Significant at *0.05, **0.01, ***0.001.

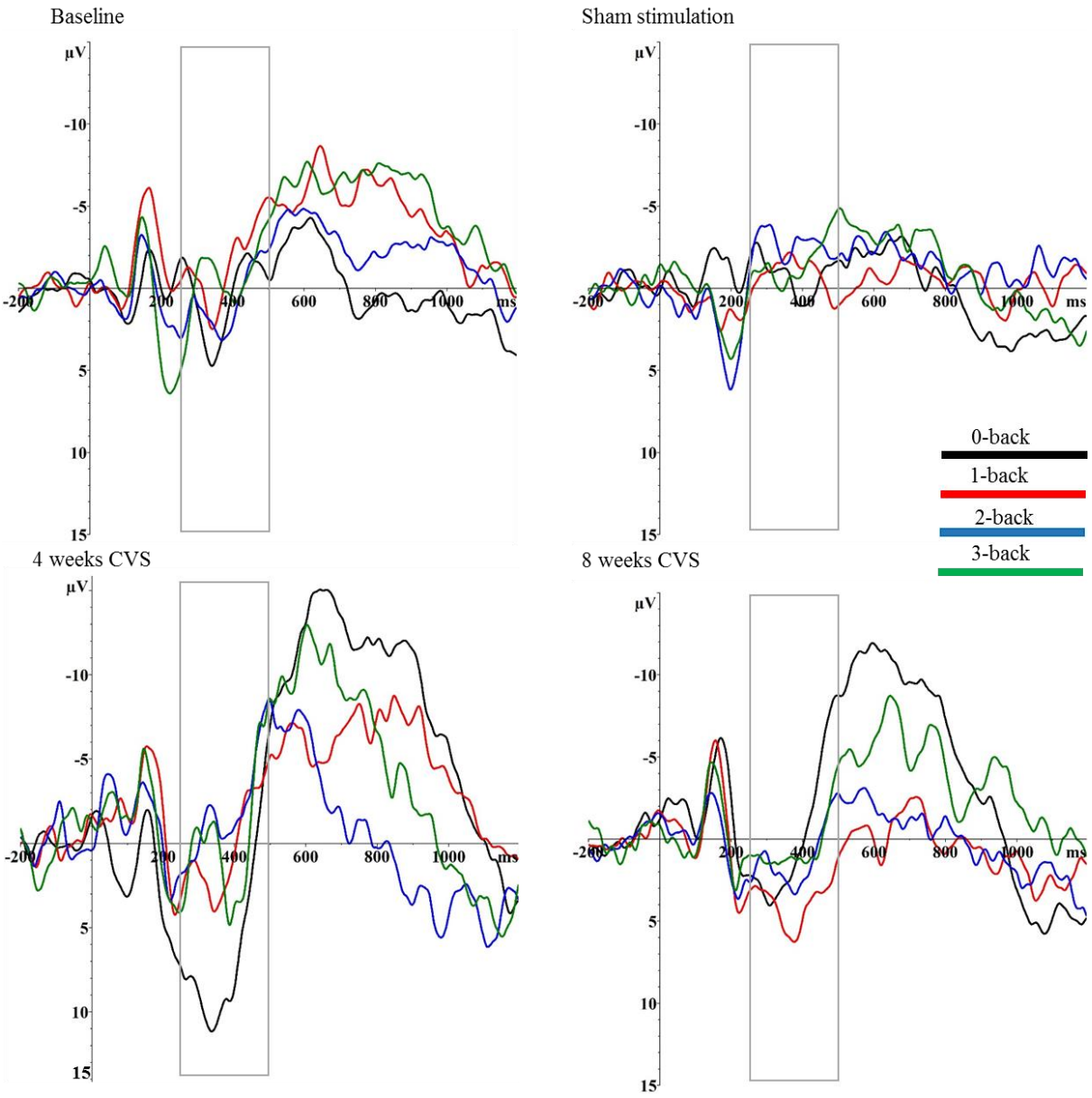


Figure 4.17. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the four EEG recordings, at the Pz electrode in participant 08.

Discussion of Electrophysiological Outcomes

The aim of this chapter was to provide electrophysiological evidence for a modulatory effect of CVS on background brain activity (spectral power) and cognitive function (ERP) within a sample of TBI patients. Analyses examined whether the absolute power of the delta, theta, and alpha bands differed between pre-CVS and active CVS recordings taken while participants rested. A separate experimental task (visuospatial n-back) also tested whether the amplitude and latency of the P300 component (as well behavioural responses) were affected

by CVS. Recall that previous research had identified electrophysiological abnormalities following TBI including, slow-wave dominance within the resting EEG and reduced P300 amplitudes and slowed P300 latencies during oddball tasks. This study aimed to normalise these responses using CVS. More specifically, resting slow-wave activity (delta and theta power) was predicted to reduce and faster-wave activity (alpha power) was expected to increase in response to active CVS relative to the pre-CVS recordings. During the experimental n-back task participants were also expected to show increased P300 amplitudes and shorter latencies following active CVS. Overall, everyone showed at least one favourable electrophysiological change providing preliminary evidence that vestibular inputs could have a beneficial effect by normalising the resting electrophysiological profiles of TBI patients. However, as with the behavioural data reported in the previous chapter, these effects were isolated and individualised.

This discussion will begin by summarising the effects that were found within the EEG power and ERP analyses, before moving onto explanations of the findings and more general suggestions for further study.

Summary of Findings

EEG power. Eight participants completed the resting EEG protocol which was intended to form a neural profile on a case-by-case basis. Table 4.17 presents an overall summary of the CVS-related effects. Although the results were varied some consistencies emerged. EEG activity generally tended to reduce rather than increase in response to CVS (eight CVS-related increases in power, eleven CVS-related decreases in power). In line with the hypothesis, several participants showed a reduction in the slower-wave activity which has been shown to characterise the EEG of TBI patients (Nuwer et al., 2005). Delta activity was decreased during CVS within four participants, although the effect appeared to onset during sham stimulation in two of these individuals (the remainder of the sample showed increased

delta *N*= 2, or no effects of CVS *N*= 2). Theta activity was also reduced in three participants (here the effects appeared to relate more closely to the onset of CVS), despite several other participants (*N*= 3) showing an increase in theta activity during CVS. The remainder of the sample showed no CVS-effects within the theta band (*N*= 2). Importantly, three of the participants (02, 05, 06) showed reduced delta and theta power during active CVS, indicating that these effects were driven by a CVS-related decreases in slow-wave activity as opposed to unconnected variability between recording sessions.

Table 4.17
Summary of CVS-Related EEG Effects within each Power Band.

Participant	Delta	Theta	Alpha
01	Frontal activity increased during CVS.	Increased during CVS.	No effects driven by CVS.
02	Frontal and parietal activity reduced during CVS (began at sham).	Reduced during CVS (began at sham).	Reduced during CVS (began at sham).
03	Reduced during CVS (began at sham).	No effects driven by CVS.	Increased after 8 weeks CVS over the central and parietal electrodes.
04	Increased after 8 weeks CVS.	Increased after 8 weeks CVS.	Increased after 8 weeks CVS over the central and parietal electrodes.
05	Reduced during CVS.	Reduced during CVS.	Reduced during CVS.
06	Reduced during CVS (activity greatest at sham).	Reduced during CVS over the central and parietal electrodes.	Reduced during CVS (highest during baseline).
07	No effects driven by CVS.	No effects driven by CVS.	Reduced during CVS over the frontal and central electrodes (highest at baseline).
08	No effects driven by CVS (lowest after sham stimulation).	Increased during CVS over the central and parietal electrodes.	Reduced during CVS (began at sham).

Note. Blue (decrease) and red (increase) fonts are used to highlight results where the hypothesised trends in spectral power were present. Effects refer to a diffuse change unless specific sessions or regions are specified.

Contrary to the hypothesis, faster-wave activity within the alpha band also tended to decrease during the active CVS recordings relative to the pre-CVS recordings. This effect

was fairly consistent occurring in five out of the eight participants. Although these findings challenge the hypothesis, they may offer some interesting insights about the participants and their recovery process which will be reviewed in the next EEG section.

ERP. Seven participants completed the ERP protocol which was included as a more direct test of cognitive functioning (particularly attention and working memory). Table 4.18 summarises the effects present in each participant across the four dependent variables and shows that the results were varied with no obvious consistencies. Unexpectedly, the hypothesised electrophysiological and behavioural improvements were largely absent. There was modest evidence to suggest that processing speed may have been facilitated in response to CVS, with P300s becoming quicker to peak within three participants (the remainder were longer *N*= 1, or showed no effect *N*= 3) and RTs becoming shorter within four participants (the remainder were longer *N*= 2, or showed no effect *N*= 1). Unfortunately, only two participants showed improvements on both outcome measures which suggests that a generalised improvement in processing speed was unlikely. Overall these electrophysiological data indicate that specific cognitive processes such as attention and stimulus categorisation were unaffected by CVS.

Only participant 08 demonstrated results which were consistent with the hypothesis. In this individual, P300 amplitudes were increased during active CVS relative to the pre-CVS recordings for the lower n-back loads. P300 amplitudes also began to respond to n-back Load during CVS, reflecting a shift towards the inverse trends observed within normative samples whereby P300 amplitudes decrease with increased n-back Load. The P300 was also quicker to peak and was accompanied by shorter RTs during CVS. However, as with the CANTAB measures of attention and memory, participant 08's accuracy scores on the n-back remained stable during CVS. The high level of performance during the baseline period may have limited this participant's potential for CVS-related behavioural improvements.

Table 4.18

Summary of CVS-Related ERP Effects within Each Dependent Variable.

Participant	P300 amplitude (μV)	P300 latency (ms)	Accuracy	RT (ms)
01	Load effects introduced during CVS. Highest amplitude during baseline 2.	Main effect of Load (shorter for higher loads).	Improved during active CVS on the 2 and 3-back.	Main effect of Load (longer for higher loads).
02	Overall amplitudes were larger during CVS. Amplitudes were decreased between the 0 and 2-back.	Longer to peak at the recording taken after 8 weeks CVS.	Accuracy declined with increasing Load in both Stimulation conditions.	Shorter on the 3-back during active CVS.
03	Highest during baseline recording.	Shortest to peak after 4 weeks CVS.	Poor performance on 3-back throughout the study, particularly after CVS (else stable).	Shorter for 1 and 3-back during CVS, but slower for 2-back during CVS.
05	No effects driven by CVS.	No effects driven by CVS.	Fluctuated across study, not driven by CVS.	Longer RTs for lower n-back loads.
06	No effects driven by CVS.	No effects driven by CVS.	No effects driven by CVS.	Shorter during CVS for the 2-back (3-back began at sham).
07	Reduced amplitudes on the 0-back after eight weeks CVS.	Shortest to peak after 4 weeks CVS.	No effects driven by CVS.	Longer RTs for higher n-back loads.
08	Larger amplitudes for 0 and 1-back during active CVS. Load effects present during active CVS only.	Overall shorter during active CVS.	Main effect of Load (less accurate for higher loads)	Shorter during active CVS during both sessions.

Note. Blue (decrease) and red (increase) fonts are used to highlight results where the hypothesised trends were present. Effects refer to a generalised change unless particular loads or sessions are specified.

Group Effects.

To further assimilate and simplify the multiple electrophysiological results presented above, group effects were again briefly explored using the Friedman test. Analyses focused on exploring whether a group based change had occurred across the four sessions described above (baseline one, baseline two/ sham stimulation, four weeks CVS, eight weeks CVS). Five tests were run to explore each power band as well as the amplitude and latency of the P300 (see Table 4.19). To attempt to reduce some of the variability amongst participants (while preserving the nature of the data), segments were normalised before being entered into the analysis. A grand mean and standard deviation were first produced for each participant for each of the five dependent variables (across all four sessions) and each segment was then normalised using the formula $Z= \frac{X-\mu}{\sigma}$, Friedman tests were then computed using these *z*-scores.

Table 4.19
Group analysis of electrophysiological responses to CVS.

Electrophysiological Measure	*N*	χ^2	*p*
Delta (μV^2)	8	2.55	.47
Theta (μV^2)	8	0.6	.90
Alpha (μV^2)	8	9.0	.03
P300 Amplitude (μV)	6	0.6	.90
P300 Latency (ms)	6	5.0	.17

Note. df= 3. Participants 04 and 06 are excluded from the ERP analyses since they did not provide data for every session.

Table 4.19 shows that only the alpha band appeared to change in response to the protocol across the group, $\chi^2(3) = 9.0$, $p<.05$. Descriptive statistics suggest that the decline in alpha power from the baseline onwards may have driven the effect (see Figure 4.18). However, post-hoc testing with Bonferroni corrected ($p<0.008$) Wilcoxon signed-rank tests revealed no significant differences between individual sessions (all *z*s >-2.52; all *p*s> .012). In line with the individualised analyses above, these group effects suggest that the alpha band

may be most susceptible to electrophysiological modulation following CVS, while the P300 ERP measures for the n-back appeared to be unaffected by CVS at the individual and group-level.

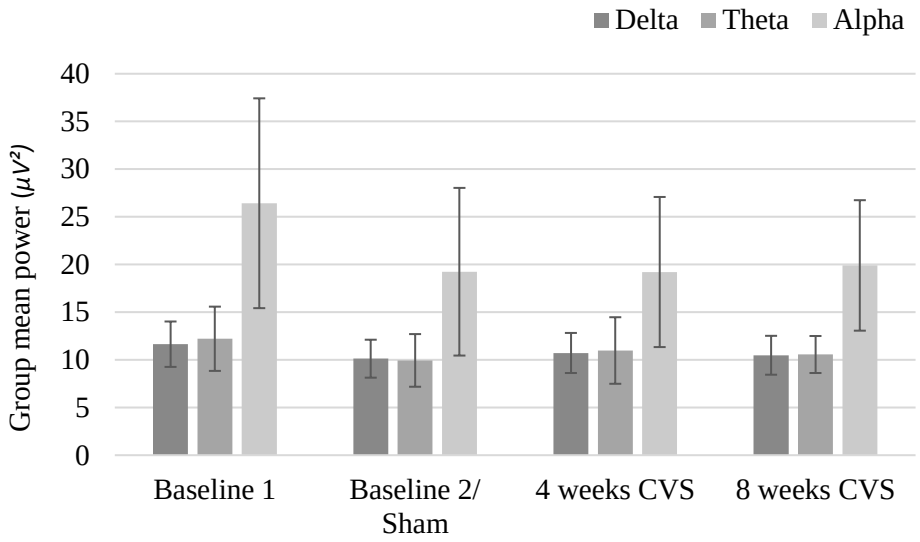


Figure 4.18. Group averages for each power band based upon the *z*-score filtered segments from each participant.

Explanation of Effects and Future Directions

EEG power. Although individualised, all of the participants showed statistically significant alterations in at least one power band in response to CVS, across more than one region. Overall these changes in spectral power are suggestive of broad-scale modulation (Wilkinson et al., 2012) and fit with the idea that CVS can elicit widespread changes in blood flow to a range of cortical and subcortical structures (Lopez et al., 2012). Importantly, four participants showed a reduction in either delta or theta power during active CVS which could reflect an emergence from the slow-wave dominance that has been found to characterise the EEG of TBI-survivors. These findings may have resulted from a CVS-related increase in brain activity at the subcortical nuclei that supply the reticular activating system, which helps to regulate arousal (Bense, 2001; Vanzan et al., 2016). It could be argued that as participants potentially became more aroused/ wakeful in response to CVS, EEG power within the delta

and theta bands (typically associated with sleep and drowsiness) was in turn decreased. Such an effect is likely to be beneficial since elevated levels of delta and theta power have been associated with more severe neurological injuries, diminished levels of awareness and poorer functional outcomes (Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Martin & Dominguez-Morales, 2008; Leon-Carrion et al., 2009).

Similar to previous literature the results were however variable and support for the hypothesis tended to arise from isolated effects as opposed to consistent trends within an individual or across the group. For example, Rapp et al. (2015) reviewed 25 studies of spectral power in TBI samples and found that although differential power was strongly indicated following TBI, the effects were inconsistent. These discrepancies have been attributed to the heterogeneity of TBI implying that the diversity of the small sample recruited here, combined with the exploratory nature of the study and the number of statistical tests that were run, could have limited the identification of electrophysiological commonalities (and potentially increased the risk of false positives).

Activity within the alpha band was particularly variable during visual inspection of the online recording and following offline analysis where it reached much greater magnitudes than the other bands in several participants (see Figures 4.9, 4.12, 4.13, 4.14). Recall that in the healthy brain alpha activity has been associated with wakefulness and cognitive processing, while in TBI-survivors alpha power is often reduced (Rapp et al., 2015; Thatcher, Walker, Gerson & Geisler, 1989). It was therefore predicted that CVS would boost faster-wave alpha activity, which contrasts with the decreases that were observed for over half of the sample (see Table 4.17). Unexpectedly, large amounts of alpha activity were however already present within four of the participants (03, 05, 06, 07) during the pre-CVS recordings which could have reduced the relevance of this normalisation hypothesis. Alternative explanations for the observed decreases in alpha power will thus be considered.

Fluctuations in alpha power have previously been related to increased fatigue (Boksem, Meijman, & Lorist, 2005; Mathewson et al., 2015). Several studies have examined spectral changes as healthy participants move from an alert to fatigued state, a review of 17 such studies showed that alpha wave activity was significantly increased (in 15 studies) as a person tired (Craig et al., 2012). Alpha activity has also been suggested to represent a cortical idling rhythm which results in a slowing of brain activity and reduced cognitive capacity (Craig et al., 2012; Simon et al., 2011). Consequently, if the current sample showed abnormally high levels of alpha activity (relative to the healthy topography) at baseline, then one could explain the current findings of reduced alpha power following CVS as a reflection of improved alertness. The severe levels of fatigue and sleepiness that were self-reported by participants (throughout the study) support the idea that alpha activity may have been elevated and that a decline could reflect a beneficial shift from alpha-related drowsiness.

Changes in alpha power can also be associated with mood and affective processing, particularly when they occur over the frontal electrodes (Mathewson et al., 2015; Thornton, 2003). Resting alpha activity in patients with active depression (Knott, Mahoney, Kennedy & Evans, 2001) as well as anxiety disorders (Cho et al., 2011) has often been heightened when compared with healthy controls. This has led several authors to suggest that while alpha activity is typically associated with a relaxed comfortable state, if activity becomes elevated amongst psychiatric samples it can reflect a hyper-vigilant state with emotional instability (Enoch et al., 1995). Since nearly all of the participants suffered from psychiatric symptoms, alpha activity may have been increased relative to normative topographies during the pre-CVS recordings (as opposed to the slow-wave dominance that was predicted), meaning the observed declines in alpha power could be positive.

To test these predictions it would now be useful to monitor participants' perceptions of their psychiatric, fatigue and sleepiness symptoms on the day of the EEG recording as well

as at the behavioural assessment meetings (this was not routinely completed in this study due to time constraints). In the present study, scores on these questionnaires did not appear to respond to CVS, however further changes might be revealed once the electrophysiological and behavioural outcomes are more closely linked. Future research could also conduct more specific investigations into these symptoms by adopting alternative neuro-analysis methods (e.g. Asymmetry Analyses for mood- Wheeler, Davidson & Tomarken, 1993; Power Ratio Index to assess shifts from alert to fatigued states- Nagata, Tagawa, Hiroi, Shishido & Uemura, 1989).

ERP. Only participant 08 showed a consistent pattern of results which could support the hypothesis (increased P300 amplitudes and reduced P300 latencies following CVS). For the remainder of the sample, significant effects tended to be limited (e.g. to one session, one n-back load) and commonalties were therefore hard to come by.

The modality of the ERPs studied and the choice of eliciting task could have reduced the presence of CVS-related effects. Because the vestibular system is known to contribute to visuospatial memory and navigation (Hitier et al., 2014), this study focused on visual ERPs and assessed working memory using an n-back task. However, other ERP paradigms are available where the effects of TBI have been better characterised (Dockree & Robertson, 2011). For example, auditory ERPs were more often studied and consistently found to be abnormal than visual ERPS (potentially because the auditory sense is more vulnerable to trauma); there is also a paucity of n-back EEG studies relative to other oddball tasks (e.g. words and pseudo words, standard and deviant tones) (Duncan et al., 2005). Since the current paradigm is relatively novel and the robustness of the associated ERP effects in TBI samples remain unknown, this could explain why few n-back responses were normalised by CVS in this study.

Assumptions of Normality

Given the aforementioned variability and deviance from the hypotheses, it is plausible that some of the participants sampled here could have displayed patterns of EEG and ERP activity at baseline that either resembled the healthy topography or diverged from the abnormalities commonly found within TBI samples (e.g. slow-wave dominance, reduced P300 amplitudes, increased P300 latencies). If their baseline pattern of brain activity tended to reflect that of healthy samples or did not contain the predicted abnormalities, then this could potentially explain why the hypothesised effects were largely absent from this study (i.e. the abnormalities were not there to be normalised). In line with this idea, those, participants who had sustained a severe TBI (02, 04, 05, 08) tended to show more changes in spectral power than those with a moderately severe TBI (01, 03, 07). Participants 02 and 08 (severe TBI) also showed more alterations on the ERP measures (two and three outcome measures respectively) than the remainder of the sample, potentially because there were more anomalies to be normalised.

Research has also shown that spectral power (Haneef et al., 2013) and ERP (Keren et al., 1998; Onofrj et al., 1991) abnormalities are more likely to occur closer to the time of injury. As most of the current sample were in a chronic rather than acute stage of recovery (average time since injury was 2.5 years), normalisation could have already begun. Nonetheless, several researchers have demonstrated atypical electrophysiological activity that persist years after the injury (Koufen & Dichgans, 1987; Ledwidge & Molfese, 2016), particularly when the TBI was moderate or severe, indicating that abnormalities could still have been prevalent within the sample (Haneef et al., 2013).

To gain a better understanding of whether the anticipated electrophysiological abnormalities are present at baseline (and thus could potentially be modified), future studies would benefit from including a closely-matched control (e.g. gender, age, IQ, medical

history, ongoing medications) for each participant to ascertain what a healthy topography/ ERP response might look like. If the TBI participant shows the predicted pattern of abnormalities relative to the control, then this would provide substantial precedents to investigate the hypothesised effects. Conversely, if the abnormalities were absent (e.g. no reduced P300 amplitudes or extended P300 latencies), then this might indicate re-examination of the hypotheses and could also help to explain the lack of CVS-related effects in the current study.

However, some researchers have advised caution regarding the utility of healthy control samples in EEG research (Boutrous, 2013). This is because EEG abnormalities (e.g. positive spikes, small sharp spikes) are also prevalent within healthy adult populations (Jabbari et al., 2000) and can hamper inferences about what can be considered a 'normal EEG' (Struve, 1985). Thus while these matched-control studies would be worthwhile, clear rigorous inclusion criteria would be needed to ensure meaningful comparisons (Nuwer, 2005; Boutrous, 2013).

Chapters 3 & 4 Discussion

Overview

Key outcomes. These chapters aimed to investigate vestibular contributions to higher level functions, particularly memory, by artificially stimulating the vestibular system. A cohort of TBI participants with neuropsychiatric deficits were selected to determine whether the cognitive, psychiatric and fatigue impairments that were observed in vestibular patients during Chapter 2 could be remediated in this symptomatic group using CVS. Convergent group-based trends were not present within this heterogeneous sample. However, several individualised effects emerged which could offer some tentative support for the hypothesis. The following sections will review these effects and explore the potential influences that CVS might have on neuropsychiatric deficit.

Secondary outcomes. The safety and tolerability of CVS was evidenced by the lack of side-effects or adverse events reported by participants, as well as the absence of any negative changes in mood, headache or fatigue. Treatment compliance was also very good in six of the eight participants who completed stimulation sessions as instructed and enjoyed following the schedule. Based on the researcher's experience with participant 05, future studies should consider excluding patients whose litigation status is ongoing (see Appendix B) since there may be a conflict between engaging in a treatment which could potentially improve their symptoms, while wanting to maintain their current profile of impairment before reaching a financial settlement (Feinstein et al., 2001). Overall the findings suggest that given adequate support, patients with severe neurological damage could complete a lengthy CVS protocol with reasonable compliance.

Explanation of Effects

Table 4.20 provides a profile of change for each participant by listing any behavioural and/ or electrophysiological measures which showed a beneficial response to CVS after four or eight weeks of stimulation.

Table 4.20
Summary of Key Outcome Measures with CVS-Related Benefits.

Participant	Behavioural	EEG	ERP
01	SSP, OTS and RTI	None	Accuracy
02	SWM_E, SWM_S, OTS	Delta, theta	P300 amplitude, RTs
03	RTI, RVP_hits	Delta, alpha	P300 latency
04	SWM_E	Alpha	N/A
05	PAL	Delta, theta	None
06	RVP_hits	Delta, theta	RTs
07	None	None	P300 latency
08	OTS, EQ-5D (%)	None	P300 amplitude, P300 latency, RTs

Note. Behavioural improvements on the CANTAB as identified by inferential statistics. No ERP data was gathered for participant 04.

Participant 02 displayed perhaps the most consistent response to the stimulation whereby he became more efficient on the SWM test (both strategy and errors) after eight weeks CVS and also showed increased P300 amplitudes during the active CVS recordings

relative to the pre-CVS recordings. Together these data suggest a potential CVS-related improvement in working memory. Delta and theta activity were also reduced indicating his overall neural profile may have been enhanced. Participants 04 and 05 likewise showed evidence of a CVS-related memory improvement, however these effects were only present on a single outcome measure (04: SWM_E; 05: PAL) so were less robust. Nevertheless, both participants demonstrated a beneficial change in EEG power which could indicate a return towards the background activity that characterises the healthy adult EEG.

Other cognitive benefits were seen in participants 03 and 06 where CVS appeared to selectively improve attention and information processing. Both participants were able to identify more targets on the RVP following CVS (RVP_hits) and each showed shorter RTs on a single outcome measure (03: RTI; 06: n-back). These individuals also displayed a reduction in slower-wave EEG activity, suggesting CVS may have boosted arousal and in turn facilitated attention and information processing.

CVS appeared to have a more diverse effect within participant 01. Although any CVS-related improvements appeared to be restricted to the behavioural measures, these were not limited to a single cognitive process and included information processing, working memory and problem solving abilities. Participant 08 also showed enhanced memory, attention and problem solving performance following CVS according to the ERP measures and the OTS. CVS did not appear to influence the cognitive performance of participant 07 who had sustained his TBI most recently.

Taken together, these findings offer some preliminary evidence of cognitive modulation in response to CVS. The effects included, but were not limited to memory processes, as several participants displayed altered attention, information processing and problem solving abilities on the CANTAB. In line with the findings from Chapter 2, where

CVS had elicited memory-related improvements these were more likely to relate to tests with a spatial focus (i.e. PAL, SWM) than those with a more pattern-based focus (i.e. DMS), therefore emphasising the relevance of vestibular signals for spatial representations of external space (Hitier et al., 2014). Beneficial changes in spectral power also accompanied the behavioural effects of five participants, indicating CVS induction might exert a broader influence on participants' neurological state which could reflect a shift towards a more favourable functional outcome (Leon-Carrion et al., 2009). The fact that concurrent ERP changes on the n-back working memory task were absent suggests that any CVS-related effects on brain activity were likely to have been diffuse rather than restricted to networks associated with the particular cognitive processes elicited by the n-back task. Nevertheless, the behavioural effects above suggest that specific visuospatial memory processes could still benefit from a potential broad scale effects of CVS.

Unfortunately, the experimental design that was needed to test the main study hypotheses did not make it easy to also investigate whether the changes in spectral power and cognitive performance reported above were associated at the group-level. This is because additional behavioural assessments (three baselines plus three or four further assessments) were completed which did not overlap with the EEG assessments (four completed). In addition, not all participants completed the sham phase of the protocol, resulting in an uneven number of data points. Regardless, since none of the Bonferroni corrected post-hoc tests showed a significant group effect of CVS (i.e. a post-hoc test where active CVS sessions were significantly different from others) in the behavioural or the electrophysiological data, investigations of any underlying association did not seem justified.

All of the above occurred in the absence of concurrent alterations in mood, fatigue or sleep suggesting vestibular signals are able to exert a direct effect on cognition that is not dependent on comorbid symptomology (Hanes & McCollum, 2006). However, since

convergent support for the hypothesis was not present within an individual participant (i.e. across most outcome measures/ all sessions), a particular outcome domain (i.e. particular assessments in multiple participants), or within group analyses, these effects of CVS are clearly dependant on a number of uncontrollable factors. Subsequent sections will explore why some of the hypothesised effects might have been absent from the current study.

Vestibular stimulation. As beneficial effects of CVS have previously been observed within the acquired brain injury population (see introduction sections of Chapters 3 and 4), some improvements in TBI symptomology were expected. Importantly, variations in terms of the stimulation parameters as well as the participant sample renders the direct comparison of the aforementioned vestibular stimulation studies with the current findings difficult (Lopez et al., 2012). This is because the various stimulation modalities (CVS, GVS, motion simulators) differ in terms of the vestibular receptors that they stimulate, the activation patterns they produce and the corresponding sensations experienced by participants, all of which could contribute to the variability between studies (Palla & Lenggenhager, 2014). Perhaps further beneficial changes could be elicited (in experimental rather than home-based settings) by stimulating all vestibular afferents with GVS (rather than just the semi-circular canals) (Fitzparick & Day, 2004), or providing a better approximation of natural movement and vestibular sensations with chair rotations (Aw, Haslwanter, Fetter & Dichgans, 2000).

The diffuse axonal injuries that characterise TBI could also attenuate the effects of vestibular stimulation due to subtle changes in the neural mechanisms required for recovery (e.g. inappropriate synaptic plasticity, reduced firing rate of neurons; Pevzner et al., 2016). Moreover, if the TBI had induced a vestibular dysfunction (that was not detected by the researcher or referring clinicians during screening), then the signals elicited by CVS may not have been properly conveyed. Although, it could also be argued that the abnormal metabolic activity induced by TBI is inherently more unstable than healthy brain activity (due to

cortical reorganisation) and might thus be more susceptible to external modulators such as vestibular stimulation (YouRong, Veeravagu & Grant, 2016). Accordingly, a growing body of literature has shown that the behavioural effects of CVS are often larger in clinical than normative samples (Gurvich et al., 2013; Mast, Merfeld & Kosslyn, 2006; Miller & Ngo, 2007; Preuss et al., 2014).

Variability within TBI. Another factor which is likely to influence responsiveness to CVS is the heterogeneity of TBI. Variations in demographics, co-existing treatments, injury profile, stage of recovery, ongoing litigation and symptomology have all been shown to impact responsiveness to TBI interventions (Belanger, Curtiss, Demery, Lebowitz & Vanderploeg, 2005; Boutros, 2014). This study sought to provide preliminary evidence that CVS could improve the neuropsychiatric symptoms of TBI. Although some inconsistencies were expected, the compensatory responses to brain trauma that have been described across multiple clinical conditions were thought to equip CVS to tackle the diversity of TBI (Wilkinson et al., 2013).

While the widespread activations elicited by CVS lends itself to address the heterogeneity of TBI, the current protocol may have been less effective at addressing this variability and hence could have prevented further beneficial effects of CVS from being uncovered. Previous research has shown that although several psychological interventions have relieved TBI symptomology over and above no treatment, this evidence is often limited to particular patient sub-groups (Snell, Surgenor, Jean, Hay-Smith & Siegert, 2009). Snell et al. (2009) suggest that research with larger TBI samples should first establish the factors that are associated with responsiveness to an intervention. Targeted sub-groups who match this criteria could then be selected for more efficient use of different treatment resources. Alternatively, patients could also be selected on the basis of specific symptoms (e.g. short-term memory impairment according to Weschler Memory Scale; Weschler, 1987) to ensure

that a homogenous deficit is present and sufficient enough to be targeted and treated (Saatman et al., 2008). In contrast, this study applied a broad set of inclusion criteria to a small sample. On the one hand this may have contributed to the variable behavioural and electrophysiological findings, potentially masking relevant treatment-effects. However, the criteria also eased recruitment over a short period of time and helped to ensure that the findings would generalise to a variety of TBI participants.

Conclusion

The study outcomes tentatively support the idea that CVS can modulate memory, cognition and resting background brain activity following TBI. Several scores on the CANTAB (particularly visuospatial memory tests) were highest during active CVS, and nearly all participants showed an improvement on at least one cognitive test during CVS according to inferential statistics. Most participants showed a decrease in power in at least one band during blocks of active CVS (delta: four, theta: three, alpha: five participants) but ERP measures were largely unaffected. The above changes occurred in the absence of concurrent alterations to psychiatric and fatigue/ sleep symptomology on the questionnaire measures, providing further evidence that vestibular signals could be directly relevant for cognitive functioning.

CVS was well-tolerated by the sample and was feasible to implement within patients' homes. However, since the current results were variable, further research is still required before it can be recommended as a treatment for TBI. Both larger-scale controlled trials and smaller case-studies would be informative in determining the utility of CVS in the management of TBI symptomology. The former could better asses the effectiveness of the intervention by assigning a larger sample of participants to an active or sham treatment, and then identifying the factors that are associated with responsiveness to the intervention (e.g.

injury profile, chronicity). The latter could examine specific symptoms (e.g. working memory impairment) in well-characterised patient groups to establish worthwhile treatment targets. Given that TBI is prevalent and induces wide-ranging, long-lasting consequences, for which effective treatments are still lacking (Comper, Bisschop, Carnide & Tricco, 2005, further investigations into alternative treatments such as CVS certainly seem worthwhile.

Chapter 5
Vestibular-Memory Interactions in Neuro-Typical Individuals.

The previous chapters provided evidence of an interaction between vestibular function and short-term visual memory in individuals with neurological abnormalities. Chapter 2 showed a significant negative association between vestibular dysfunction (measured using a balance platform) and visuospatial memory performance, while chapters three and four demonstrated altered visual memory following repeated sessions of CVS in some individuals with TBI. Importantly, none of these findings were directly dependent on comorbid psychiatric and fatigue symptoms. Having now identified aspects of memory affected by vestibular input, the question now arises of how in psychological terms, this occurs? One possibility is that vestibular activations lead to a generic arousal that affects many cognitive processes, including visual memory. Another possibility is that visual memory is configured to make unique and specific use of the vestibular signal. This chapter will explore these two possibilities.

This introduction will first review parts of the multisensory literature which show visual memory enhancement, with the aim of identifying suitable paradigms to explore how vestibular signals affect memory. Next it will recap findings relating to the impact of artificial vestibular stimulation on memory and will consider what knowledge gaps remain about the psychological mechanisms that might account for these effects. Finally, the experimental paradigm implemented in the current experiment will be introduced and the hypotheses presented.

Crossmodal Interactions in Visual Memory

Human brains form a complete perception of the environment by integrating information from multiple sensory modalities (Meylan & Murray, 2007). Experiencing an event in a multisensory context is thought to enrich the ongoing sensory experience, as well

as influence how subsequent incoming sensory stimuli are later processed (see Figure 5.1A & B). More specifically, when stimuli are encoded within a multisensory context, associations are produced between the different modalities so that the sensory brain regions involved during the encoding of a multisensory experience are later re-engaged at retrieval, even when recalled through a single sensory modality (Gottfried, Smith, Rugg, & Dolan, 2004; von Kriegstein & Giraud, 2006; Nyberg, Habib, McIntosh, & Tulving, 2000).

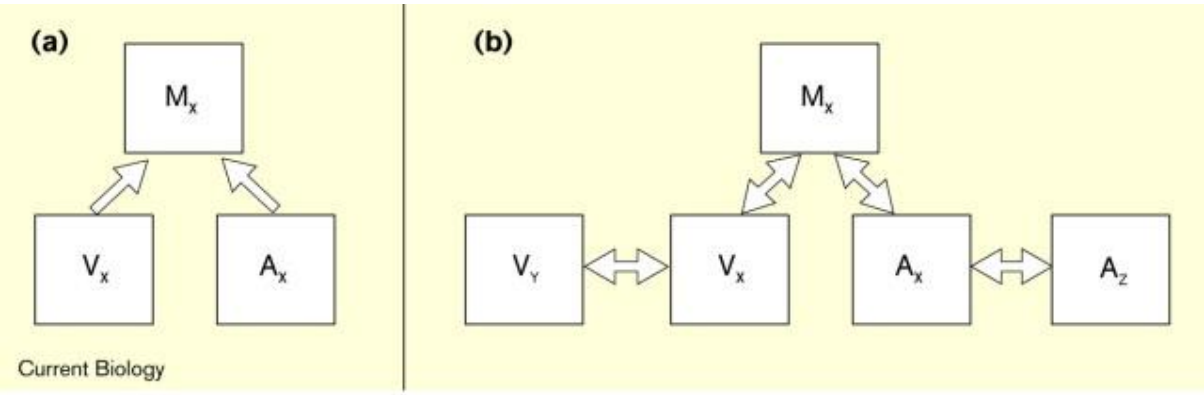


Figure 5.1. Schematic representation of multisensory interactions, taken from Driver and Spence (2000). Figure (a) illustrates how information from different sensory modalities such as audition (Ax) and vision (Vx) might converge to provide information about the same external property (x) and in turn generate a multimodal representation (Mx). Figure (b) depicts the idea that multimodal representations may feedback to influence unimodal representations (vertical arrows). The horizontal arrows show that crossmodal connections concerning one stimulus property (x) could also affect how incoming unimodal information is encoded (y or z).

Some researchers have suggested that these neurophysiological changes may support the theory of 'reintegration' (Hamilton, 1859), which suggests that a whole memory can be reinstated by a partial constituent of the former encoded representation (Blomberg, 2013; Shams & Seitz, 2008; Thelen & Murray, 2013). In line with this idea, recent evidence has demonstrated that crossmodal cortical changes can be triggered in response to the recall of a unisensory stimulus even after very brief multisensory experiences (see Murray & Sperdin, 2010; Shams, Wozny, Kim, & Seitz, 2011 for reviews). Of most relevance to this thesis, several behavioural studies have shown that the retrieval of unisensory visual memories can be enhanced if encoded in a crossmodal context, relative to stimuli learnt in a visual-only

context (Goolkasian & Foos, 2005; Guo & Guo, 2005; Lehmann & Murray, 2005; Shams & Seitz, 2008; Thompson & Pavioi, 1994).

Investigations into the reintegration of memories in humans have tended to explore interactions between the visual, auditory and tactile senses using experimental paradigms which briefly present computerised stimuli such as object drawings, pure tones, and somatosensory vibrations. For example, Murray and colleagues (Lehmann & Murray, 2005; Murray et al., 2004; Murray & Sperdin, 2010; Thelen & Murray, 2013; Thelen, Matusz & Murray, 2014; Thelen, Talsma & Murray, 2015) previously used a continuous recognition task to present visual stimuli either unimodally or alongside auditory or tactile stimuli. Participants then had to recall whether a visual stimulus was either novel or had previously been seen during the trial block. Across several experiments the authors identified improved memory performance for stimuli encoded in a crossmodal pairing, especially when these stimuli were semantically congruent. These effects continued to emerge despite the fact that the crossmodal pairing was only present during a single-trial and was irrelevant to the task (Thelen et al., 2014). Moreover, these single-trial crossmodal memories activated differential brain networks which were associated with improved unisensory recall (Thelen & Murray, 2013), indicating even brief exposures to a crossmodal context can have a robust impact on later unisensory processing (Thelen et al., 2015).

The Case for a Vestibular-Visual Memory Interaction

Multisensory interactions between visual inputs and a "sixth vestibular sense" (Golberg., 2012) have not yet been studied in relation to memory. This is surprising since vestibular signals in the central nervous system immediately become multimodal and continuously converge with other sensory (mainly visual, proprioceptive) and motor inputs (Angelaki & Cullen, 2008). Moreover, anatomical and physiological evidence already gives us good reason to believe that vestibular signals may make a significant contribution to

memory. Recall that several of the key vestibulo-cortical pathways that have been hypothesised involve the transmission of spatial information for orienting and remembering environments (Hitier et al., 2014). In line with these proposed networks, numerous studies have demonstrated impaired spatial memory and navigation abilities amongst humans and animals with vestibular dysfunction (see Brandt et al., 2017; Smith et al., 2010; Smith & Zheng, 2013; Smith, 2016 for reviews). Taken together, these findings coupled with those reported in previous chapters, indicate that investigations into the crossmodal interactions between visual and vestibular senses might also be worthwhile. This chapter aimed to examine the influence of a crossmodal visual-vestibular encoding context on successive visual memory recall in healthy participants using a similar approach to the multisensory literature discussed above.

Artificial Vestibular Stimulation and Memory

Vestibular stimulation permits targeted activation of the vestibular receptors (albeit in a different manner from natural vestibular stimulation; Lopez et al., 2012), which enables vestibular-cognitive effects to be experimentally studied under conditions that approximate the crossmodal paradigms described above (Fitzpatrick & Day, 2004; Utz et al., 2010). Although these paradigms have yet to include vestibular stimuli, a handful of studies have already provided suggestive evidence that artificially stimulating the vestibular system can facilitate memory within healthy participants (see also Ghahraman et al., 2016 for animal evidence).

Bächtold et al. (2001) first found that the locations of objects were recalled more quickly after unilateral left ear stimulation using cold water, while a second experiment facilitated verbal memory recall for visually presented words after right ear stimulation. The authors concluded that unilateral CVS had enhanced the functioning of the contralateral cerebral structures and the specific cognitive processes associated with them. Wilkinson et al.

(2008) later applied small sub-sensory GVS currents (below the threshold of inducing distracting reflexes) to participants whilst they learnt the names of several faces. Once again RTs were facilitated, but the effects were dependent on the stimulation configuration. Participants who received anodal and cathodal stochastic (noise-enhanced) GVS applied to the left and right vestibular nerves respectively later recalled details about the faces more quickly than those who had received either the opposite configuration or sham stimulation. More recently, Ghaheri et al. (2014) provided further evidence of vestibular-induced memory enhancements when their intervention group showed improved re-test performance on the Corsi block task (Kessels et al., 2000) after receiving sub-threshold bipolar GVS, relative to a control group who received sham stimulation.

Psychological Mechanisms

The preceding discussion along with other data presented in this thesis show that vestibular signals are implicated in memory. However, the psychological mechanisms which underpin these effects remain poorly understood. Existing research has not yet explored whether vestibular signals aid memory by way of generic enhancement, perhaps by increasing arousal/ attentional focus via a widespread boost in metabolic activity (as proposed by Wilkinson et al., 2008, 2014); or if the effects of vestibular stimulation are instead more specific and direct (Bottini & Gandola, 2015), such that visual memory is sensitive to the nature of the vestibular input with the brain utilising its variability to help differentiate one visual memory from another.

In support of the first explanation, widespread increases in spectral power have been observed in response to GVS which could potentially reflect vestibular induced changes in cortical arousal (Kim et al., 2013; Wilkinson et al., 2012). Further neuroimaging evidence has also revealed that multiple cortical and subcortical regions including the retroinsular cortex, cingulate cortex, sylvian fissure, temporal-parietal cortex and the lateral and medial premotor

cortex are activated by artificial vestibular stimulation (see Lopez et al., 2012 and zu Eulenburg, Caspers, Roski & Eickhoff, 2012 for reviews). Amongst these regions is the reticular activation formation, the brain's core arousal system (Wilkinson et al., 2012). Vestibular stimulation has been shown to boost activity within this structure (Bense et al., 2001) and to elicit beneficial effects in disorders characterised by reduced awareness (Vanzan et al., 2016). More generally, the fact that these projection areas are so widely distributed means that no single cognitive process is likely to be uniquely affected by the vestibular afference. Instead, these activations could induce beneficial metabolic changes which facilitate memory non-specifically through a generalised increase in cognitive arousal and efficiency. In line with this idea, dual-task studies have evidenced a vestibular-cognitive connection whereby postural instability worsened cognitive performance by reducing the availability of attentional capacity limits (see Bigelow & Agrawal, 2015; Hanes & McCollum, 2006; Smith & Zheng, 2013 for reviews). Importantly, these effects were not dependent on the content of the co-occurring mental activity (spatial versus non-spatial) and extended to multiple cognitive processes once attentional resources had been depleted by unsteadiness (Yardley et al., 2001).

On the other hand, clinical evidence from patients with bilateral vestibular dysfunction tends to dispute these generalised effects or at least point out that distinct effects exist too. These individuals have shown a specific impairment to spatial memory that is accompanied by hippocampal atrophy and dissociates from other aspects of memory and general intelligence which remain intact (Brandt et al., 2005; Kremmyda et al., 2016; Shautzer et al., 2003). Thus, at least within some vestibular syndromes, the impact of disturbed or reduced vestibular signalling appears to be relatively limited to specific memory processes of a spatial nature (Smith et al., 2010). One explanation for these findings is that the ever-changing self-motion information contained within vestibular signals is particularly

important for spatial memory since it helps update representations of the individual within 2-D (stationary egocentric mode: up/ down and right/ left) and 3-D environments (mobile allocentric mode: position relative to other objects) (Brandt et al., 2005; Brandt & Dieterich, 2016; Smith et al., 2010).

In keeping with this second explanation, evidence from the multisensory literature also suggests that when multiple senses combine during the encoding of a visual stimulus, the content from these sensory signals is incorporated into the unimodal visual memory representation (Laurienti, Kraft, Maldjian, Burdette & Wallace, 2004). For example, Lehman & Murray (2005) demonstrated that encoding object images (e.g. image of a dog) with sounds only improved visual recall when the crossmodal input was semantically congruent (e.g. dog bark), relative to purely episodic (auditory tone), and semantically incongruent sounds (e.g. bell chimes). This suggests that the effect was being driven by the particular content of the auditory signal rather than generalised arousal induced by hearing the sound.

It could be argued that the content of vestibular inputs is likely to be especially relevant to visual memory processes since vestibular inputs are "always on" (i.e. the vestibular labyrinths constantly fire even when the head is not moving) (Day & Fitzpatrick, 2005; Highstein, 2004). These vestibular signals provide valuable self-motion information about the constant changes in body, head and eye position which could be integrated with other sensory inputs and used as a baseline reference to enable accurate and synchronised motor and cognitive actions (Angelaki & Cullen, 2008; Goldberg, 2012; Smith et al., 2010). More specifically, the self-motion content of these vestibular signals could be incorporated into visual memory representations to help individuate one memory from another, and in turn enhance unimodal visual processing. This idea is based on the fact that the encoding of each visual event is invariably associated with a unique vestibular signal; at any one moment in time, the movement and position of the head is slightly different from the last. One possibility

is that the visual system uses this unique, coincident information to help individuate one visual memory from the next. If shown to be the case, then the results will provide one theoretical account of how memory exploits vestibular signals.

The experiments reported in this chapter aimed to characterise the relationship between the visual and vestibular modalities by examining whether visual stimuli encoded at the same time as vestibular signals were recalled faster or more accurately than stimuli encoded only visually. To be clear, this research attempts to advance upon the findings of Bächtold et al. (2001), Dilda et al. (2012), Ghaheri et al. (2014) and Wilkinson et al. (2008) which appeared to argue against a generalised enhancement effect on cognition by showing that vestibular effects on memory were dependent on the side of stimulation (i.e. activation of a particular hemisphere/ specific brain structures involved in cognitive processing) and particular types of vestibular activity (i.e. integration of different afferent signals) being delivered (Bottini & Gandola, 2015). However, since these studies were not designed to provide mechanistic inferences and do not dissociate hemispheric arousal from a process-specific account, further investigations would now be useful to explore whether vestibular signals affect visual memory via a non-specific enhancement or through similar crossmodal mechanisms to the other sensory modalities where temporally coincident auditory and tactile inputs have enhanced visual memory performance. Examining the influence of vestibular stimulation on visual memory is relevant since it could (i) provide a mechanistic account of the role of the vestibular system in human memory; (ii) improve understanding about the experimental conditions necessary for visual memory enhancement and (iii) inform therapeutic techniques in patients with amnesia.

The following sections will describe the methods and results of four experiments which paired the onset of to-be-remembered visual stimuli with a temporally coincident GVS signal. The results provide preliminary evidence that pairing a single visual stimulus with a

unique GVS signal can facilitate its recall and therefore support a more specific versus generic arousal-based account of vestibular-memory interactions.

Experiment 1: Is Recall Improved for Visual Stimuli Paired With a GVS Signal?

Experiment 1 adapted the spatial memory task that was applied by Bätchtold et al. (2001) to attempt to reproduce and extend the finding of improved visual recall during vestibular stimulation. Participants were required to learn the identity and location (left or right side of the screen) of a set of objects during an encoding phase (whilst receiving vestibular stimulation), and then to recall these objects and locations when they were presented only visually (recall phase). To advance upon this study and address how coincident vestibular signals might influence memory recall, brief pulses of sub-sensory GVS were paired with the onset of to-be-remembered visual stimuli (object images). Crucially, the mapping between visual and vestibular stimuli was altered across three experimental conditions so that a vestibular signal accompanied either one object location (unilateral); two object locations (bilateral); or no vestibular current was discharged. If visual memory incorporates variations in vestibular content to individuate memories, then recall should be highest in the unilateral condition where the GVS signal is only ever discharged when stimuli appear at a unique to-be-remembered location, compared to the bilateral condition where the GVS signal is not unique and is discharged wherever a visual stimulus appears regardless of its location, and the no-stimulation condition where no vestibular marker is available. If however, vestibular inputs exert a generic impact on memory, then performance on both the unilateral and bilateral conditions will similarly exceed the no-stimulation condition.

The paradigm was designed to produce a perceptual mapping between the visual and vestibular inputs by ensuring that they were delivered close together in time. Although there are several ways to ensure that multisensory inputs are integrated into single representation, temporal proximity seemed a sensible starting point because (i) it is a simple and effective

manipulation of crossmodal integration to implement (Spence, 2011), and (ii) visual processing has previously been facilitated by temporally coincident vestibular stimulation (Wilkinson et al., 2012).

One further element was added to the paradigm to accommodate the dual-process framework of recognition memory, which comprises stages of familiarity ('knowing') and recollection ('remembering') (Mollison & Curran, 2012; van Petten, Senkfor & Newberg, 2000). Thus the recall phase contained an object recognition judgement where participants determined whether a stimulus had been studied previously (familiarity), and as in Bächtold et al.'s (2001) spatial task, a question regarding the location that the object was presented in (recollection). Both elements of recognition were included to coordinate with previous research where crossmodal facilitations of object familiarity have been demonstrated (Lehmann & Murray, 2005), while also recognising the visuospatial role of the vestibular system (Brandt et al., 2005). The paradigm will also offer further insights into the memory processes that are most likely to be affected by vestibular inputs (i.e. familiarity or recollection).

Method (1)

Participants

Participants in this chapter (Experiements 1-4) were recruited from the University of Kent's (UoK) Research Participation Scheme (RPS) which enables students to sign up to research studies for course credit. The cohort is mostly comprised of right-handed females aged 18-30 (68%), 16% of the sample were right-handed males within the same age category.

Forty eight adults from the RPS cohort took part in this hour long experiment. Twenty-four individuals were recruited for a pilot phase of testing which monitored task difficulty and 24 participated in the finalised study protocol. Sample size was determined by the resources allocated to the study and resembled that of Wilkinson et al. (2008). To

minimise any potential side-effects, only participants without a history of vestibular, neurological or hearing disorders were enrolled. The study was approved by the UoK's Ethics Committee.

Stimuli and Apparatus

Two hundred and forty six greyscale photographs depicting everyday objects were obtained from two standardised sets (A Pool of Pairs of Related Objects; Kovalenko, Lyudmyla, Chaumon & Busch, 2012 and the Bank of Standardized Stimuli; Brodeur, Dionne-Dostie, Montreuil & Lepage, 2010). All images were resized to 265^2 pixels and were displayed against a white background.

The experiment was written with E-Prime and presented on a 15inch computer screen positioned in participants' midsagittal plane at eye level. To limit natural vestibular stimulation (the otoliths fire even when motionless as they detect gravitational pull) which could reduce the uniqueness of the GVS signal, a padded chin rest was used to keep participants' head position constant. Free movement was permitted during several allocated breaks to minimise discomfort.

Task difficulty was titrated during several preliminary pilot tests (where no GVS was administered) to produce a stimulus set which could easily be learnt but would avoid reaching ceiling levels. Difficulty was increased by producing three image sets each depicting a single object category (musical instruments, tools, and fruit/ vegetables), presented in greyscale. Each object from the encoding phase was also matched with a semantically and perceptually similar distractor image in the recall phase.

Design

A within-subjects design was used whereby each participant completed three experimental blocks, each consisting of an encoding phase where objects and their associated

locations were learnt while GVS was administered, and a recall phase where participants' memory for the stimuli was tested without stimulation. Each block was assigned a different GVS parameter (unilateral, bilateral, no-stimulation) and a different set of images. A Latin Square was used to counterbalance the order in which the blocks were completed as well as the stimulation condition and visual object category assigned to each block. Participants were informed that they would receive stimulation during some parts of the experiment, but not others.

Procedure

Upon arrival, participants completed a practice trial containing a shortened encoding and recall phase (no GVS administered), before completing three experimental blocks. Breaks were offered at the end of each phase of the experiment. Rests after the encoding phase were set to two minutes to reduce variability in memory processes related to forgetting and rehearsal. Breaks after each recall phase were not timed, participants could rest for as long as they needed.

Encoding phase. Each trial began with a central fixation cross displayed for 3500ms; the object image was then displayed to the left or right of the fixation cross for 800ms (see Figure 5.2). Forty different objects were shown during each encoding phase (in a randomised order) and each was repeated four times. To encourage the formation of visual memories, participants were instructed to pay attention (no responses were required) to the identity of the objects and their position on the screen in preparation for a later memory test.

Recall phase. Participants were presented with the 40 objects that they had just studied during the encoding phase, randomly intermixed with 40 new object photographs. A central fixation cross was first displayed for 2000ms, followed by the object image which was also presented centrally for 800ms. A blank screen then appeared and remained until

participants responded (see Figure 5.2). Responses were collected using three keys on the bottom row of a standard UK keyboard. The three button press indicated whether the image was new to the study ('z'), or had been previously shown on either the left ('x') or right ('c') side of the screen during the encoding phase. Participants were asked to use the index, middle and ring finger of their dominant hand and were encouraged to respond quickly and accurately. The blank screen permitted longer deliberation without altering the maximum exposure to the test image.

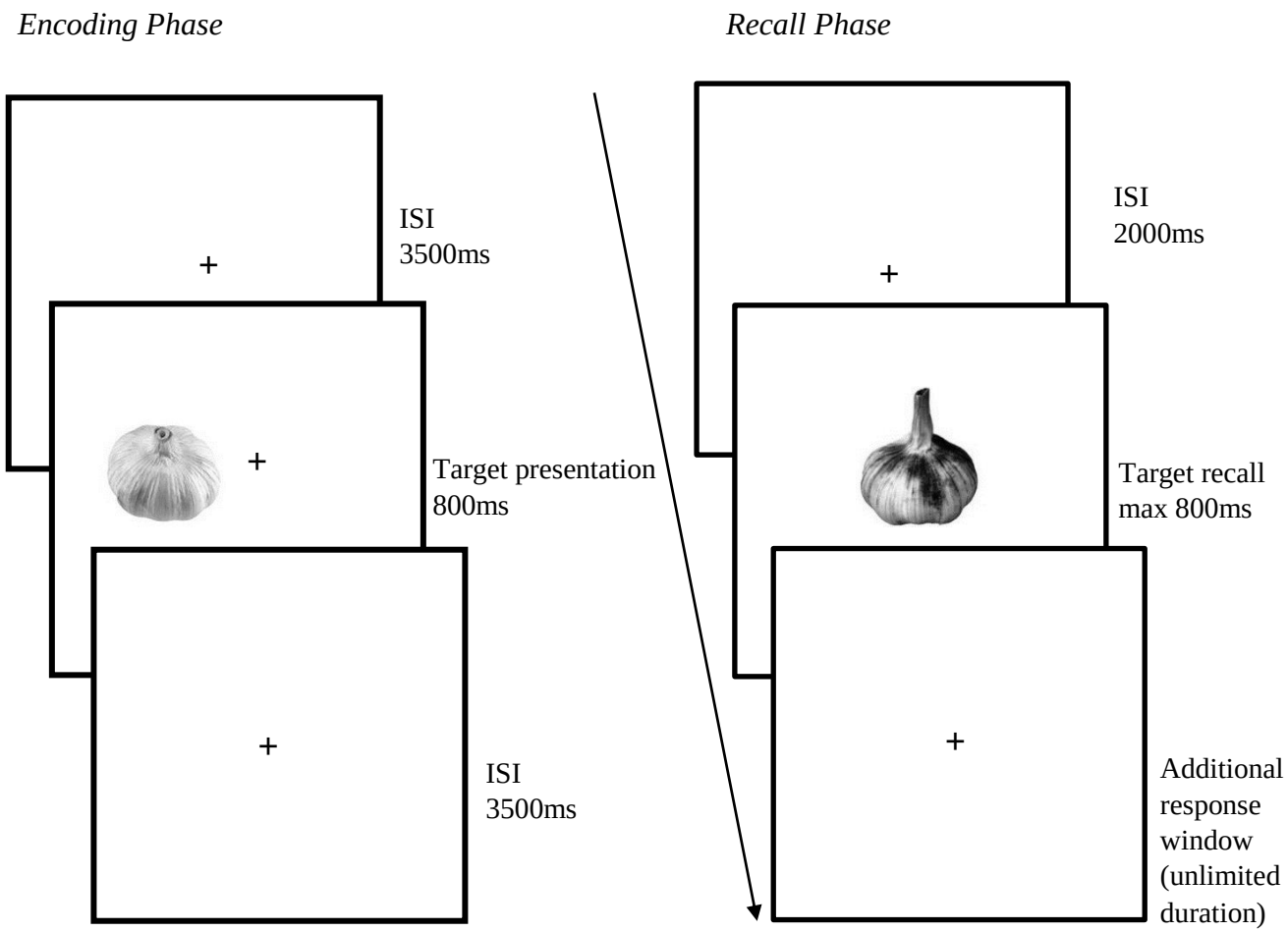


Figure 5.2. Schematic drawing of the encoding and recall phases of the Experiment 1. Participants passively learnt stimuli during the encoding phase and then recalled whether or not the object had previously been viewed and if so, on which side of the screen had it appeared.

Stimulation Protocol

Stimulation was only delivered during the encoding phase and the same stimulation parameters were applied across the unilateral and bilateral conditions. Electrical pulses were triggered by a defined event in E-Prime so that a subset of visual objects could be paired with a coincident GVS signal. Twenty objects (repeated four times) were paired with GVS, meaning 80 pulses were released in each block.

Bilateral bipolar current was delivered through a pair of 5.1 x 10.2cm carbon-rubber, self-adhesive, disposable electrodes (Covidien, Uni-Patch Inc.) placed over the participants' mastoid processes. To ensure efficient electrical contact with the electrodes, the surrounding skin was cleansed with an alcohol wipe then exfoliated with abrasive gel at the beginning of the session. Electrodes were also held in place by an elasticated headband. The electrodes were connected to a neuroConn DC-Stimulator using the configuration of anode (positive) left and cathode (negative) right (as in Wilkinson et al., 2008). During the no-stimulation trial the apparatus remained the same but no currents were discharged.

An electrical current of 0.4mA was chosen after previous studies indicated that this intensity was unlikely to be felt, yet capable of inducing behavioural and electrophysiological changes (Dilda, et al., 2012; Utz et al., 2010; Wilkinson et al., 2012). Nevertheless, Questionnaire (see Appendix D) and verbal responses from participants were gathered at the end of the session to estimate the perceived intensity of the stimulation and the sensations it evoked (see Appendix D). These confirmed that the GVS was well tolerated and subtle. Any participants who noticed an association between a class of visual stimuli (e.g. images of tools when shown on the left of the screen) and a GVS pulse were discounted (N= 3), since their performance could relate to the somatosensory sensation of being stimulated rather than to the vestibular inputs.

Since this experiment reflected a first attempt at synchronising the GVS and visual signals, a conservative ISI (3500ms) and pulse duration (500ms) were selected. These durations ensured that the neuroConn DC- Stimulator could clear the signal and re-check impedance levels before the next pulse was discharged, while enabling the investigation of crossmodal processing by ensuring that the GVS signal accompanied the onset of visual stimuli. Although this limited the total exposure to GVS, previous fMRI research has demonstrated that the neural responses elicited by direct current GVS are greatest at the onset and offset of the signal and tend to decline over the stimulation period (Stephan et al., 2005).

Results (1)

Data Considerations

All results were taken from the recall phase where participants could respond to the objects with one of three options 'x' (left), 'c' (right) and 'z' (new). Data were analysed separately for object and source recognition. To analyse object recognition 'x' and 'c' responses were combined to form a generic old response and 'z' responses corresponded to a new response. Source recognition was computed upon the old objects and analyses examined whether participants could recall whether an object had been shown on the left or right.

Several repeated measures ANOVAs were conducted to compare recall across the three Stimulation conditions (unilateral *versus* bilateral *versus* no-stimulation). Separate ANOVAs were run for source (left *versus* right Location) and object (old *versus* new Object) recall across four dependent variables: accuracy, RT, discrimination (*d*') and criterion (*c*). *d*' is considered to be a bias free measure of an individual's capacity to recognise experimental stimuli which when used in combination with *c*, a measure of response bias, can provide a more precise measure of performance (more detail provided below). The RT analyses are not

presented here (but can be found in Appendix D) since counterbalancing protocols for response hand were not implemented to account for the unconventional three button press.

Where an ANOVA was conducted, all main effects are reported regardless of significance. In keeping with the key aims of the study (and to avoid false positives), only significant main effects or interactions involving the Stimulation variable were followed up with Bonferroni post-hoc tests. A corrective epsilon was not applied to the degrees of freedom (all ANOVA effects remained robust without this). Recall was expected to be facilitated during blocks paired with GVS (unilateral and bilateral conditions), relative to blocks which received no-stimulation across all of the outcome measures. Additionally, if performance was stronger during the unilateral relative to the bilateral condition, then this would suggest that vestibular inputs have a direct and specific influence on visual memories as opposed to inducing a non-specific enhancing effect.

Accuracy

Object recognition. Mean accuracy scores were entered into a 2 (Object) x 3 (Stimulation) ANOVA. A significant main effect of Object [$F(1, 23)= 19.04$, $p<.001$, $\eta_p^2= .99$] revealed that old objects ($M= 0.82$) were recalled more accurately than new objects ($M= 0.62$), suggesting a degree of learning by the participants. The main effect of Stimulation [$F(2, 46)= 1.76$, $p=.18$, $\eta_p^2=.07$] and the two-way interaction [$F(2, 46)= 0.79$, $p=.46$, $\eta_p^2=.03$] were both absent indicating Stimulation had not affected familiarity judgements (see Figure 5.3).

Source recognition. Mean accuracy scores for Source judgements were entered into a 2 (Location) x 3 (Stimulation) ANOVA. A significant main effect of Stimulation [$F(2, 46)= 3.72$, $p<0.05$, $\eta_p^2=.14$] emerged such that accuracy was reduced in the bilateral condition (see Figure 5.3). Post-hoc comparisons completed to investigate this main effect revealed a

marginally significant difference between the bilateral (*M*= 0.63) and no-stimulation (*M*= 0.69) conditions only, *t*(23)= -2.52, *p*= .06 (all other *p*s>.14). A significant main effect of Location [*F*(1, 23)= 4.31, *p*<0.05, η_p^2=.05] also showed that accuracy was improved for objects shown on the right (*M*= 0.69) relative to the left (*M*= 0.65) of the screen. The two-way interaction failed to reach significance [*F*(2, 46)= 0.86, *p*=.43, η_p^2 =.04]. Contrary to the hypothesis, these effects suggest that source accuracy was not improved by the presence of the GVS signals over and above the no-stimulation condition.

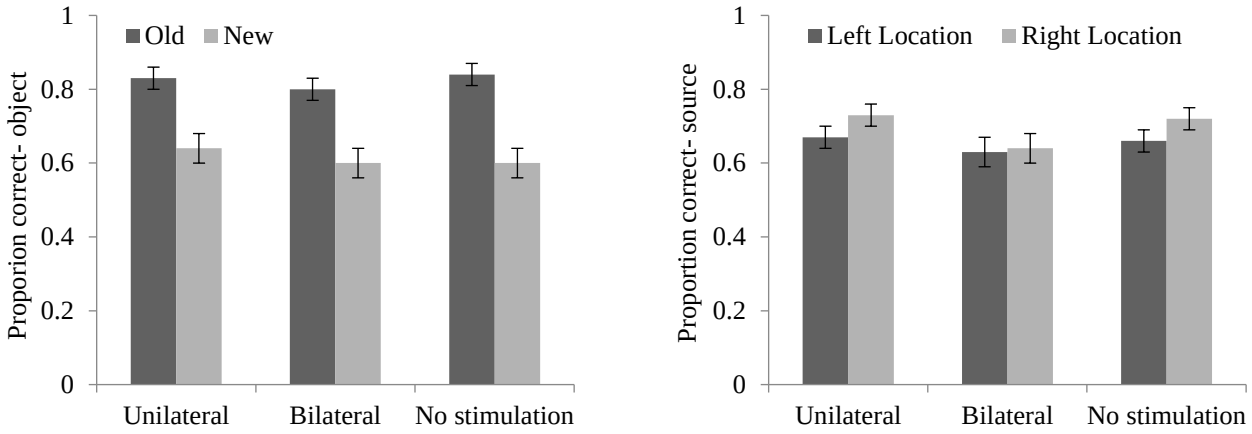


Figure 5.3. Object and source accuracy across the Stimulation conditions.

Carryover

Unexpectedly, the analyses above did not demonstrate a clear advantage of GVS on accuracy. Moreover, within the source accuracy analysis the no-stimulation condition actually produced marginally higher recall scores than the bilateral condition. One potential explanation is that source recognition within the no-stimulation condition had received a carryover effect from the GVS trials that preceded it. Therefore an independent samples *t*-test was used to compare the overall source accuracy of those participants who received the no-stimulation block last versus first. There were no significant differences between the two groups [*t*(14)= -0.05, *p*=. 96], which argues against this explanation.

Sensitivity (*d*') & Response Bias (*c*)

Both *c* and *d*' measures were computed from the hit and false alarm rates of the object and source recognition data (described separately below) using the following formulae:

$d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$

$c = -\frac{1}{2} Z(\text{false alarm rate}) + Z(\text{hit rate})$.

To ensure that extreme scores could not be obtained (*c* and *d*' are undefined for hit/ false alarm rates of one or zero because the corresponding *z*-scores are infinite) a log-linear transformation was made to all hit rates and false alarms by adding 0.5 to each frequency and dividing by N+1, where N is the number of old or new trials (Hautus, 1995; Snodgrass & Corwin, 1988):

Hit rate: (Hit rate frequency + 0.5)/ (N Old + 1)

False alarm rate: (False alarm frequency + 0.5)/ (N New + 1)

Object recognition. Hit rates (correctly classing a previously seen object as 'old') and false alarm rates (incorrect identification of a new object as old) were corrected and used to calculate *d*' and *c*. Separate ANOVAs then compared the *d'* and *c* parameters across the Stimulation conditions. In line with the accuracy responses above, Stimulation did not affect object recognition (*d*' $F(2, 46)=0.85$, $p=.44$, $\eta_p^2=.04$; *c* $F(2, 46)= 1.50$ $p=.23$, $\eta_p^2=.06$).

Source recognition. Sensitivity within the source judgments was calculated such that the right source was the target distribution, meaning a hit was classed as responding 'right' to an item that was shown on the right. The left source was the lure distribution, meaning a false alarm was a 'right' response to an item shown on the left. The assignment of the target distribution is arbitrary since the same results can be obtained if the distributions are switched (Mollison & Curran, 2012). Corrected hit rates and false alarms were again used to produce the *d*' and *c* parameters which were then entered into ANOVAs.

d' scores also showed a main effect of Stimulation, $F(2, 46)= 3.36$, $p<.05$, $\eta_p^2=.13$. Post-hoc comparisons revealed a marginal difference [$t(23)= 2.55$, $p=.054$] between the unilateral ($M= 1.79$) and bilateral ($M= 1.37$) conditions where sensitivity was highest and lowest respectively (all other *p*s>.12). Contrary to the hypothesis, these effects suggest that the Stimulation variable influenced source recall through a marginal performance drop in the bilateral condition (see Figure 5.4). No significant differences in response bias (*c*) were present amongst the Stimulation conditions [$F(2, 46)= 1.03$, $p=.36$ $\eta_p^2=.04$].

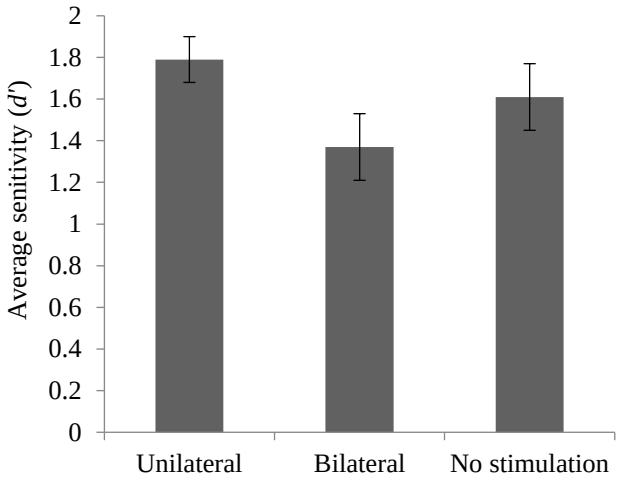


Figure 5.4 Source sensitivity (*d*') across the Stimulation conditions.

Discussion (1)

Experiment 1 revealed an effect of Stimulation on source, but not object memory. Contrary to the hypothesis, recall was marginally reduced when multiple objects and locations were paired with a GVS signal (bilateral), relative to the no-stimulation (accuracy-marginal effect) and unilateral (*d*'– marginal effect) conditions. Importantly, since this performance drop missed significance within post-hoc testing and did not extend to the unilateral condition, any concerns about GVS worsening cognitive performance are at this stage only marginal.

Nonetheless the absence of a beneficial Stimulation effect on memory (i.e. where unilateral and bilateral conditions are better recalled than the no-stimulation condition) does

contrast with previous research (Ghaheri et al., 2014; Wilkinson et al., 2008), including the study by Bächtold et al. (2001) from which the current paradigm was adapted. These memory enhancements may not have been replicated here if the sub-sensory GVS signals that were delivered failed to produce an arousing effect in the same way that supra-sensory CVS might have; or because any general arousal effects were restricted to a particular hemisphere (the current paradigm did not allow for lateralised effects to be tested).

The findings also diverge from several multisensory studies which have facilitated the recall of visual stimuli by encoding them within a multisensory context (Murray & Sperdin, 2010). Given that the vestibular and visual senses closely interact to coordinate balance and movement (Goldberg & Hudspeth, 2000), the co-occurrence of vestibular-visual inputs was expected to enhance visual memory. Although the unilateral condition trended towards outperforming the no-stimulation condition in terms of source accuracy and sensitivity, neither difference reached significance. Taken together these effects could lead to one of two conclusions: either encoding visual stimuli alongside a unique GVS signal has no effect on recall, or there is an effect which could not be uncovered by the current paradigm.

In support of the latter conclusion, previous research has also highlighted conditions which can constrain the binding of multisensory inputs into a single representation. One important factor appears to be the perceptual association between multisensory inputs (Spence & Driver, 2004). Studies which have employed a one-to-one perceptual relation between crossmodal inputs in which two specific stimuli are seen as directly associated with one another have been more successful at boosting memory performance (Spence, 2011). For example, when Botta et al. (2011) presented a single auditory cue at a given location (either left or right) alongside an array of visual stimuli, the tone did not affect the visual objects. After revising the mapping by organising the visual array into two lateralised objects, only one of which was paired with an auditory cue (also delivered to the left or right), Botta,

Lupiáñez, and Sanabria (2013) managed to elicit one-to-one crossmodal facilitations of visual memory. Lehman and Murray (2005) have also facilitated visual recall for objects encoded alongside a single corresponding semantic sound (e.g. image of a bell was paired with a dong). In light of these findings it could be argued that the one-to-many pairings in the current paradigm (i.e. a single GVS pulse mapped to multiple visual stimuli appearing on one side of the screen) were too unspecific and thus failed to produce an effect on memory. Although the onsets of the vestibular and visual signals temporally coincided, other elements of the crossmodal pairing remained ambiguous, a closer one-to-one mapping may therefore be required to enhance recall.

In summary, Experiment 1 showed that encoding multiple visual stimuli alongside a temporally coincident vestibular signal did not facilitate memory. Experiment 2 therefore tested whether facilitation could occur when only one visual stimulus was paired with a GVS signal.

Experiment 2: Memory Recall for a Visual Stimulus That is Uniquely Paired with a GVS Signal.

Experiment 2 introduced a one-to-one mapping between a single visual stimulus (as opposed to many) and a single incoming GVS signal to examine whether this mapping was a necessary precursor for vestibular-based memory enhancement. The emphasis here was on developing a paradigm capable of eliciting vestibular-based memory enhancement regardless of the underlying mechanism. If successful, further experiments would then be needed to investigate how this effect occurred (i.e. via generic arousal or specific signal content).

To promote the integration of crossmodal inputs into a combined memory representation, Experiment 2 also focused upon visuospatial memory for the locations in which objects had previously been encoded. This was because the findings of Experiment 1 showed that spatial source, but not object memory judgements were receptive to GVS, such

that recall was marginally worsened during the bilateral condition. Additionally, previous research conducted with both humans and rats has highlighted a stronger connection between vestibular loss (via a vestibular neurectomy) and spatial rather than non-spatial aspects of memory (Besnard et al., 2012; Brandt et al., 2005; Kremmyda et al., 2016).

A spatial matrix task was created to probe spatial memory and explore one-to-one crossmodal mappings. This task required participants to learn to associate individual objects with unique locations (object-location association), a test phase then measured the degree to which participants could recall the locations in which visual objects were previously shown (Bridge & Paller, 2012; Uttl & Graf, 1993). These kinds of tasks have been extensively implemented because they can be easily manipulated to address various hypotheses about spatial memory processing (Bridge & Paller, 2012; Martin, Houssemand, Schiltz, Burnod, & Alexandre, 2008).

In the current experiment, the matrix task was used to permit comparisons between the recall of a single crossmodal stimulus (target visual stimulus combined with a unique GVS signal), against unisensory visual stimuli (which were not paired with GVS signals). As mentioned, this one-to-one mapping was introduced to improve the specificity of the crossmodal pairing and thus reduce any potential ambiguity surrounding the one-to-many mappings that were used in Experiment 1. However, as only one visual stimulus was being paired with a vestibular signal there were fewer observations relative to Experiment 1. Thus, to ensure participants received adequate exposure to the crossmodal association and to produce sufficient data for analysis, multiple trial blocks were run. Participants completed two study sessions held on consecutive days, each consisting of ten blocks. Because repeating the task several times could result in participants reaching ceiling levels of performance, participants were given a large number (49) of object-location associations to remember to ensure that the task was sufficiently difficult.

To maximise the opportunity for crossmodal facilitation, coincident GVS signals were discharged at both encoding and recall (as well as a priming phase described later), compared to just the encoding phase in Experiment 1. Previous evidence suggests that this may increase the likelihood of effect since memory retrieval can be enhanced by reinstating the cues that were present at encoding during recall (as per the 'encoding specificity principle'; Tulving & Thomson, 1973). Moreover, if multisensory stimuli become integrated via an associative mechanism as opposed to a more immediate implicit association, then multisensory associations may only be formed once stimuli have been co-presented several times. Breaking the association between the sensory inputs could also result in a 'dissociation cost' whereby any facilitatory effects of the association are reduced once the sensory inputs are presented separately (i.e. at encoding and recall) (Hecht, Reiner & Karni, 2009). More generally, learning in a visual motion detection task which received audio-visual as opposed to visual-only training over a five day period was shown to be facilitated (Shams & Seitz, 2008), suggesting that with repeated exposure even task-irrelevant crossmodal associations can become beneficial (Seitz, Kim & Shams, 2006). It was hoped that by reinstating the vestibular inputs at recall, further effects of GVS on visual memory may emerge. If demonstrated, then further research would need to determine whether the effect of the vestibular inputs was localised to the encoding and/ or recall phases.

As well as pairing the visual and vestibular stimuli on multiple occasions, the amplitude of the vestibular signal was also increased. This change was motivated by the aforementioned memory studies which reported memory improvements following vestibular stimulation at stronger intensities and for longer durations (Bächtold et al., 2001: supra-sensory CVS; Wilkinson et al., 2008: continuous 0.8mA GVS signal). It may have been that the stimulation amplitude delivered in Experiment 1 was too small to elicit beneficial effects and that with stronger vestibular inputs, significant vestibular-visual interactions might occur.

Experiment 2 therefore increased the amplitude of the GVS signal from 0.4mA to 0.8mA (the intensity adopted by Wilkinson et al. 2008, albeit in a different format) but retained the pulse configuration to ensure that the signals temporally coincided with the presentation of the visual stimulus. To control for any attentional effects or skin sensations introduced by this higher intensity, a separate control study was included in which the electrodes were positioned on the neck (completed with a different participant sample at a subsequent time point) to retain the somatosensory component of the electrical signal without activating the vestibular organs.

In sum, Experiment 2 investigated whether the recall of a visual stimulus was improved (over multiple trial blocks) when singularly paired with a GVS signal, relative to other stimuli which were only presented visually. If vestibular inputs can facilitate individual visual memories, then a visual stimulus that is paired with a GVS signal should be better recalled than those visual stimuli that are not paired. If this effect is merely the result of a generic attentional enhancement arising from the supra-sensory tactile skin sensations of being stimulated, then recall should likewise be facilitated for a visual stimulus that is paired with a somatosensory signal. Note that this experiment was not designed to test between the mechanistic accounts of vestibular-memory effects that were mentioned previously. Instead the study aimed to demonstrate improved recall for a single visual stimulus that was paired with a GVS signal, if this is the case then further investigations into underlying the mechanisms (i.e. via generic arousal or the specific individuating content of vestibular signals) would be justified.

Method (2)

Participants

Forty six students were recruited using the same means as in Experiment 1. Twenty three participated in the active vestibular stimulation experiment and 23 in the separate somatosensory control experiment. Participants who had taken part in Experiment 1 were not permitted to sign-up for this study.

Stimulus Displays

Forty nine greyscale photographs depicting tools (taken from Experiment 1) were presented on a white background and resized to 119^2 pixels. The photographs were shown within (encoding phase) and alongside (recall phase) a 7x7 square grid (869^2 pixels) that was created in GNU Image Manipulation Program. The grid had a black outline and interior gridlines and a white background. Each object was randomly assigned a unique grid position which remained the same across participants throughout the experiment.

As in Experiment 1 participants' head position was held constant during experimental trials using a chin rest.

Design

All participants completed two experimental Sessions (each lasting one hour 45 minutes) which took place on consecutive days and had exactly the same procedures. Each session comprised ten blocks which contained a priming phase where the individual grid locations were primed or highlighted (more information provided in procedure), an encoding phase where the spatial display was learnt, and a recall phase where participants had to remember where a static centrally presented item had previously been positioned.

Each participant was assigned a single target crossmodal association which was paired with an electrical signal throughout the study. Target association was counterbalanced across participant duos and comparison pairs were formed so that the target association in one participant acted as a control association in another, and vice versa. For example, if a GVS pulse was delivered alongside location zero in participant one and at location seven in participant two, then the control location for participant one was location seven and location zero for participant two (see Figure 5.5). Identical comparison pairs were used in the active vestibular and somatosensory control experiments. The comparison pairs helped to control for the varying difficulty of different grid positions and ensured that an equal number of crossmodal (one target) and unimodal responses (one target selected from 48 non-targets) were compared.

Alternative approaches are available which would incorporate more of the data set such as testing for statistical differences using *z*-scores, but these do not account for the imbalanced sampling distributions between the unimodal and crossmodal stimuli. This is important since there would be a better sampling and therefore a closer estimation of the underlying mean for the unimodal than crossmodal stimuli, thus contrasting with the assumptions of typical *z*-score analyses where each mean score tends to be founded on the same number of individual observations. This limitation can be resolved through the use of comparison pairs.

Participants' skin was first prepared for GVS as described in Experiment 1, with the electrodes positioned over the mastoids or the neck. Once the GVS electrodes were in place, participants completed the questionnaire about the perceived intensity of the stimulation and the sensations it evoked (see Appendix D). The questionnaire was then repeated at the end of each Session. More stimulation sensations were reported at the end of the study - illusory perceptions of stimulation were largely absent at study onset. Unlike Experiment 1,

participants were not excluded on the basis of this questionnaire since the stimulation was suprasensory and the effects of somatosensory sensations were estimated in a separate control experiment.

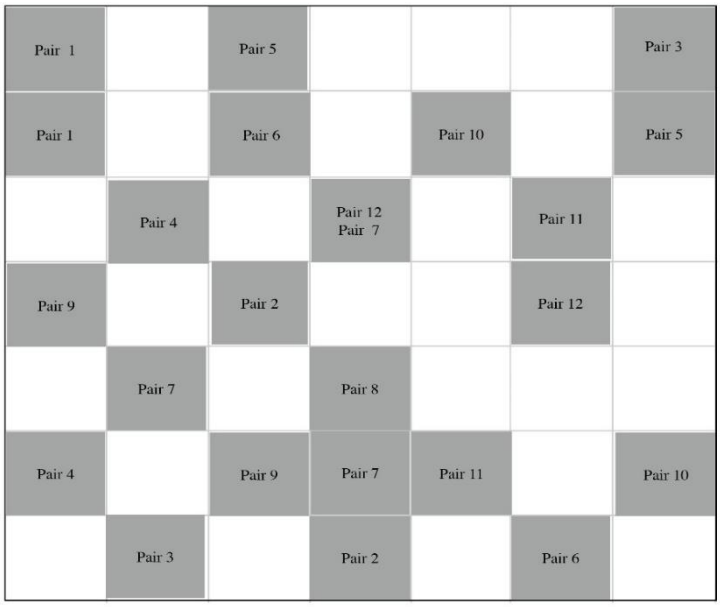


Figure 5.5. Comparison pairs used in Experiment 2.

Procedure

Priming task. Every trial block began with the priming task which highlighted each individual grid location using a bold outline in a randomised order for 500ms (see Figure 5.6). Participants were asked to click on the highlighted location using the mouse, an ISI (blank grid) would then follow for 750ms. A GVS signal was released when the critical location was highlighted, thus serving to prime the association between the target spatial location and a unique vestibular signal. During block one of the experiment, participants completed four repetitions of the priming task, in all other blocks two repetitions were completed. An un-timed break was offered after the priming phase.

Encoding phase. Participants saw a blank grid (ISI) which was displayed for 750ms, followed by an individual object photograph presented within an assigned grid location for 500ms (see Figure 5.6). Forty nine different objects were shown in a randomised order during

each encoding phase. A GVS signal was released when the target object appeared within its assigned location, thus serving to prime the object-location association that was paired with GVS. Participants did not need to make any responses but were asked to concentrate on learning the display for an upcoming memory test. A set break of 90s was given after the encoding phase to reduce variability in memory processes like forgetting and rehearsal.

Recall phase. Participants' memory for the spatial display was then tested. Each trial began with a central fixation cross shown for 750ms to redirect participants' attention towards the same position at the beginning of each trial. Next an individual object was displayed above an empty spatial grid (the grid occupied the same space as in the encoding phase), a GVS signal was released alongside the critical object thus serving to prime the object that was paired with GVS (see Figure 5.6). Participants were instructed to press the spacebar as soon as they were ready to make their response and then to use the mouse to click on the square in which they recalled seeing the object (using their dominant hand). It was hoped that by organising participants' responses in this way RTs for the recall of an object and the motor action of navigating the mouse could be separated, therefore reducing variability and providing a more informative estimate of recall.

Participants were encouraged to respond as quickly and as accurately as possible and were given accuracy feedback at the end of each recall phase to promote engagement. A 60s break was given at the end of each recall phase.

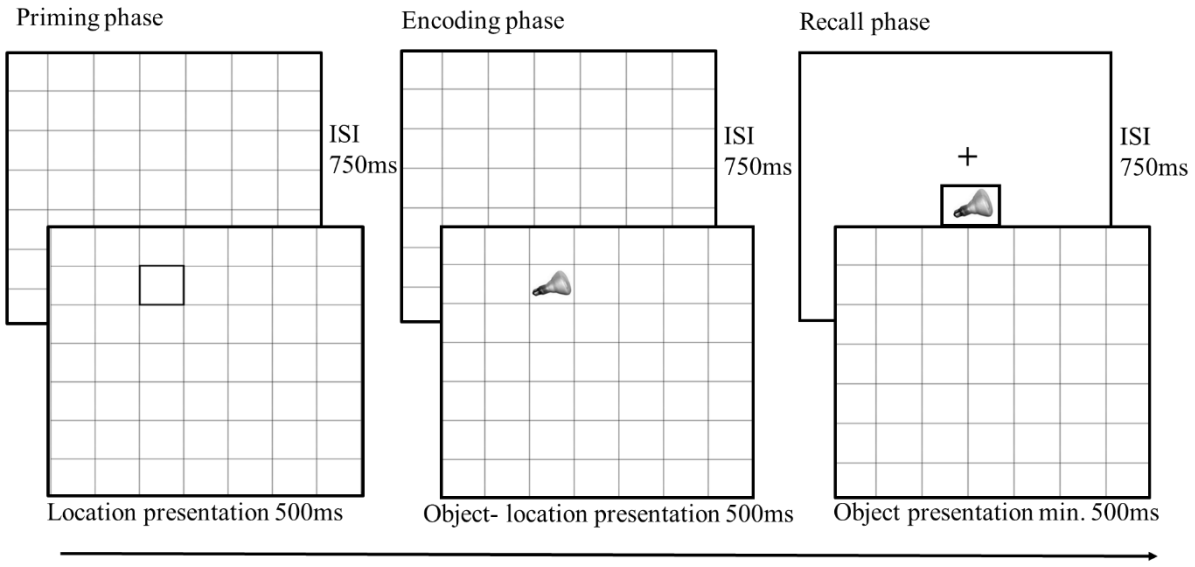


Figure. 5.6. Example stimuli displayed during each phase of Experiment 2. Each block began with a priming phase where each unique grid location was highlighted. The encoding phase then presented individual objects within their assigned grid locations. After a 90s break, each object was presented above the grid and participants recalled its position. A GVS signal was released to accompany the onset of the key visual stimulus during each phase.

Stimulation Protocol

Bilateral bipolar current (anode left and cathode right) was discharged to match the onset of the target stimulus throughout each phase of the experiment. A supra-sensory GVS signal of 0.8mA lasting 500ms was adopted for all stimulation trials. A total of 84 pulses were released over the course of the experiment (42 on each day: 22 across all priming tasks and ten in each encoding and recall phase). Participants in the active vestibular experiment wore GVS electrodes over their mastoid processes; those in the control experiment wore the electrodes on the neck (5cm below the mastoid processes; Lenggenhager et al., 2008).

Results (2)

Data Considerations

All analyses were conducted upon the comparison pairs and thus responses to just two visual stimuli are presented: the object-location association that was paired with GVS and the counterbalanced control stimulus that was not paired with GVS. The two experiments (vestibular and somatosensory stimuli) were analysed separately given that different samples

were recruited and each experiment was carried out consecutively. Further, the key aim of the analysis was to first establish whether a visual stimulus was better recalled when paired with a GVS pulse compared to a unimodal control, rather than a visual stimulus paired with a somatosensory signal. The somatosensory experiment simply provided a way of checking whether any crossmodal visual-vestibular effects were likely due to the arousing effects or cutaneous sensations elicited by supra-sensory GVS stimulation.

Three responses to the comparison pairs were analysed as dependent variables: accuracy, RTs and graded errors. Graded errors were calculated from the distance between the axis position that a participant recalled seeing an object in and the correct location, a visual example can be seen in Figure 5.7. These responses were included to examine how participants' spatial memory performance changed over the experiment. It was hoped that by including these graded error responses any potential subtle shifts (which may not be reflected by participants' overall task accuracy) towards the approximate part of the grid in response to the GVS signal might be uncovered (as seen in, Bridge & Pallar, 2012).

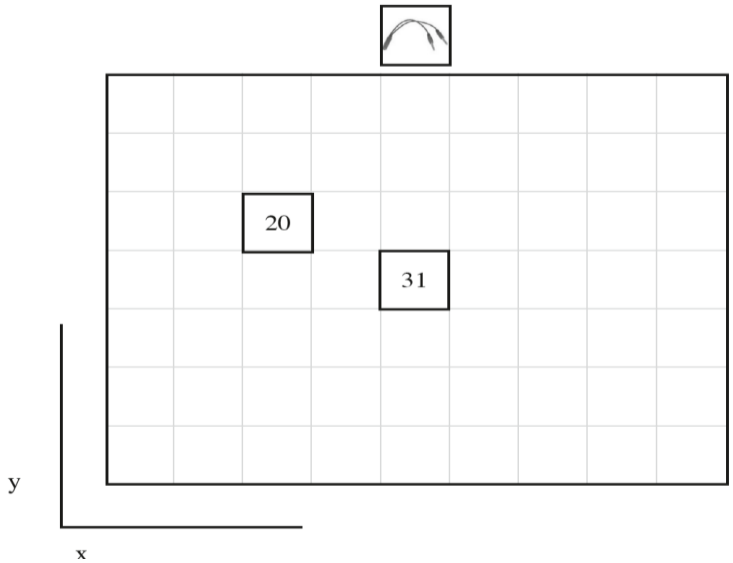


Figure 5.7. Graphic representation of the method used to calculate error scores. In this example the correct response (20) and the participant's response (31) differ by 2 X coordinates and 1 Y coordinate resulting in an error score of 2.24 ($\sqrt{dx^2 + dy^2}$) (Page, 2011).

Unlike typical RT investigations, here the analysis was not restricted to correct trials because of high levels of missing data. Many trials were not answered correctly, especially during the early part of session one and thus would have been excluded from the analysis. This was particularly problematic in this study where only responses to the key comparison pair were being analysed. These RTs should therefore be considered as exploratory since it is unclear what cognitive processes underlie these responses, particularly those that are incorrect. To try and improve the quality of the responses that were collected, outliers from the key trials (correct and incorrect) were removed using a *z*-score correction (see Chapter 4 statistical analysis section).

These dependent variables were analysed according to three independent variables. Of primary importance is the Association variable, which describes whether participants were responding to an active crossmodal target or a control unimodal stimulus. Experimental Session and trial Block were also considered to explore whether crossmodal effects emerged over the course of the study. Instead of analysing individual trial blocks which would be formed of just one response per Association, the first five and the last five trial blocks were combined to form an early and late Block. This variable aimed to reduce some of the noise that could have occurred during a single trial and in turn produce more reliable mean values.

Each dependent variable was entered into an Association (active *versus* control) x Session (one *versus* two) x Block (early *versus* late) repeated measures ANOVA. Analyses focused on determining whether active associations were better recalled than control associations across the study. Therefore all main effects are reported alongside any interactions involving the Association variable. Where an Association x Session x Block interaction was present, post-hoc analyses concentrated on the effects of Association within each combination of Session and Block (i.e. does recall change in response to Association during each Session and within each Block). This decision was motivated by the key aims of

the study which sought to explore whether recall was differentially affected by active and control associations over multiple trial repetitions. Post-hoc testing also considered the effects of Block and Session within each Association variable to explore the rate of learning for active/ control stimuli separately across the study (i.e. when does learning tend to improve/ plateau for active and control stimuli respectively). All post-hoc pairwise comparisons applied the Bonferroni adjustment.

Vestibular Stimulation

Accuracy. Contrary to the hypothesis, a main effect of Association was absent, $F(1, 22)= 1.87$, $p=.19$, $\eta_p^2=.08$. As expected, accuracy was influenced by the main effects of Block [$F(1, 22)= 67.51$, $p<.001$, $\eta_p^2=.75$] and Session [$F(1, 22)= 204.36$, $p<.001$, $\eta_p^2=.90$], such that recall was improved from the early ($M= 0.35$) to latter ($M= 0.57$) parts of the sessions and from Session one ($M= 0.25$) to two ($M= 0.67$) (see Figure 5.8). Interestingly, a significant three-way interaction was also present [$F(1, 22)= 7.1$, $p<.05$, $\eta_p^2 =.24$] and post-hoc tests were therefore completed to interrogate the interaction.

Post-hoc testing first examined whether there were any effects of Association across the study (i.e. within each combination of Block and Session). Comparisons showed that active associations ($M= 0.47$) were recalled significantly more accurately than control associations ($M= 0.27$) during the latter part of Session one [$t(22)= 2.25$, $p<0.05$] (see Figure 5.8), but not during other parts of the study (all ps>.12). Comparisons of Block then examined whether any learning effects had taken place during each Session for the active and control associations respectively. Within the active associations, accuracy was significantly improved between the early ($M= 0.15$) and late ($M= 0.47$) Block during Session one [$t(22)= -4.47$, $p<.001$], but appeared to plateau during Session two ($p= 0.26$). Conversely, within the control associations accuracy improved from the early to late Block during both Session one

(early M= 0.10; late M= 0.27; $t(22) = -2.40$, $p<.05$) and Session two (early M= 0.50; late M= 0.81) where the effect was stronger [$t(22)= -4.04$, $p<.05$]. Finally, post-hoc tests of Session examined whether each Block position had improved between sessions one and two, for active and control associations respectively. All comparisons were significant (all ps<.05) and showed that accuracy was improved between Sessions one and two for both the early and late blocks across both active and control associations. The largest accuracy gains had occurred between the early parts of the sessions [$t(22)= -6.55$, $p<.001$] for the active associations (early-active Session one M= 0.15; early-active Session two M= 0.66), conversely the control associations showed more accuracy gains between the latter parts [$t(22)= -7.53$, $p<.001$] of Session one (M= 0.27) and two (M = 0.81). No further interactions were present (all Fs <1.28, all ps>.27).

Taken together, these effects suggest that the active visual-vestibular pairing was temporarily recalled more accurately (late Block session one) and plateaued more quickly than the control association (see Figure 5.8).

Graded error responses. Contrary to the hypothesis, errors were also unaffected by Association [$F(1, 22)= 1.71$, $p=.21$, $\eta_p^2=.07$], although significant main effects of Block [$F(1, 22)= 94.32$, $p<.001$, $\eta_p^2 =.81$] and Session [$F(1, 22)= 37.29$, $p<.001$, $\eta_p^2=.63$] were present. As expected, errors were reduced from the early (M= 2.11) to late (M= 1.36) blocks and from Session one (M= 2.51) to two (M= 0.96) (see Figure 5.8). No other interactions involving the Association variable reached significance (all Fs<1.02, all ps>.32). Error rates improved across the study but these changes were not driven by the one-to-one Association.

Reaction time. Unexpectedly, the main effects of Association [$F(1, 22)= 2.55$, $p=.13$, $\eta_p^2=.11$], Block [$F(1, 22)= 2.30$, $p=.14$, $\eta_p^2=.10$] and Session [$F(1, 22)= 5.57$, $p= .99$, $\eta_p^2=$

.01] were all non-significant. Since the three-way interaction was also absent, analyses explored any two-way interactions involving the Association variable.

An Association x Block interaction was present [$F(1, 22)= 5.45$, $p<.05$, $\eta_p^2= .21$] and post-hoc tests first examined whether there were any effects of Association within each Block position. Comparisons revealed that there were no differences between the associations during the early Block ($p= .90$). However, during the late Block RTs were significantly shorter [$t(21)= -2.62$, $p<.05$] towards active ($M= 890$ms) than control associations ($M=$ 1085ms). Post-hoc tests of Block then examined whether RTs were altered between early and late blocks within each Association. Within the active Association trials, participants' responses became shorter during the latter ($M= 890$ms) relative to the earlier ($M= 1060$ms) Block, $t(21)= 4.03$, $p<.05$. Conversely during the control Association trials, no effect of Block was present ($p=.82$). Although these RT data are exploratory, these effects suggest that responses were facilitated by the presence of the GVS signal during the latter Block where they were fastest (see Figure 5.8). No other interactions involving the Association variable reached significance (all Fs<1.74, all ps>.20).

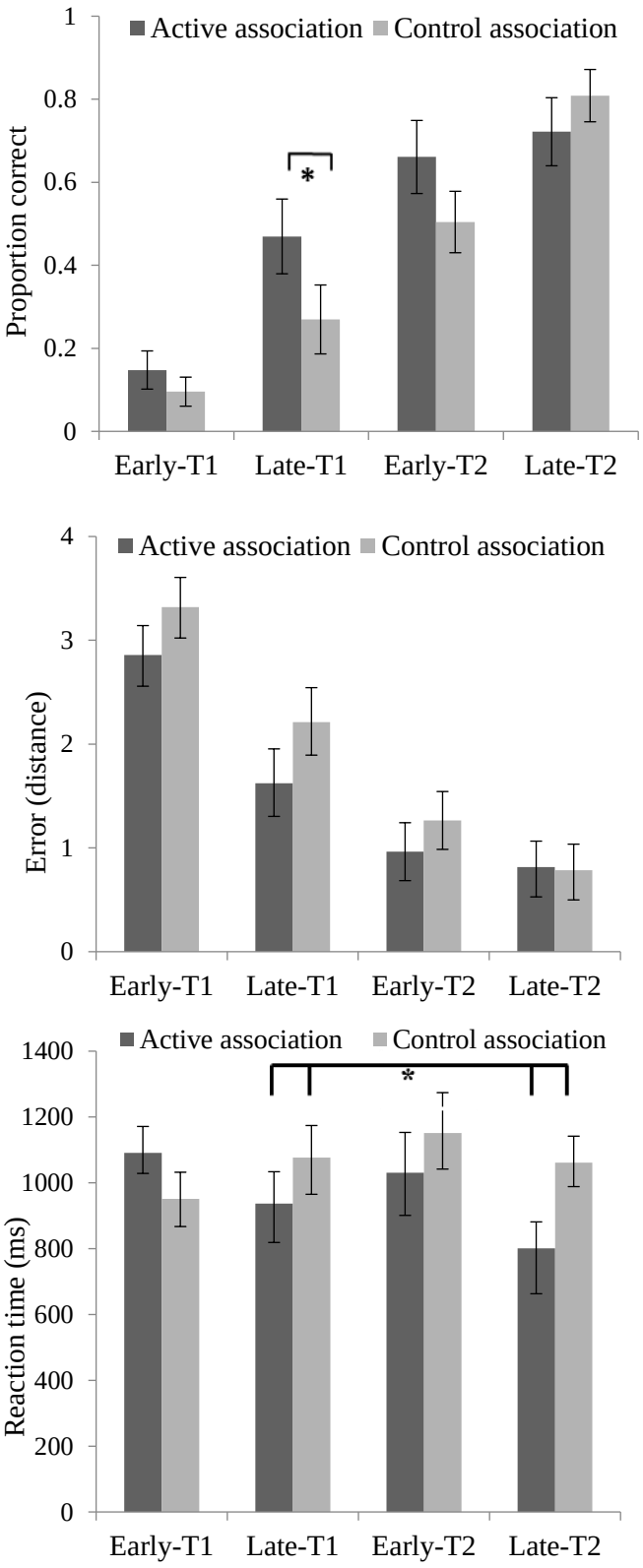


Figure 5.8. Average accuracy, errors and RTs across Experiment 2 for those participants who received vestibular stimulation. For ease of interpretation only significant post-hoc comparisons of Association are marked (*).

Somatosensory Stimulation

Accuracy. Responses were unaffected by Association [$F(1, 22)= 0.01$, $p=.91$, $\eta_p^2=.001$]. However, significant main effects of Block [$F(1, 22)= 110.48$, $p<.001$, $\eta_p^2=.83$] and Session [$F(1, 22)= 52.30$, $p<.001$, $\eta_p^2=.70$] were present, which reflected improved accuracy from the early ($M= 0.35$) to late ($M= 0.59$) blocks and from Session one ($M= 0.30$) to two ($M= 0.64$) as anticipated. Since a three-way interaction was absent, analyses focused on any significant two-way interactions involving the Stimulation variable.

An Association x Block interaction was revealed [$F(1, 22)= 4.61$, $p<.05$, $\eta_p^2=.17$] and post-hoc tests first examined whether active and control stimuli were differentially recalled at each Block position. Testing showed that the associations were performed with similar levels of accuracy throughout the experiment (all ps>.43). Comparisons of Block (within each Association) then revealed that accuracy was similarly improved from the early (active $M= 0.32$; control $M= 0.38$) to late (active $M= 0.63$; control $M= 0.56$) Block for both active [$t(22)= -7.77$, $p<.001$] and control associations [$t(22)= -4.87$, $p<.001$] (see Figure 5.9). No other interactions were significant (all Fs <0.36, all ps>0.21). Overall these effects suggest that accuracy improved across the experiment, but this was not driven by the presence of cutaneous sensations or proprioceptive stimulation of the neck.

Graded error responses. A main effect of Association was also absent from the error responses [$F(1, 22)= 0.17$, $p=.69$, $\eta_p^2=.01$]. Like the accuracy data, significant main effects of Block [$F(1, 22)= 77.22$, $p<.001$, $\eta_p^2=.78$] and Session [$F(1, 22)= 59.52$, $p<.001$, $\eta_p^2=.73$] revealed that errors were decreased from the early ($M= 2.01$) to late ($M= 1.05$) Block and from Session one ($M= 2.16$) to two ($M= 0.91$) as anticipated (see Figure 5.9). Since a significant three-way interaction was absent, analyses examined any two-way interactions involving the Association variable.

Only an Association x Block interaction emerged [$F(1, 22)= 7.68$, $p<.05$, $\eta_p^2= .26$].

Post-hoc tests first examined the effects of Association within each Block position and revealed that active and control stimuli were similarly recalled across both blocks (all *p*s>.15). Comparisons between the early and late blocks within each Association showed that errors were significantly reduced from the early (active *M*= 2.22; control *M*= 1.80) to late (active *M*= 0.95; control *M*= 1.16) Block for both active [*t*(22)= 4.68 *p*<.001] and control associations [*t*(22)= 5.01, *p*<.001] (see Figure 5.9). Similar to the accuracy data, errors were reduced between the early and late Block but this effect was not driven by somatosensory stimulation. No other effects involving the Association variable reached significance (all *F*s<4.20, all *p*s>.05).

Reaction time. Response times failed to show a main effect of Association [*F*(1, 22)= 0.28, *p*=.60, η_p^2=.01] , Block *F*(1, 22)= 0.05, *p*=.83, η_p^2=.002] or Session [*F*(1, 22)= 1.20, *p*=.29, η_p^2=.05]. A three-way interaction was also absent, however, since a significant Association x Block interaction was present [*F*(1, 22)= 11.14, *p*<.001, η_p^2=.34] further post-hoc tests were performed.

Comparisons first examined whether any effects of Association were present within each Block. No significant differences were present between the active and control associations in either Block (all *p*s>.10). Post-hoc tests then explored whether any effects of Block were present within active and control associations respectively. RTs were significantly shortened between the early (*M*= 1107ms) and late (*M*= 981ms) Block within the active Association trials [*t*(22)= 2.62, *p*<.05], while RTs remained stable across blocks for the control association (*p*=.10). All other interactions involving the Association variable failed to reach significance (all *F*s<0.82, all *p*s>.30). In sum, RTs within the active somatosensory association became shorter across the study but did not differ from the control association (see Figure 5.9).

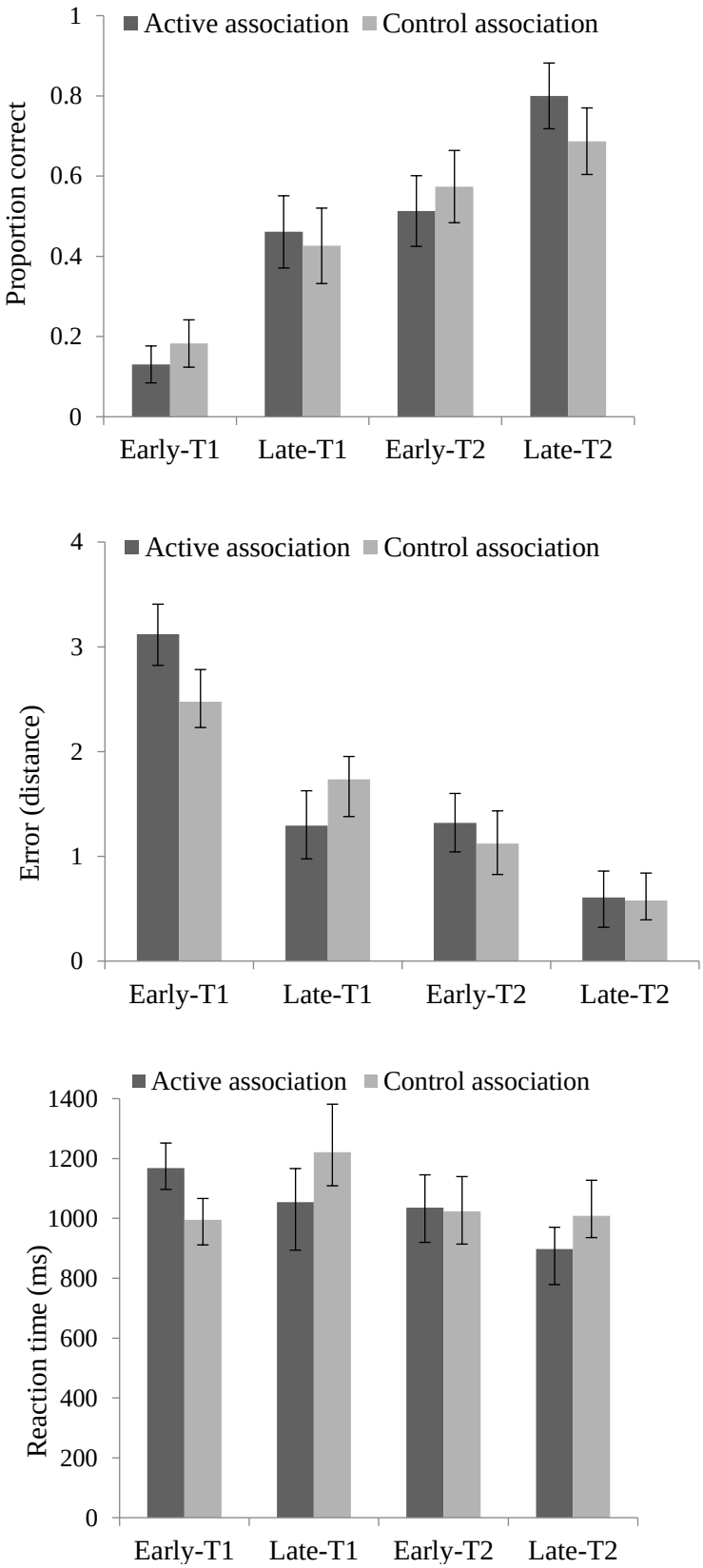


Figure 5.9. Average accuracy, error and RTs across Experiment 2 for those participants who received somatosensory stimulation.

Discussion (2)

Key Findings

Experiment 2 explored whether the recall of a visual stimulus could be facilitated if it was singularly paired with a coincident vestibular signal. Contrary to the hypothesis, the omnibus effect of Association did not reach significance within the vestibular (or somatosensory) stimulation experiment as measured by accuracy, graded errors or RTs. However, some support for the hypothesis was provided by the simple main effects of Association within the sample that received vestibular stimulation.

Firstly, active vestibular associations were recalled more accurately than control associations during the latter part of Session one. This was not the case in the somatosensory experiment, where simple effects of Association were absent. Exploratory RTs were also facilitated for active vestibular associations relative to control associations during the late Block. Again no similar RT effects were present within the somatosensory experiment where active and control stimuli were responded to a similar speed. Accuracy responses towards the active vestibular stimuli also appeared to reach asymptote more quickly during Session two relative to the control associations. While accuracy for the control associations continued to improve across blocks during both sessions, in the active vestibular condition no effect of Block was present on Session two. This finding was not present within the somatosensory experiment where accuracy continued to increase for both active and control associations during Session two. Taken together, these data provide preliminary evidence that pairing a visual stimulus with a unique vestibular signal can facilitate recall for visuospatial details at certain learning time-points. Moreover, the absence of Association effects within the separate somatosensory experiment indicates that the GVS-related memory improvements were likely due to the activation of the vestibular structures as opposed to the cutaneous sensations elicited by supra-sensory stimulation.

Interestingly, the scale of improvement for the active vestibular association appeared to be greater during Session one and reach an asymptote within Session two, while the rate of learning for the control association was more gradual. One possible explanation is that the crossmodal vestibular association sped the rate at which visual stimuli were learnt. However, since average accuracy at the late Block position on Session two was actually higher for control than active associations in the vestibular experiment (though the difference was non-significant), any potential asymptote effects were not necessarily beneficial.

Upon further visual inspection of the accuracy data (see Figure 5.8) it appears that an overall omnibus effect of Association may have been absent from the vestibular experiment because the effect was restricted to those time-points where learning was most likely to take place (i.e. midway through the experiment). Recall that during the initial early Block all locations appeared to be poorly recalled regardless of whether they were processed in a crossmodal or unimodal context. However, as Session one progressed and participants' began to encode more of the spatial display, an association between the vestibular and visual inputs could potentially have been formed with these stimuli becoming co-represented with additional priming (Hecht, 2009). In turn the active target started to outperform the control association resulting in a significant comparison for the late Block position. This performance advantage continued during the early Block of Session two but did not reach significance. Then as both active and control associations received more rehearsal, performance reached a similarly high magnitude and began to plateau in the active condition (a similar trend was seen in the graded error responses). Although no effects of Association were significant within the somatosensory experiment, it is worth noting that a less consistent pattern of learning was present. Here active associations were recalled more accurately during the late Block of Session one, but the control associations then outperformed the active associations at the early Block of Session two (see Figure 5.9).

Taken together, the findings from Experiment 2 showed some beneficial effects of a one-to-one vestibular mapping on memory. Importantly, there were no effects of Association within a separate somatosensory control experiment, suggesting the vestibular inputs themselves were of relevance. However, the paradigm lacked efficiency in that many unimodal data points were collected but were not analysed (i.e. inferences were drawn from only a few data points, two per participant). Further efforts could also have be made to improve the quality of the RTs gathered (i.e. by providing participant feedback to encourage less variable and efficient responding), and to better understand what memory processes underlie the paradigm (familiarity/ recollection). With this in mind, a third experiment was completed to address these methodological constraints and determine whether the present findings could be replicated.

Experiment 3: A Partial Replication of Experiment 2.

Experiment 3 applied the same paradigm as Experiment 2 with several methodological changes to both replicate and strengthen the effect. Firstly, because the previous experiment had shown subtle effects of Association during particular parts of the study, Experiment 3 elevated the statistical power of each Block position by increasing the number of data points from five to twelve. It was hoped that by adding more trials, further significant effects and more reliable estimates of Association could be obtained.

Second, to try and improve the efficiency of the paradigm the number of to-be-learnt stimuli were reduced (since only two were actually analysed). To compensate, the difficulty of each comparison pair was increased by displaying non-object images that were harder to tell apart (more detail provided in Experiment 4) within an enlarged grid (9 x 7) that no longer had interior grid lines, thus discouraging participants from using counting strategies (e.g. the object was shown in the third column, two rows from the bottom; see Figure 5.10). Additionally, as the previous experiment demonstrated that only visual memories trained in a

visual-vestibular crossmodal pairing were differentially recalled relative to a unimodal control, the somatosensory condition was dropped and coincident sub-sensory (0.3mA for 500ms) rather than supra-sensory GVS pulses were administered. It was hoped that the increased number of block repetitions would compensate for this reduction in GVS amplitude and suffice to drive the one-to-one mapping. In line with this idea, previous reports have already shown that training crossmodal stimuli together across multiple trials can facilitate crossmodal binding (Hecht et al., 2009; Shams & Seitz, 2008).

Lastly, to improve the quality of the data gathered several adjustments were made to the recall phase. Trial by trial RT feedback and response limits (3000ms) were introduced for both the spacebar press (recall) and mouse-click (object placement) to encourage less variable responses. Another behavioural response ("Please indicate how confident you are in your answer") was also added to explore the retrieval processes which might underlie the data within this paradigm (for implementation of confidence response see Bergström, Vogelsang, Benoit & Simons, 2015). Previous research has shown that items with low confidence judgements are likely to entail more monitoring and processing of the retrieved information before a decision is made (e.g. second memory interrogation or a slower memory search of the partly learned material), since the results of the initial retrieval attempt were likely ambiguous (i.e. close to the old/ new response criterion; Henson, Rugg, Shallice & Dolan, 2000). In contrast, retrieval experiences for items with high confidence judgements are less likely to be ambiguous and hence require reduced monitoring giving rise to shorter latencies (Ratcliff & Murchdoch, 1976). Confidence ratings were therefore monitored across the study to determine whether active/ control stimuli might be differentially retrieved.

Twenty three UoK students completed the study (*N*= 2 removed based on GVS perception questionnaires). As in Experiment 2, if vestibular inputs can enhance visual

memory, then an active Association (where a visual stimulus was singularly paired with a GVS signal) should be better recalled than a control association presented visually.

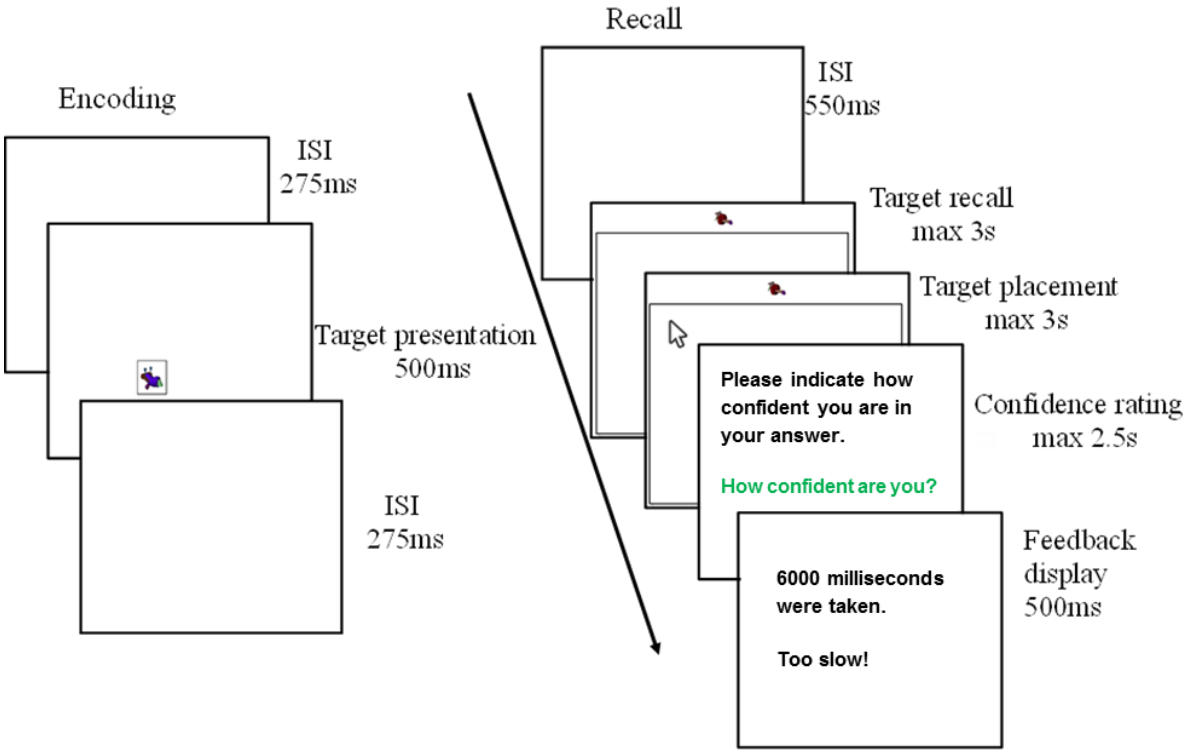


Figure 5.10. Illustration of the encoding and recall phases from Experiment 3. During the encoding task participants were asked to learn where individual non-object images were positioned. Participants then needed to recall where an image had previously been presented by clicking on a spatial location. A GVS signal was released to accompany the onset of the key stimulus during both phases. The priming phase from Experiment 2 was dropped and replaced with an extra repetition of the encoding phase.

In the following section the results are reported only briefly to maintain the focus of this chapter and because they did not confirm the hypothesis strongly.

Results (3)

Descriptive statistics showed that active associations were recalled more accurately and within closer proximity to the target location than control associations from the latter Block of Session one onwards (see Figure 5.11), though these differences did not reach statistical significance (all Fs< 2.54, ps>.13). Confidence responses were driven by a general

learning effect rather than in response to the Association variable and exploratory RTs were unaffected by the independent variables.

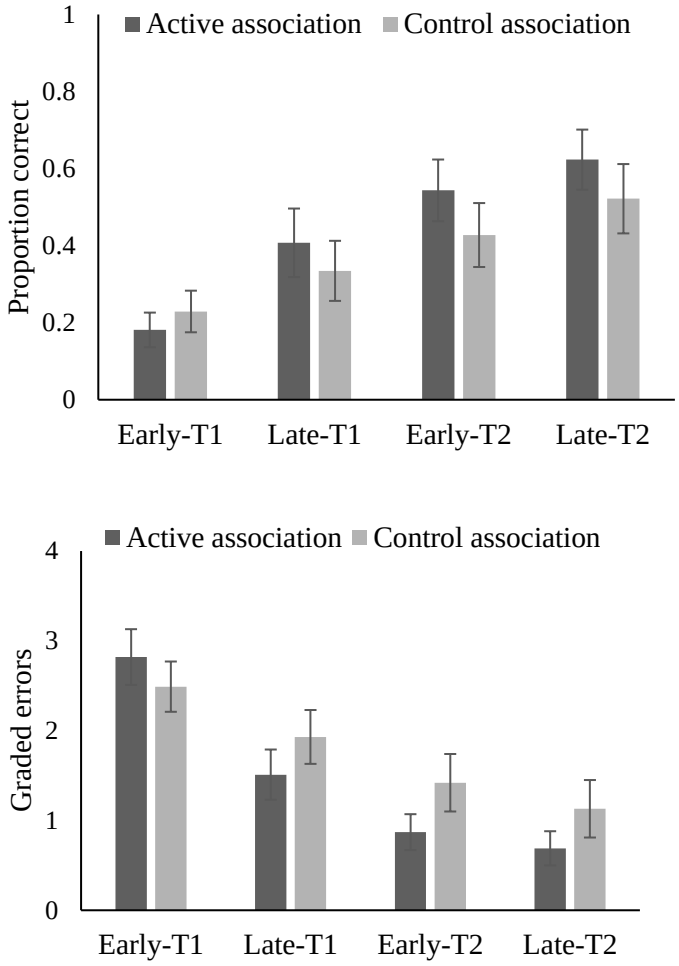


Figure 5.11. Accuracy and graded errors for active and control stimuli across Experiment 3.

Discussion (3)

Experiment 3 aimed to reproduce and streamline the spatial matrix paradigm from Experiment 2 to explore whether replicative effects of a one-to-one mapping could be demonstrated. Despite a promising pattern of descriptive statistics within the accuracy and graded error variables (see Figure 5.11), these efforts did not result in any significant effects of Association, nor were the asymptote trends observed in Experiment 2 reproduced. Unfortunately, the absence of these effects are difficult to pinpoint since multiple methodological changes were simultaneously implemented (to fit within the time constraints

of this PhD project), making it difficult to isolate whether particular variables contributed to the findings, or if in fact the results of Experiment 2 were a false positive that does not replicate.

Experiments 1-3 were designed to place greater emphasis on accuracy since similar crossmodal literature has primarily evidenced an effect of crossmodal priming on accuracy not RT (Lehmann & Murray, 2005; Murray et al., 2004). However, one concern with these paradigms is that a more implicit effect of GVS may have been missed within participant's responses. The RT data in Experiment 1 used an unconventional three-button press and within Experiments 2 and 3 RTs for just two trials per block (comparison pairs) were analysed meaning both correct and incorrect responses were included. Importantly, previous studies which have investigated the effects of vestibular stimulation on memory have shown RTs to be relevant, especially when accuracy is high. For example, Bächtold et al. (2001) investigated the impact of CVS on memory and showed that while accuracy was unaffected by CVS (ceiling levels), RTs on the verbal (right ear CVS) and spatial memory (left ear CVS) tasks were facilitated. Wilkinson et al. (2008) also demonstrated that the beneficial effects of anode-left noise-enhanced GVS on facial recall were greater within mean correct RTs than the accuracy data. Conversely, both Dilda et al. (2012) and Lee et al. (2014b) found a significant reduction in memory-related errors following GVS in the absence of an RT effect. However, there were some methodological issues with both experiments (Dilda et al. recorded just 20 trials and Lee et al. measured RTs using a stopwatch). Improving the design of the next experiment to permit more effective recording of RTs may therefore help to highlight more discrete effects of the crossmodal pairing that were previously missed. This might be particularly relevant when applying sub-sensory vestibular signals (0.3mA) which are likely to impact recall covertly. The final study of this chapter attempted to address this

potential gap by implementing an implicit memory paradigm where memory was indirectly probed and RT was the key dependent variable.

In summary, Experiments 2 and 3 provide suggestive, but by no means definitive, support that encoding a single visual stimulus alongside a vestibular signal can facilitate visual recall. One final experiment was therefore conducted using an entirely different paradigm based on visual search for a predefined target, to test whether singularly pairing a visual stimulus with a sub-sensory GVS signal could elicit more subtle changes in memory as indexed by RTs. If an effect is found, then the design of this paradigm will also permit inferences into whether vestibular signals affect visual memory via a generic arousal mechanism or more specifically through the individuating content of the signal, as well as which aspects of the memory representation might be most likely to incorporate vestibular signals.

Experiment 4: Visual Search for a Stimulus that is Uniquely Paired with a GVS Signal.

The statistical approach adopted in Experiments 2 and 3 limited the interpretation of RTs due to small trial numbers. The final study in this chapter introduced a new paradigm which overcame these problems and indirectly tested participants' visuospatial memories.

Recall that Experiments 1-3 assessed explicit memory because participants had to actively retrieve visual information (i.e. participants were instructed to memorise and recall the experimental stimuli). However, it might be that the content of vestibular signals relates more closely to implicit than explicit visual memories given that vestibular signals are constantly discharged alongside incoming visual information in everyday contexts without eliciting any overt sensations that reach consciousness (Angelaki & Cullen, 2008; Day & Fitzpatrick, 2005). If true, then an underlying effect of GVS could have been missed in the previous experiments. To address this, Experiment 4 tested whether participants had formed

implicit memory representations using RTs (i.e. participants were not instructed to memorise or recall the experimental stimuli). An implicit memory is indicated by a change in performance or processing efficiency ('priming effect') as a result of a prior experience (e.g. previous exposure to a stimulus affects the speed at which that stimulus is later identified), but is not necessarily intended or accompanied by conscious recollection of the prior episode (Baars & Gage, 2010; Musen, 1996; Ring, Gaigg, & Bowler, 2015).

A further benefit of using a priming paradigm to test implicit memory is that priming effects have been demonstrated to occur even after a single learning trial (Musen, 1996) and typically require less attentional resources during encoding than for explicit memories (Mulligan, 1998). If priming effects can be elicited after relatively few trials, then this may permit more efficient testing of crossmodal associations compared to Experiments 2 and 3 which required two testing sessions.

After reviewing the implicit memory literature, a suitable experimental paradigm was therefore identified which could be adapted for the present study. Manelis, Hanson and Hanson (2011) investigated implicit visuospatial memories using priming effects. First the researchers had participants incidentally encode the locations that objects were associated with using a simple stimulus-detection task, where objects were displayed within a grid and participants would have to respond to an object as soon as it appeared. Then during a visual search task, participants had to decide whether or not a target was present within a display and click on the target once it had been found (or click "not present"). There were several different trial types but of most relevance to the current study were those that showed implicitly primed objects in the same locations that they were encoded within during the detection task; unprimed trials where primed objects were placed in different locations from the detection task; and new trials which presented objects that had not been shown during the detection task. RTs were shorter for stimuli that had been primed during the detection task

relative to both new stimuli and unprimed trials where the location had changed. The authors interpreted this finding as an indication that implicit memories had been formed (further detail given in the methods section below).

Manelis et al. also incorporated fMRI to show that the same occipital and parietal brain regions that were involved during the encoding of visuospatial stimuli were later re-engaged at recall, indicating that as within explicit memory, reintegration (Hamiliton, 1859) could be an important mechanism for implicit memory. This is of relevance because the aim here was to explore whether a crossmodal visual-vestibular memory could be reinstated by the visual constituent of the encoded representation. If this task engages the same brain regions during the detection and search tasks, then this may provide an effective backdrop for crossmodal interactions to take place (Nyberg et al., 2000; Nyberg et al., 2001; Persson & Nyberg, 2000).

In sum, this experiment explored whether pairing the onset of a single visual stimulus with a unique sub-sensory GVS signal during a detection task facilitated the rate at which this target was found during a subsequent visual search task. Crucially, search for the crossmodal stimulus was compared to a unimodal stimulus that was encoded without a vestibular signal (control), as well as a unimodal stimulus that was not viewed and hence not primed during encoding (new). If vestibular signals are retained in visual memories in a useful way then a visual stimulus that was singularly paired with a GVS signal was expected to be found more quickly than stimuli that were presented only visually (unimodal control or new stimuli) during the detection task. The results describe behaviours that are consistent with the hypothesis.

Method (4)

Participants

Twenty six UoK students who had not taken part in any of the previous experiments were recruited.

Stimulus Displays

Forty five images displaying novel objects or "Fribbles" (these stimuli were also used in Experiment 3) were taken from the stimulus set by Barry, Griffith, De Rossi and Hermans (2014). These are artificial, 3-D stimuli which mimic the structures of animals and can be experimentally manipulated in terms of similarity by altering the central body structure (species), or attached appendages (four features differing in colour and shape). Three images of coloured dots (red, blue purple – similar shades to the Fribble stimuli) were also created in GNU Image Manipulation Program. All images were resized to 119^2 pixels and presented on a white background. These images were shown within and alongside a 9x7 grid also created in GNU Image Manipulation Program. The grid had a black outline, black interior gridlines, and a white background.

Participants' head position was again held constant during experimental trials using a chin rest.

Design

All participants completed a single experimental session comprised of thirteen trial blocks. Each block contained an encoding phase where the positions of objects were incidentally learnt and a test phase where visual search for primed and unprimed stimuli was assessed. A single target object-location association was paired with a GVS signal during the encoding phase only.

To ensure that any priming effects were not stimulus specific, two arrays were created which varied the grid locations and images within the visual search display. These arrays were counterbalanced across participants so that half of the sample completed a version of the

experiment with array A and half with array B. Responses for both arrays were later combined for the analysis.

Procedure

To disguise the memory-related nature of the study, the experiment was advertised as an investigation into "Speed of Detection". Participants were told that the study was investigating how quickly individuals were able to detect stimuli and were encouraged to respond as quickly and accurately as possible throughout the experiment (in accordance with Manelis et al., 2011).

Following informed consent, participants' skin was prepared for stimulation and the electrodes placed over the mastoids. After an impedance check, participants began the experimental tasks. Susceptibility and perceptions towards the GVS were assessed at the end of the study using the perception sheet from Experiments 1-3 (see Appendix D). Any participants who noticed an association between a visual stimulus and a GVS pulse were discounted (N= 1) to eliminate any influence of somatosensory sensation on performance. Participants were debriefed and informed that their memory had been tested at the end of the session. The experimental tasks are described below.

Encoding phase (detection task). A simple RT task was first performed to allow participants to incidentally encode the images and the locations in which they appeared (see Figure 5.12). The trial began with an empty grid (ISI) displayed for 550ms which was followed by the presentation of an image within the grid for a maximum of 1000ms. Participants were instructed to press the spacebar as quickly as possible when they saw an image (regardless of its identity) appear inside the grid. The empty grid was then re-presented at a variable ISI between 500-800ms (included to prevent participants predicting when to

respond and to account for the requirements of the stimulation device). A GVS signal was discharged to match the onset of the target stimulus.

During the detection task, object images were randomly interleaved with images of dots which were not tested at recall. Their purpose was to provide a baseline measure of RT sensitive to when participants had no intention of memorising stimulus-location since by virtue of looking the same, no single dot could be remembered as appearing in a unique location (Manellis et al., 2011). RTs for both stimuli types were compared to determine whether participants had tried to process object images with more effort than dot images (i.e. remember their location). As proposed by the previous researchers, if participants were unaware that their memory for the images was being tested, then there should be no need to use any elaborate encoding strategies towards the objects and thus no significant differences in RTs towards dots and objects should emerge.

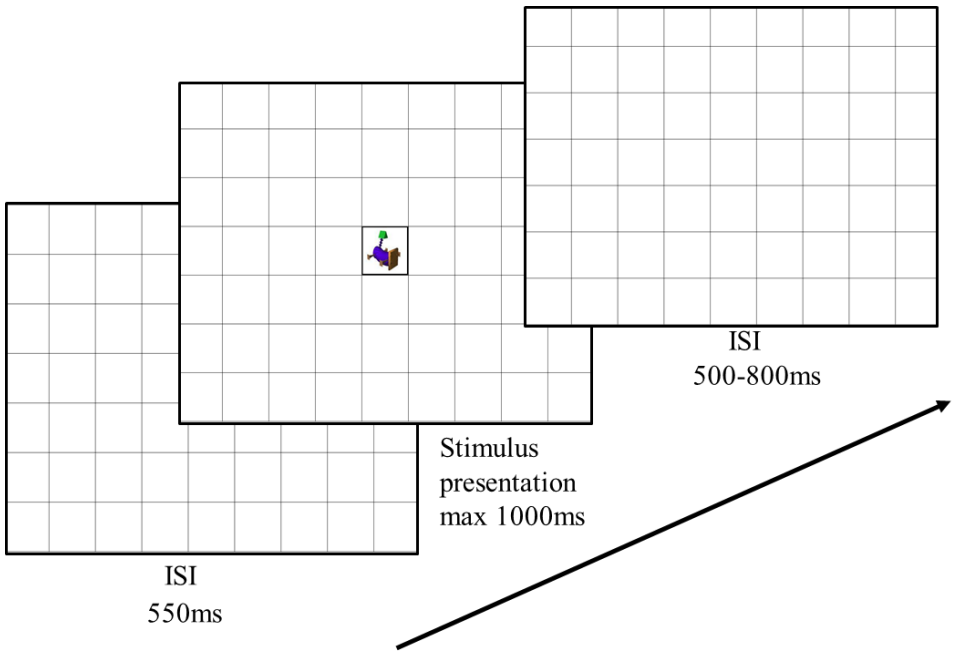


Figure 5.12. Illustration of the detection task (encoding phase) from Experiment 4. Participants were asked to respond by pressing the spacebar as soon as they saw an image appear within the display. A GVS signal was released to accompany the onset of the key visual stimulus.

The detection task consisted of three block repetitions, there were 31 trials per block (21 objects and ten dots). The three dot images (red, blue, purple) were re-presented in three or four different locations during each block repetition. To try and avoid participants processing the dots and objects differently, two of the objects were also re-presented in two different locations and were not tested at recall. A break of 100s was given in between the encoding and test phases.

Test phase (search task). Participants' implicit memory for the encoded display was then indirectly tested using a search task (see Figure 5.13). Each trial began by displaying a search target for 2,000ms, centrally at the top of the screen (above the area that the spatial grid would appear in). This search target could be an image that had previously been viewed during the detection task, or a new image (2: 3 ratio). After a brief variable ISI (500-800ms), a search display containing twelve images then appeared. Participants needed to find and click on the target within the display as quickly as possible; if they decided the target was not in the display then they needed to click a "Not Present" button above the grid. To encourage quick responding, participants were given a maximum of 3500ms to make this response. If participants initially answered incorrectly (and were within the time limits) they were able to select another area in the display. Including this control meant that participants were discouraged from selecting non-target areas in the grid to move onto the next trial. Only responses from the first attempt were included in the analysis. Another brief variable ISI followed the search display and breaks of 30s were given at the end of each test phase.

Central to the key comparison trials (see Figure 5.14) were the search responses that participants made towards the image which had previously been paired with a GVS signal during the detection task when it was shown at its original location (GVS image in GVS location). Another key trial corresponded to a unimodal control image presented in its original encoded location from during the detection task (control image in control location).

Contrasting these two trials provided a similar test to the comparison pairs used in Experiments 2 and 3. That is, it allowed investigations into whether it was easier to find a target visual stimulus that had previously been paired with a GVS signal compared to a visual stimulus that had also been seen but was not paired with GVS.

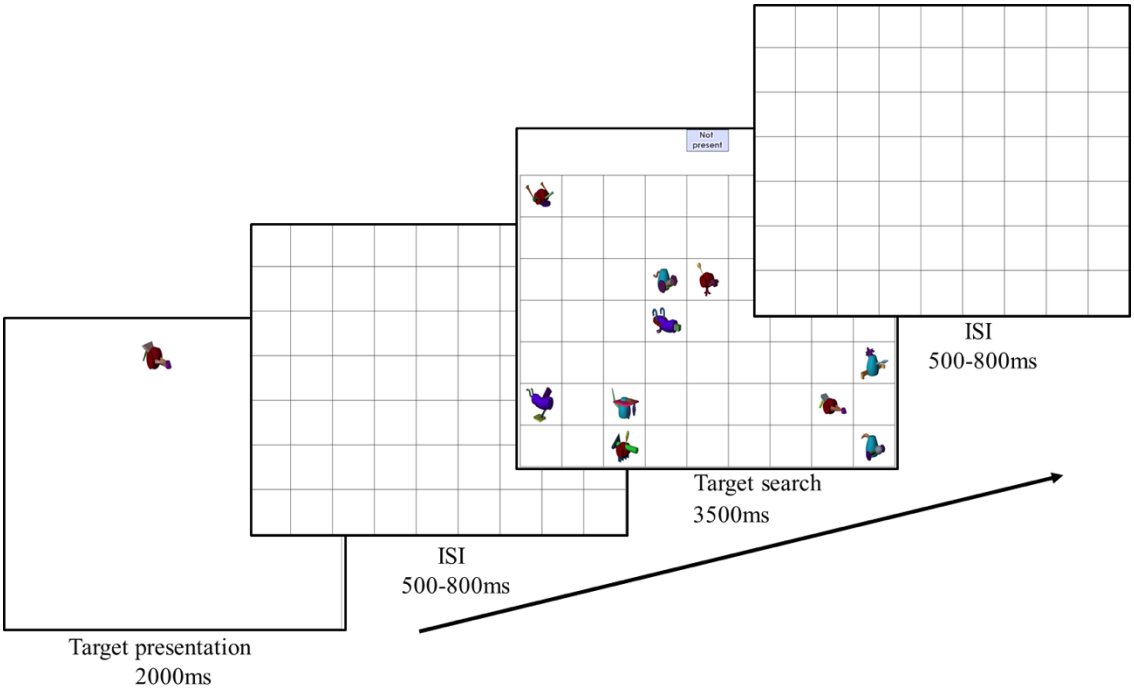


Figure 5.13. Illustration of the search task (test phase) from Experiment 4. Participants were instructed to click on the image if it was present within the search display or select the "Not present" button.

The remaining four key comparisons were included to explore whether GVS signals differentially affect implicit memories for either the identity of an image or the spatial location in which it was encoded. More specifically, if coincident GVS signals improve visual search for the identity of an image (rather than the location it was positioned within), then an image that was paired with a GVS signal will be responded to more quickly compared to other key images (i.e. a unimodal control image, or a new image), regardless of whether it is placed within its original primed location or an alternative control location. On the other hand, if GVS signals facilitate visual search towards the spatial location in which an image appeared during stimulation, then a location that was encoded with a GVS signal will be responded to more quickly during the search task regardless of which images are placed

within it (i.e. the GVS image that was paired at encoding, the unimodal control image, or a new image).

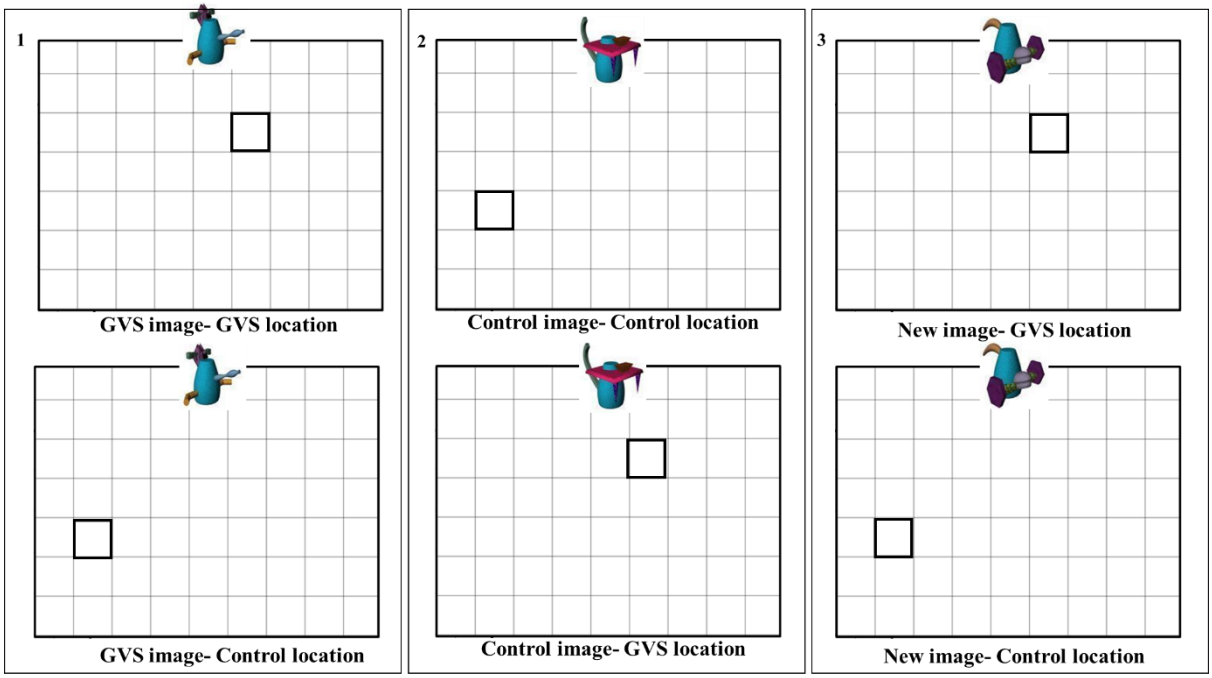


Figure 5.14. Illustration of the six key comparison trials.
Box one shows the active image and its original location that was encoded with a GVS signal (GVS-GVS) and a control location which it was not encoded with (GVS-Control). Box two displays a control image shown and its original location from the detection task (Control-Control), as well as in the location that was paired with a GVS signal (Control-GVS). Box three shows a new image (absent from the detection task) displayed at both the GVS (New-GVS) and control locations (New-Control). Note that images from the key comparisons each shared the same body shape to attempt to constrain difficulty and prevent ceiling effects.

The experiment was also designed to permit further inferences into the mechanisms underlying vestibular-memory effects. If GVS signals exert a more generic arousal effect on implicit memory, then searches for all stimuli should be similarly facilitated by vestibular inputs. This could manifest in primed images (GVS and control) outperforming the new image if any facilitatory effects are short-lived, or could even manifest as a null effect if the arousal induced by GVS extends beyond the encoding phase and into the search task where new stimuli are introduced. Alternatively, if those target stimuli that were paired with GVS are searched for more quickly, then this would suggest a more specific effect whereby vestibular signals individuate aspects of the visual memory representation.

One concern with this design is that search responses for the key comparisons may be facilitated due to the additional exposure that they receive (each object appears as the search target twice). To address this potential problem, images from the background search display in the key comparison trials (see Figure 5.13) were also used as search targets, although most only appeared as the search target once. Exposure to the key comparison stimuli was also reduced by only presenting these stimuli within the background search display for the six key comparison trials, the remaining fourteen trials used a different background spatial display (efforts were made to ensure the spatial displays were perceptually similar). Importantly, the identity and location of the background images for the key comparison trials always remained the same to ensure any changes in performance were due to the key comparisons as opposed to properties of the spatial display.

Stimulation Protocol

Bilateral bipolar current (anode left and cathode right) was discharged to match the onset of the target visual stimulus during the detection task.

A sub-sensory GVS signal of 0.3mA lasting 1000ms was discharged after this current was shown to be below most participants' sensory thresholds during Experiment 2. A total of 39 pulses were released over the course of the experiment. Although this total is reduced from the previous study, the duration of the pulse was doubled to try and encourage the integration of vestibular and visual inputs into a single memory representation.

Results (4)

Data Considerations

The key dependent variable in this experiment was RT. Although accuracy data was analysed it was not prioritised because performance on the search task was anticipated to approach ceiling. Any extreme RT outliers were first removed from the data being entered

into the analysis (either from the whole data set or just the key comparison trials) using a *z*-score correction.

Firstly, the RTs of dot and object trials from the detection task were compared. There were small but significant differences between participants' RTs for dot and all object trials, $t(25)= 2.58$, $p<.05$. RTs were shorter during object ($M= 274$ms) than dot ($M= 277$ms) trials suggesting participants had not used more elaborate (explicit) processing strategies for the objects.

Analyses then determined whether implicit memories were indicated in the test phase by comparing correct filtered RTs (both key and non-key comparison trials) for primed stimuli (from the detection task), with stimuli that were new to the search task. The expected priming effect was present such that, old items ($M= 1588$ms) were responded to more quickly than new items ($M= 18455$ms), $t(25)= -13.11$, $p<.001$.

Next the analyses established whether any effects were likely to be dependent on stimulus properties by comparing correct filtered RTs across the two stimulus arrays. No effects of stimulus array were present within either the key comparison trials [$t(24)= -0.88$, $p=.39$], nor the search task as a whole [$t(26)= 0.42$, $p=.68$] and thus responses from all participants were combined to yield a larger sample.

Key Comparisons

After checking that the above prerequisites had been met, all further analyses were conducted upon the six key comparison trials (see Figure 5.14). Accuracy and RT responses to the key comparisons were analysed using repeated measures ANOVAs with Image identity (control *versus* GVS *versus* new) and spatial Location (control *versus* GVS) as within subjects factors. The main effects of spatial Location or Image identity were first interrogated to explore whether either stimulus feature benefitted from being encoded alongside a GVS

signal relative to unimodal stimuli. The analyses then determined whether the presence of a one-to-one crossmodal mapping facilitated visual search towards the object-location association that was paired with GVS, as indicated by a significant Image x Location with the GVS-GVS condition outperforming other key trials. Only correct RTs were analysed and all post-hoc comparisons used the Bonferroni adjustment.

Reaction time. A significant main effect of Location [$F(1, 23)= 4.49$, $p<.05$, $\eta_p^2 =.16$] revealed that RTs were shorter when images were presented in a Location that was paired with a GVS signal at encoding (M= 1293ms) relative to a unimodal control Location (M= 1407ms). Figure 5.15 shows that this effect extended to all three images, suggesting the GVS signal may have facilitated participants' searches towards this spatial location. Unexpectedly, neither the main effect of Image [$F(2, 46)= 1.16$, $p=.32$, $\eta_p^2 =.05$], nor the two-way interaction [$F(2, 46)= 0.23$, $p=.79$, $\eta_p^2 =.01$] reached significance. The same analysis was also conducted upon just the first five trial blocks, since implicit priming effects are likely to be stronger during these earlier blocks (Manellis et al., 2011). A similar pattern of results was again present but none of the main effects reached significance (all Fs <2.58, all ps>.12, see Appendix D).

Accuracy. These responses approached ceiling levels (see Figure 5.15) and showed no significant main effects (Image $F(2, 48)= 1.91$, $p=.16$, $\eta_p^2 =.07$; Location $F(1,24)= 0.23$, $p=.64$, $\eta_p^2 =.01$) nor an Image x Location interaction ($F(2, 48)= 0.004$, $p=.55$, $\eta_p^2 =.02$).

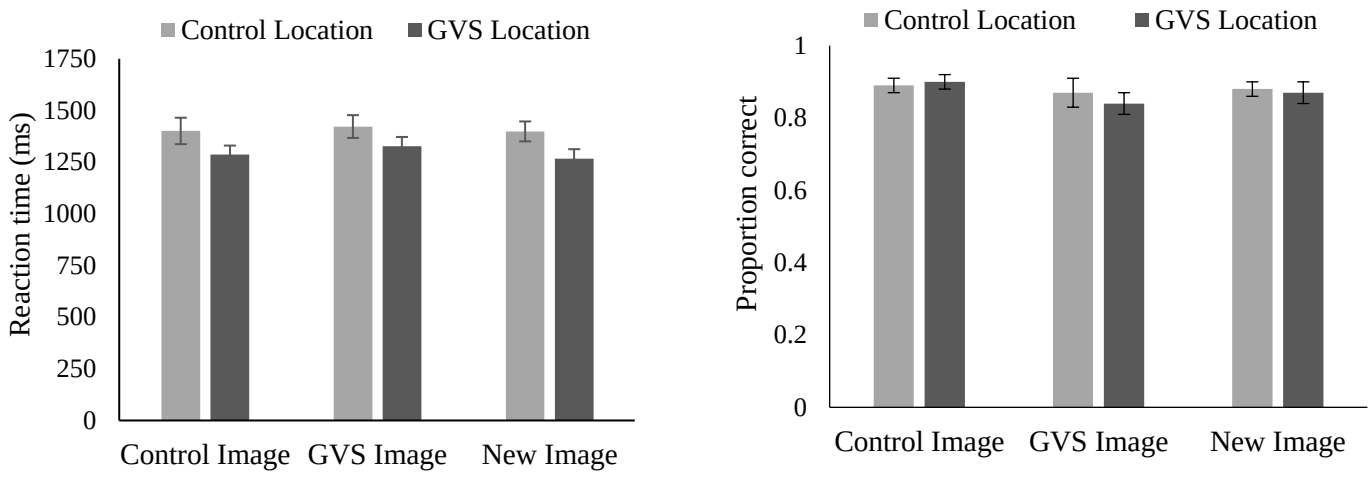


Figure 5.15. RT and accuracy data for the six key comparisons across both arrays.

Discussion (4)

Experiment 4 was designed to examine whether a visual stimulus that was incidentally encoded alongside a sub-sensory vestibular signal would later be found more quickly than unpaired unimodal stimuli. If coincident vestibular signals somehow mark or tag locations or images in visual memory, then the search for a location, object or object-location association that was paired with GVS should be facilitated relative to stimuli encoded in a unimodal (visual) context.

Consistent with the above hypothesis, the results indicate that implicitly priming a particular object at a unique spatial location with a brief pulse of GVS can speed the rate at which multiple objects appearing at this location are later found during a search task. Interestingly, the effect extended to images that had not appeared there before (new image) and even applied to images that had been encoded within another location (control image). The GVS signal appeared to highlight the visuospatial location in such a way that all three images were responded to more quickly when placed in that location, relative to a control location. This advantage occurred with no loss in response accuracy (no significant effects

were present in the accuracy data) and was not significantly influenced by stimulus properties (no significant difference between the two stimulus arrays).

Contrary to the hypothesis, RTs were not shortest during the trial which presented the target image that had been primed at the location paired with a GVS signal at encoding. The results appear to indicate that vestibular signals may be particularly relevant for individuating spatial aspects of visual memory and not an image's identity nor the combination of an image and its encoded location. Consequently, one could explain the current findings (main effect of Location), as reflecting the incorporation of vestibular signals within visual memories to mark one spatial location from another.

This finding is also consistent with Experiment 1 where pairing multiple objects with a GVS signal did not appear to influence old/ new familiarity judgements about the identity of an object, and could potentially explain why an omnibus effect of Association was absent from Experiments 2 and 3. Recall that within Experiments 2 and 3 GVS signals were released during the recall phase when the search target was shown above the grid and participants had to place the image within the correct location. This repeated priming of visual and vestibular stimuli was included to encourage reintegration of the crossmodal representation, however in doing so the GVS signal may have become dissociated from the key spatial location and could even have primed another spatial location (above the grid), potentially reducing any crossmodal gains that were present (Hecht et al., 2009).

Since beginning the write-up of this thesis a replication study (N= 29) has now been completed in collaboration with an MSc student. The main effect of Location was reproduced and extended to unpaired images (new and control) when presented within the location that was encoded alongside a GVS signal. Again vestibular signals appeared to have a specific effect on spatial aspects of the memory representation, while information relating to an

object's identity or an object-location association did not show a statistical advantage of GVS. Importantly, this study reduced potential concerns about false positives (i.e. the effect of Location in Experiment 4 could be reproduced) as well as the influence of stimulus properties by using two different stimulus arrays that more carefully counterbalanced the locations of the key comparison stimuli to prevent any one location from standing out. Stimulus specific-effects were also estimated by including the image and location that were paired with GVS in one array as non-key stimuli in the opposite array to obtain a baseline level of difficulty (without the influence of GVS). However, since the background stimuli comprising the search display still varied across the two arrays, any resulting discrepancies cannot be attributed to the presence of GVS alone.

Despite the limitations described above, Experiment 4 provides initial evidence that incidentally encoding a visual stimulus alongside a vestibular signal can facilitate searches towards spatial elements of the representation during an implicit memory test. Since only particular visual properties were affected by the presence of GVS signals, the results appear to argue against a generic arousal effect and instead suggest that vestibular signals might individuate spatial aspects of the visual memory representation. Further investigations will now be needed to explore how a spatial location might come to be highlighted by GVS in this way. For example, the vestibular signal could carry relevant spatial information (i.e. is the head is upright or moving and in what direction/ at what speed is it travelling?; Wilkinson et al., 2013) that adds to and enhances the visual memory representation in a similar way to other cells that are associated with cognitive mapping (e.g. place, grid, head direction; Brandt et al., 2017; Brandt et al., 2017; Jacob et al., 2014). Alternatively, the effect could be more attention-based such that GVS individuates the part of the visual field that is currently being attended to. Both accounts would also need to rule out the possibility that the effect is contingent upon the motor response that is made during the detection task when the spatial

location is paired with a GVS pulse (e.g. by using eye tracking and removing the keyboard response). A discussion of the findings from Experiments 1-4 is provided below.

Chapter Discussion

This chapter sought to explore the psychological mechanisms underlying vestibular contributions to visual memory. Several experiments assessed whether visual memory performance could be facilitated by the presence of artificial vestibular signals and if so how this effect might occur (i.e. via generic arousal or through the specific signal content being incorporated into visual memory representations). The following sections provide an overview of the findings and insights gained from each experiment as well as from the chapter as whole, before discussing any relevant limitations and how these could potentially be addressed.

Summary of Results

Experiment 1 examined whether multiple visual stimuli were recalled more accurately if paired with a temporally coincident vestibular signal. Contrary to the hypothesis, performance did not differ between conditions in which GVS signals were discharged (unilateral, bilateral) and a no stimulation condition where they were not. Moreover, a marginal performance drop was observed in the bilateral condition where a GVS signal accompanied the presentation of multiple visual stimuli. One possible reason for this failure was that the one-to-many mapping which paired several visual features (objects and locations) with a unique GVS pulse may have been unlikely to support or enhance memory recall. Experiments 2 and 3 tried again to uncover an effect by replacing the previous one-to-many mapping with a one-to-one mapping between the sensory inputs, whereby a single visual stimulus was paired with a GVS signal. It was hoped that doing so would reduce any ambiguity associated with the crossmodal mapping and ease the integration of vestibular inputs into the visual memory representation. In line with this idea, the results showed that

participants were more likely to recall the location in which an object had been encoded when this association was paired with a vestibular signal (relative to a unimodal control association), during the middle section of the experiment where learning may have been more likely to take place. To build on this finding and improve the quality and power of the RT data that had been gathered, Experiment 4 shifted to a new paradigm which tested memory indirectly and permitted more effective measurements of RT. The paradigm also allowed investigations into the effects of a coincident vestibular stimulus on different visual properties (image identity, spatial location and object-location association). In line with the hypothesis, Experiment 4 showed that pairing a spatial location with a unique GVS signal at encoding facilitated the speed at which targets at this location were found, relative to a unimodal control location.

Together Experiments 1-4 provide preliminary evidence that encoding a visual stimulus with a unique coincident GVS signal can facilitate later unimodal processing of the visual stimulus.

Theoretical Mechanisms

Another key aim of this chapter was to advance upon previous findings (Bächtold et al., 2001; Dilda et al., 2012; Ghaheri et al., 2014; Wilkinson et al., 2008) by providing a theoretical account of how visual memory might exploit vestibular signals; i.e. via a generalised enhancement or through the specific signal content being incorporated into visual memory representations. Although the current findings cannot provide a complete explanation of the psychological mechanisms of vestibular-memory interactions, they do offer some theoretical insights. Firstly, the fact that participants' performance was not improved by the presence of vestibular signals in Experiment 1 where there was a one-to-many mapping, but was facilitated by a one-to-one mapping during parts of Experiment 2 and

Experiment 4, suggests that vestibular signals (alike the other sensory modalities) may inform visual memory at the level of a specific episode. Secondly, if vestibular signals were able to exert a more general non-specific arousal effect on memory processes, then one might expect the processing of all experimental stimuli to be enhanced given that they were presented soon after a GVS pulse (i.e. null effects for Experiments 1-4) (Wilkinson et al., 2008). Instead, responses towards visual stimuli that were paired a GVS signal were facilitated relative to unimodal stimuli during particular parts of the experiment where learning was more likely to place (Experiments 2 and 3) and towards spatial aspects of the memory representation (Experiment 4). Discharging temporally coincident vestibular signals did not simply enhance performance towards all visual stimuli. Overall the results provide some tentative evidence that visual memory might be sensitive to the nature of the vestibular input, with the brain utilising the specific momentary signal content in a similar way to the other sensory modalities where temporally coincident auditory and tactile inputs have enhanced visual memory performance (Lehmann & Murray, 2005; Murray et al., 2004; Murray & Sperdin, 2010).

These effects appear to diverge from previous reports whereby vestibular stimulation has enhanced memory performance in the absence of a one-to-one mapping (i.e. stimulation was delivered continuously and accompanied multiple stimuli: Bächtold et al., 2001; Dilda et al., 2012; Ghaheri et al., 2014; Wilkinson et al., 2008). This raises the possibility that a generic arousal mechanism of vestibular stimulation exists in addition to the more specific account presented here. It could be argued that the brief sub-sensory pulses of GVS used in the current chapter may not have revealed a non-specific arousal response to stimulation because the vestibular inputs delivered were insufficient or differed in some way to the previous studies. Additionally, the paradigm did not permit hemispheric inferences into the impact of different stimulation configurations which may have been relevant in replicating a

non-specific effect. Both Bächtold et al. and Wilkinson et al. evidenced a memory facilitation for multiple visual stimuli when applying vestibular stimulation which activated the right hemisphere (left ear CVS, anodal GVS to left mastoid). Although these results could reflect generic hemispheric arousal, a more specific account could also underlie the effect whereby vestibular inputs selectively activate particular brain structures which boost specific processing resources associated with the memory task. The current findings seem to fit with the latter explanation and provide further evidence that the content of vestibular inputs may enhance memory processes in addition to an arousal component.

This chapter can also offer some insights into which memory processes might be facilitated by vestibular inputs. Within Experiments 2 and 3 participants were asked to memorise the spatial matrix display and then to explicitly retrieve the location in which individual objects had previously been presented, thus providing an indication of participants' ability to consciously recall an episode. Although the results did not show the predicted omnibus effect of Association, there was tentative support that pairing a single visual stimulus with a GVS signal could facilitate recall relative to an unpaired unimodal stimulus, consistent with a vestibular contribution to explicit episodic memory.

Experiment 4 instead tested visual memory indirectly using a detection (encoding) and visual search (recall) task. Participants were not instructed to memorise the spatial matrix display and efforts were made to make the encoding and recall tasks appear unrelated. Nonetheless, memory processes were still indicated by a priming effect for previously viewed stimuli. Further, pairing a spatial location with a GVS signal during the detection task appeared to facilitate the speed at which this location was later responded to during the search task. The memory processes that were facilitated in this task seem to differ from the episodic memories that were explicitly tested in Experiments 2 and 3. Instead, Experiment 4 appeared to reflect an effect of vestibular inputs on more implicit memory processes that retain the

spatial location of visual attention/ focus, such that when the GVS signal was delivered it somehow marked the target spatial location as different or privileged which in turn facilitated later searches for this stimulus. This effect may relate to the pathways that the vestibular system shares with neurons that are involved in generating cognitive maps of the environment (such as grid, place, border and head direction cells). Spatial memory is based on the retrieval of details from these maps (Brandt et al., 2017; Hitier et al., 2014). Vestibular signals could therefore carry relevant implicit information that adds to the visual memory representation by marking an individual spatial location (e.g. what direction was the head facing in relation to the spatial location, vestibular gravitational down, body acceleration), in turn aiding later navigation/ searches back to this remembered location

Further research would now be worthwhile to better determine which aspects of memory are likely to be reliant on vestibular inputs. Researchers could also begin to investigate which stage of memory processing (e.g. encoding, recall) vestibular signals are most likely to impact. The data from Experiment 4 (as well as that of Bächtold et al., 2001) appear to indicate that vestibular signals may be particularly influential when they are encoded alongside visual stimuli, potentially because the GVS signals that were delivered at recall (and the priming phase) during Experiments 2 and 3 broke the association between vestibular inputs and the target spatial location. However, more direct investigations are needed before any conclusions can be made about whether the timing of vestibular stimulation is relevant (Bigelow & Agrawal, 2015). Researchers might also want to investigate how often visual and vestibular inputs must be experienced together before they can be co-represented (Hecht et al., 2009). Recall that Experiments 1-4 all included multiple repetitions of the crossmodal pairing across several trial blocks to attempt to integrate the sensory inputs in an associative manner. Further experiments could now investigate how many repetitions of the crossmodal pairing are required before the inputs can be bound into a

single memory representation and if a single-trial could suffice to elicit beneficial memory effects. As single-trial learning effects have already been demonstrated within other sensory modalities using simple continuous recognition paradigms (Murray & Sperdin, 2010; Thelen & Murray, 2013; Thelen et al., 2015), these effects may well extend to visual-vestibular interactions too.

The preceding discussion highlights the important gains that this chapter offers towards evidencing and understanding how vestibular signals might affect memory. Nonetheless, it should be noted that omnibus effects of GVS were frequently absent (main effects present in Experiments 1 and 4 only) and the observed patterns of improvement contained inconsistencies (i.e. Experiment 1 recall for the no stimulation and unilateral conditions was similar; Experiment 2 the control association appeared to outperform the active association during the final block; Experiment 4 the object-location association encoded with GVS did not elicit the fastest RT). Potential explanations for the absence or strength of these effects are explored below.

Limitations

The influence of GVS may have been reduced if the vestibular sense, like the other sensory modalities, is subjected to binding constraints (spatio-temporal and semantic congruency; Spence, 2011). Efforts were made to ensure that the onset of the visual and vestibular stimuli temporally coincided to conform with previous studies which have shown that multisensory stimuli are more likely to be integrated when presented close together in time (Stevenson & Wallace, 2013; van Atteveldt, Formisano, Blomer & Goebel, 2007). To do so the onset of the GVS and visual stimuli were matched across the experiments. However, to measure RTs in response to the key stimuli, the offsets of the visual and vestibular stimuli were not always synchronised (participants' RT could be shorter or longer than the GVS

signal duration) which could have interfered with crossmodal binding. Importantly, van Wassenhove, Grant and Poeppel (2007) showed that auditory and visual stimuli separated in time by as much as 200ms were still perceived as simultaneous, indicating that the short time-lag between the visual and vestibular inputs should not have prevented crossmodal integration.

It should however be noted that the temporal proximity of crossmodal stimuli appears to be particularly important in contexts where the to-be-bound stimuli are incongruent or are not naturally related (Donohue, Appelbaum, Park, Roberts & Woldorff, 2013; Stevenson & Wallace, 2013). van Atteveldt et al. (2007) demonstrated interactions between the temporal proximity and content of crossmodal stimuli, such that sounds which matched the identity of a visual stimulus were less affected by temporal disparity relative to those sounds with a different identity to the image. These findings may be relevant to this study, where it could be argued that the content provided by the visual and vestibular inputs was incongruent (i.e. visual inputs indicate the head is stationary, while GVS signals reflect an illusory head movement/ shift in gravitational pull).

Another potential barrier to crossmodal integration may have related to the method of vestibular stimulation. Vestibular receptors are sensitive to head motion, but stimulation techniques other than true motion are often used so that sufficient vestibular stimuli can be comfortably applied in experimental settings (Lopez et al., 2008). This chapter implemented GVS which alters the firing rate of the otoliths and the semicircular canals (Fitzpatrick & Day, 2004). However, GVS also involves unnatural peripheral stimulation meaning it can activate brain regions which would not be associated with natural vestibular stimulation (Ferrè, Kaliuzhna, Herbelin, Haggard & Blanke, 2014). Further crossmodal interactions may therefore be encouraged by stimulating the vestibular system under conditions in which the visual and vestibular systems naturally operate. Passive whole-body yaw rotations permit

such stimulation and the corresponding peripheral vestibular signals can also be more carefully controlled to further isolate the contribution of the vestibular inputs (Palla & Lenggenhager, 2014). Future research could consider matching the speed/ direction of the chair rotation with a visual stimulus such as an optic flow display at encoding. Recall for various elements of the visual display could then be tested to determine whether further crossmodal binding is possible when the semantic and perceptual correspondence between the sensory inputs is improved.

The stimulation parameters adopted in this study may have also limited vestibular-memory interactions effects by failing to activate the vestibular afferents to a sufficient degree. Brief GVS pulses were released to temporally coincide with the presentation of visual displays. This configuration was adopted so that crossmodal effects could be studied in a way that was comparable with existing multisensory research (Lehman & Murray, 2005; Murray & Sperdin, 2010). Additionally, the fact that even very brief GVS pulses (lasting a few ms) have been shown to induce vestibular reflexes (Watson & Colebatch, 1998) and postural changes (Britton et al., 1993), indicates that this modality is capable of inducing behavioural effects. However, it should be noted that the vestibular inputs delivered in Experiments 1-4 were relatively few in comparison to other vestibular stimulation studies (stimulation delivered for several minutes or throughout a task) which have altered memory performance (Bächtold et al., 2001; Dilda et al., 2012; Lee et al., 2014b; Wilkinson et al., 2008). Applying currents in brief bursts can also make the GVS more noticeable, meaning smaller amplitudes must be adopted to avoid the signal becoming supra-sensory (Fitzpartrick & Day, 2004).

This chapter aimed to build an effective paradigm by developing the one-to-one approach, but future research could now experiment with different stimulation parameters using alternative paradigms. For example, continuous GVS signals could be delivered for longer periods to increase the activation of the peripheral afferents. The side of vestibular

activation could also be switched to accompany a visual stimulus presented on the right or left side of space to determine whether or not particular stimulation configurations which provide specific information are more likely to impact memory (i.e. a general arousal effect versus lateralised signal content that matches the side of space that the visual stimulus was presented within; Bigelow & Agrawal, 2015). Additional demographic data would also be useful here to explore whether interactions with handedness are at play (i.e. do lateralised activations of the vestibular system differently affect the memory performance of left-vs.-right handers?). Importantly, the experiments in this chapter indicate that delivering waves of GVS may not benefit visual memory if the one-to-one mapping between a visual stimulus and vestibular signal is undermined, future research should therefore ensure that the crossmodal pairing is unambiguous regardless of the stimulation parameters used.

Conclusion

This chapter has provided the first evidence that pairing a single visuospatial stimulus with a unique GVS signal can facilitate later unimodal visual processing. The results appear to argue against a generic arousal effect of GVS on visual memory and in favour of a more specific individuating account. The chapter offered a possible psychological mechanism for vestibular-memory interactions, in which the content of vestibular signals is used to mark one visual memory from another, particularly spatial aspects of the memory representation.

Chapter 6
General Discussion

Overview

A growing body of evidence has demonstrated altered cognitive function and wellbeing following vestibular dysfunction and artificial vestibular stimulation. Advances in neuroimaging have also provided new insights into the cortical pathways that might support such interactions (see Smith, 2016 for a review). Yet, the psychological reach of the vestibular system still remains poorly understood and as a consequence the role of vestibular inputs are often downplayed within cognitive theory. The relatively late discovery and understanding of the vestibular system as a determinant of cognitive function (relative to the other sensory modalities) also means that the theoretical mechanisms underpinning vestibular-cognitive effects are still incomplete (Grabherr et al., 2015). This thesis aimed to review and extend upon existing literature by exploring if and how vestibular signals might contribute to cognitive processing in clinical and healthy populations. Visuospatial memory was selected as the focal starting-point, since there is already a strong body of evidence linking vestibular dysfunction with impaired spatial memory and navigation (Smith, 2016).

The overall goal of the thesis was to provide evidence to support an interaction between the vestibular and memory systems and to understand how vestibular inputs might inform visual memory and other allied cognitive processes. In Chapter 2, neuropsychiatric and balance investigations were performed in a sample of patients with vestibular dysfunction. This study explored whether memory and other relevant cognitive processes were dependent on vestibular function and the extent to which this association was influenced by the presence of comorbid psychiatric and fatigue variables. Chapters 3 and 4 sought to remediate some of the memory and other allied cognitive deficits found in Chapter 2 by applying artificial vestibular stimulation to a sample of TBI patients with significant

neuropsychiatric deficit. Having identified several affected memory processes in Chapters 2-4, Chapter 5 then investigated how vestibular signals might be used to aid memory function. A series of experiments used artificial vestibular inputs to explore whether visual memory can incorporate unique, coincident vestibular to enhance individual memory representations.

Summary of Results

In Chapter 2, patients with vestibular dysfunction (predominantly VM) completed a broad, standardised battery of cognitive, psychiatric, fatigue/ sleep and balance assessments during their initial visit to a neuro-otology clinic. The findings both confirmed and extended upon previous studies by demonstrating high prevalence rates (>50% of the sample) of clinically significant anxiety, fatigue and sleep disturbance, alongside below average cognitive performance (relative to age-matched normative data) on tests of sustained attention, working memory capacity, spatial working memory and short-term memory for complex patterns. Moreover, EFA and SEM analyses showed that vestibular function (as indexed by postural stability) accounted for a significant proportion of the variance (17%) in visuospatial memory performance, independent of any age-related effects. Importantly, this association could not be explained by the presence of psychiatric or fatigue/ sleep symptoms. Taken together, the results demonstrate the widespread impact that vestibular dysfunction can have on various aspects of wellbeing (notably fatigue/ sleep and anxiety) and show that objective cognitive performance, particularly on tests of short-term visuospatial memory, was directly related to vestibular functioning.

Chapters 3 and 4 then explored whether the neuropsychiatric disturbances described above could be remediated using CVS. Eight patients who had sustained moderate to severe TBIs completed a 20/ 24 week protocol in which daily sessions of sham stimulation (N= 6) and then active CVS (N= 8) were delivered for four and eight weeks respectively. Neuropsychiatric symptoms were monitored behaviourally at key stages of the protocol and

electrophysiological recordings were also taken to see if certain EEG/ ERP patterns could be normalised. Resting spectral power was quantified across the delta, theta and alpha bands, P300 amplitudes and latencies were also measured during a visual n-back task as indicators of attention and working memory. The data did not appear to evidence a consistent beneficial response to CVS. Yet individualised changes were present, with seven out of the eight participants showing a significant behavioural improvement from their pre-CVS baseline on at least one cognitive measure following CVS. All participants also showed alterations in background brain activity over at least one power band. However contrary to the hypothesis, power was generally decreased across both the slower (delta *N*= 4, theta *N*= 3) and faster bands (alpha *N*= 5). Only participant 08 demonstrated beneficial ERP changes which could support the hypothesis. In contrast, psychiatric and fatigue symptomology were unaffected by CVS. Overall, this study provided tentative justification for further investigations of CVS interventions and evidenced a connection between vestibular and short-term visual memory functioning that was not dependent on comorbid psychiatric and fatigue symptomology. Further beneficial effects of CVS were likely prevented by the fact that a small and heterogeneous sample was recruited using a relatively broad criteria.

Finally, Chapter 5 sought to uncover potential mechanisms behind the memory effects observed in previous chapters. Four exploratory experiments paired the onset of to-be-remembered visual stimuli with a temporally coincident GVS signal and compared recall/ search for these crossmodal stimuli against unimodal visual stimuli that were not paired with a signal. Several paradigms were implemented to determine whether any beneficial stimulation effects could be demonstrated (Experiments 1-4) and by what mechanism these effects were likely to occur (Experiments 1 and 4). Two potential mechanisms were explored: a generic arousal account which posits that vestibular activations may upregulate brain activity leading to widespread cognitive gains, including memory (Wilkinson et al., 2008);

and a more specific account where visual memory makes use of vestibular signal content to individuate one memory from another. Experiment 1 demonstrated that a one-to-many mapping between a unique GVS signal and multiple visual objects and locations did not facilitate recall over and above a unimodal condition where no GVS was administered, contrasting with both the generic and specific accounts. Experiments 2 and 3 then introduced a one-to-one mapping between a single visual stimulus and a unique GVS signal and evidenced improved recall for the crossmodal target during parts of the experiment in which learning was more likely to take place. Finally, Experiment 4 incorporated a different paradigm so that implicit memories for various elements of the memory representation (image identity, spatial location, and object-location association) could be investigated and used RTs as the primary outcome. Priming a single spatial location with a GVS signal during memory encoding facilitated later visual search towards this location, regardless of which image was presented within it. Similar enhancements were not present towards the identity of an image nor the association between an objection and the location it was encoded within. Taken together, the results indicated that pairing a GVS signal with a single visual stimulus, particularly a spatial location, facilitated later unimodal processing. This outcome is consistent with the idea that vestibular signals are integrated within visual memories to help mark one spatial location from another, beyond any generic effect reported elsewhere in the literature.

Theoretical Insights

This thesis studied different samples and applied various experimental paradigms to provide new insights into the types of memory influenced by vestibular signals, previous studies have lacked such specificity. Firstly, Chapter 2 implemented the standardised CANTAB to reveal a high prevalence of memory impairment, particularly on tests of working memory abilities including memory capacity for a spatial sequence (56%) and the

manipulation and retention of spatial information (53%). Such pervasive effects are not typically found following other sensory deficits, highlighting the potentially special role of the vestibular system in memory processing (Highstein, 2004). Vestibular dysfunction (posturography) also directly contributed to performance on a cognitive factor which loaded strongly on tests relating to spatial working memory and learning object-location associations. Secondly, Chapter 3 demonstrated individualised behavioural improvements amongst five of the eight TBI participants on at least one memory measure following CVS. All five participants showed a change on a test that involved a spatial component (SSP, SWM, PAL, n-back); most of these tests did not emphasise pattern/ object recognition. Taken together, these clinical investigations indicate that vestibular inputs are likely to be particularly relevant when mentally manipulating or remembering visuospatial information over short periods of time. This association may relate to vestibular connections to spatial working memory centres which are thought to include the frontal cortex, basal ganglia and hippocampus (see Chapter 1; Baier et al., 2010; Bigelow et al., 2015b).

By implementing a series of experimental tasks Chapter 5 was then able to show that this connection between the vestibular and short-term visuospatial memory systems could operate under various encoding and test conditions. GVS enhanced episodic visual recall during Experiment 2 where participants were explicitly told to memorise a visual display. Additionally, GVS facilitated more implicit memory processes that retain the spatial location of visual attention/ focus during Experiment 4 where the memory-related nature of the task was disguised. Both implicit and explicit aspects of short-term visual memory are therefore likely to be reliant on the ever-changing content of vestibular inputs

As well as characterising the memory processes likely to be affected by vestibular inputs, it was also important to explore the nature of this connection at the psychological level. Chapter 2 initially investigated whether vestibular inputs influence cognitive

processing directly (potentially via disturbances to the vestibulo-cortical network) or indirectly through comorbid symptomology (Bigelow & Agrawal, 2015). The results demonstrated a direct association between visuospatial memory abilities and performance on a balance platform. Chapters 3 also provided suggestive evidence to support a direct pathway since any CVS-related changes in cognitive performance were not dependent on co-occurring alterations in mood or fatigue.

Having shown that vestibular signals can make an independent contribution to memory functioning, later chapters then explored whether this contribution might occur via a generic arousal mechanism or could in fact be more specific with memory processes utilising the contents of vestibular signals. During Chapter 4 the most consistent findings related to spectral power, which appeared to decrease in response to CVS across all three bands. These widespread decreases in spectral power fit with the idea that vestibular inputs can elicit non-specific changes in cortical arousal (Wilkinson et al., 2012). The activation of cortico-limbic reticular circuits which comprise key elements of the brain's core arousal system are thought to underlie these global arousal effects (Bottini & Gandola, 2015) and could explain why multiple neurological and psychiatric disorders have previously been alleviated by vestibular stimulation (Wilkinson et al., 2014). However, the fact that patterns of CVS-related improvement were inconsistent (across participants or within a single individual) or absent from the mood and fatigue measures, suggests that the results were not simply operating according to this broad "one-size-fits all" approach and that more specific modulatory effects may have been present (Grabherr et al., 2015).

Chapter 5 was able to test whether vestibular stimulation functions with more specificity by pairing the onset of visual stimuli with temporally coincident vestibular signals. The experiments showed that vestibular-memory interactions do not tend to operate via generalised increases in arousal alone. Instead, any effects were subtle and only occurred

when there was a clear one-to-one mapping between visual and vestibular stimuli. Experiment 4 also provided evidence to suggest that the self-motion information contained within vestibular signals may be particularly relevant to spatial aspects of the memory representation. More specifically, while the identity of an image and the object-location association were unaffected by the presence of GVS, searches towards a location that had previously been paired with a GVS signal was improved. Overall, the results from Chapter 5 suggest that vestibular signals may provide content that is relevant to and integrated within visuospatial memory representations.

Vestibular inputs are diffusely projected to a range of neural circuits (Lopez et al., 2012, Suzuki et al., 2001), and can modulate several important neurotransmitters (Black et al., 2016). Thus it is perhaps unsurprising that various cognitive, autonomic and affective changes have been documented following vestibular dysfunction and stimulation (see Bigelow & Agrawal, 2015; Grabherr et al., 2015; Miller & Ngo, 2007; Utz et al., 2010 for reviews). However, the current data suggest vestibular inputs are likely to play a more specific role, particularly in visuospatial memory processes, over and above any general disorientation or compensation mechanisms that might occur following vestibular dysfunction and vestibular stimulation (Hanes & McCollum, 2006; Wilkinson et al., 2013).

Chapter 5 provided one theoretical mechanism which could potentially explain the more specific role of vestibular signals within visuospatial memory processing. Given that humans and wildlife need to navigate and remember spatial environments for their survival, the contents of vestibular signals could carry relevant spatial information (i.e. is the head is upright, is it moving, what speed/ direction am I travelling?; Wilkinson et al., 2013) that enables them to represent and update their movements within 2-D (static-egocentric mode: up-down/ left-right) and 3-D (dynamic- allocentric mode: rotational and linear) environments (Brandt & Dieterich, 2016; Brandt et al., 2017). Vestibular signals may therefore enhance

visual memory representations by adding to the cognitive maps that are produced by place, grid and head direction cells and provide a kind of internal compass which represents one's position and distance in space (Brandt et al., 2017; Jacob et al., 2014). Correspondingly, when vestibular system becomes dysfunctional, tasks which draw upon these spatial resources, either directly (e.g. navigation, spatial memory; Brandt et al., 2005) or more implicitly (e.g. mental imagery; Grabherr et al., 2011; Péruch et al., 2011 or arithmetic; Risey & Briner, 1990), are likely to be amongst the most impaired.

Overall the findings from this thesis fit within an emerging body of literature that has shown human memory to be affected by vestibular dysfunction (Bigelow et al., 2015b; Brandt et al., 2005; Kremmydal et al., 2016; Schautzer et al., 2003) and vestibular stimulation (Bächtold et al., 2001; Dilda et al., 2012; Ghaheri et al., 2014; Wilkinson et al., 2008). The present findings also build upon these studies to show this connection can be evidenced across multiple vestibular pathologies (even those with partial loss or intermittent vestibular symptoms) and using previously unapplied artificial stimulation configurations, that if anything provide less coincident vestibular input relative to other studies (i.e. offline CVS, brief sub-sensory pulses). Further, by implementing a different set of standardised objective cognitive tests and experimental paradigms which can more carefully characterise visual memory function, this thesis has been able to show that the effects of vestibular inputs are likely to be greater on memory tasks with a spatial rather than pattern-based emphasis, and can extend across both explicit or implicit memory tasks. Combined, the findings evidence a real, yet subtle vestibular contribution to memory function with visuospatial memory processes appearing directly reliant on vestibular signals and unusual/ increased vestibular inputs enhancing visuospatial memory performance, irrespective of any comorbid symptomology and at the level of a single memory representation.

Clinical Implications

Chapter 2 revealed a high prevalence of cognitive disorder amongst neuro-otology patients which corroborates the pervasiveness that patients have previously self-reported (Grimm et al., 1989: 85% self-reported memory loss and 80% reported confusion; Black et al., 2004: 22 out of 33 patients self-reported memory loss). Moreover, the study showed that this impairment was directly related to vestibular dysfunction. These findings have profound implications for how to manage patients with vestibular dysfunction. Currently, these individuals do not typically receive cognitive screening and their cognitive complaints can often be downplayed as psychiatric/ fatigue-related in origin, or missed completely if they do not volunteer the information (Hanes & McCollum, 2004). This is significant as by failing to address these cognitive symptoms the vestibular condition could be worsened (Yardley & Redfern, 2001). Additionally, since cognitive impairments can arise independently of psychiatric or fatigue symptomology, attempts to remediate cognitive deficits via psychiatric therapy may not be helpful and, depending on the prescribed medication (e.g. pregabalin, benzodiazepines), may even exacerbate them (Stewart, 2005; Park & Kwon, 2008). Instead, referral to a memory clinic or neuropsychologist should be considered to strengthen the patient's remaining cognitive abilities (Brandt et al., 2017).

A second suggestion is that greater use be made of the high concurrence of cognitive deficits, particularly visuospatial memory, during the initial assessment of an individual who complains of dizziness since these symptoms might actually be primary indicators of vestibular pathology (Hanes & McCollum, 2006). Attributing balance problems to a vestibular disorder is not always straightforward - patients can often visit several other specialists (e.g. ENT, neurology) and receive inappropriate treatments (e.g. betahistine, prochlorperazine for the surface symptoms of nausea) before seeing a neuro-otologist. Recall that the current sample had suffered from their balance problem for an average of 3.15 years

before attending their first neuro-otology appointment. To this end, delivering a brief cognitive screen could be useful to determine which patients might benefit from referral to a tertiary neuro-otology service and more comprehensive cognitive assessment. The Neuropsychological Vertigo Inventory (Lacroix et al., 2016) could be a potentially relevant instrument, although further validation is still required to determine how reliably it can identify these neuropsychological impairments and whether it is suitably tailored to the visuospatial memory deficits that have been associated with vestibular dysfunction (see Chapter 2; Brandt et al., 2005; Bigelow et al., 2015b; Kremmyda et al., 2016; Schautzer et al., 2003).

Chapter 2 underscored the relevance of vestibular inputs to cognition and wellbeing and raised the exciting possibility that artificially stimulating the vestibular system might remediate the neuropsychiatric deficits associated with several clinical conditions. Chapters 3 and 4 tested this hypothesis by applying CVS to a sample of TBI survivors. Although, individualised CVS-related improvements were demonstrated, consistent effects were largely absent across the sample or within a single participant. Further research is thus required before CVS can be recommended as a treatment for TBI. Multi-center, double-blinded, placebo-controlled and randomised investigations could potentially address the heterogeneity of TBI by recruiting larger samples and running them through a range of standardised assessments (encompassing cognition, affect, fatigue and activities of daily living) to identify the factors associated with responsiveness to CVS (Snell et al., 2009). Alternatively these studies could employ more restrictive inclusion criteria to ensure the sample share key clinical features (e.g. working memory impairment, temporal lesions, sustained injury within 12 month period) and then target a single core deficit using a few streamlined assessments (e.g. working memory: Digit span; Weschler, 1987 and the Corsi block-tapping task; Kessels et al., 2000). The fact that CVS is non-invasive, easily applicable, places minimal demands

on the patient and can activate several cortical and subcortical structures simultaneously, means that further attempts to remediate these neuropsychiatric symptoms with CVS are likely to be worthwhile (Grabherr et al., 2015).

Future research could also explore the therapeutic potential of vestibular stimulation in other clinical conditions that are characterised by memory deficits. For example, one of the earliest symptoms in AD is an impairment to topographical memory. Patients can often find themselves getting lost whilst navigating both familiar and unfamiliar environments which restricts their independence and causes further concern for their carers (Bird et al., 2010). Interestingly, Previc (2013) suggested that vestibular loss is likely to contribute to the development of AD. The author highlighted the major projection that emanates from the horizontal semi-circular canals and leads to the hippocampus and parahippocampal gyrus, as well as associated regions such as the posterior parietal-temporal and posterior-cingulate cortices, all of which are strongly implicated in topographical memory and are damaged during the early stages of AD.

If vestibular damage can hinder topographical memory systems and therefore contribute to AD symptoms, then vestibular stimulation may help to prevent or slow the disease trajectory. The findings from Chapter 5 suggest that GVS signals could be applied to aid navigation to a remembered location (e.g. a patient's home or a room within the home) by highlighting or tagging spatial elements of a visual memory representation. Since spatial memory and navigation decline with age and are an important feature of several neurological conditions (including AD and mild cognitive impairment; Brandt et al., 2017), future research could now explore the therapeutic potential of GVS as an intervention for neurological conditions which present with these impairments. The relevance of such studies are highlighted by recent reports that age-related vestibular loss is associated with lower cognitive performance and adverse geriatric outcomes (increased odds of falling, inability to

complete activities of daily living), meaning therapeutic efforts which promote vestibular sensitivity (such as GVS) could help to thwart these devastating and costly outcomes (Bigelow et al., 2015b; Semenov et al., 2016). Furthermore, incorporating screens for vestibular and visuospatial memory impairments within the clinical routine of the elderly may help to identify individuals who are at-risk of dementia and allow for earlier intervention (Brandt et al., 2017; Harun et al., 2016a; Harun et al., 2016b).

Limitations

The insights gained from this thesis are subject to a number of limitations. Many of these issues have been discussed in previous chapters but one overarching limitation has been the focus on visuospatial processing. As stated previously, visuospatial memory was selected as the starting point since existing literature has already indicated a strong connection between vestibular inputs and spatial memory (Smith et al., 2010; Smith & Zheng, 2013). Efforts were also made to incorporate other cognitive, electrophysiological, psychiatric and fatigue assessments since memory impairments are unlikely to occur in insolation within vestibular and TBI patients and given the exploratory nature of these studies. However, since the CANTAB is a visual battery (all sub-tests involved processing visual stimuli and also a degree of spatial information), it is difficult to isolate the contribution that the choice of assessments made to the findings presented in this thesis (i.e. a specialised contribution of vestibular signals to visuospatial memory). While there is already strong evidence to suggest visuospatial memory processes are likely to be more affected by vestibular inputs than other non-spatial processes (e.g. non-spatial memory on the Wechsler Memory Scale and general IQ, Brandt et al., 2005 and Schautzer et al., 2003; verbal memory and executive function, Bigelow et al., 2015b), future research which directly compares the relevance of vestibular inputs for spatial and non-spatial short-term memory representations is likely to be beneficial.

Further insights might now be gained by delivering cognitive tests in different sensory formats (e.g. auditory, olfactory, and tactile) which place less emphasis on visuospatial processing. Individual memory processes could also be probed in more depth using alternative standardised assessments of particular memory sub-divisions (e.g. long-term, working, autobiographical, and procedural). Experimental paradigms could additionally investigate at which stage of memory processing (e.g. encoding or recall) vestibular inputs are likely to be most informative by systematically varying when vestibular inputs are delivered alongside to-be-remembered stimuli (Bigelow & Agrawal, 2015). While the current research and existing literature give reason to suggest that short-term visuospatial memory is likely to be particularly receptive to vestibular inputs (Smith et al., 2010), perhaps when these are delivered during the encoding phase (see Chapter 5 and Bächtold et al., 2001), further studies would now be useful to directly test these predictions and explore vestibular-memory interactions in more depth.

Another critique relates to the vestibular stimulation protocols that were applied in Chapters 3-5. Although the designs of these protocols were based on previous research (e.g. Bächtold et al., 2001; Vanzan et al., 2016; Wilkinson et al., 2008; Wilkinson et al., 2013), the broader limitations associated with each technique may have influenced the results and accompanying conclusions (Palla & Lenggenhager, 2014). One concern is that any memory facilitations were due to unspecific effects as opposed to vestibular activations (Grabherr et al., 2015). Here efforts were made to isolate the contribution of vestibular inputs by minimising natural head movements (using a chin rest and wedge pillows) and including sham/ sub-sensory stimulation conditions to estimate the influence of tactile/ proprioception stimulation sensations. However, future studies could consider carefully titrating the amplitude of the GVS signal (or the time-rate-of temperature change during CVS) since the percept induced by vestibular stimulation is likely to vary between participants (Palla &

Lenggenhager, 2014). Researchers could also experiment with different amplitudes within the same participant to determine whether any beneficial effects are dependent on particular intensities being delivered. If a dosage-effect is present, this might indicate a generic arousal mechanism (Bigelow & Agrawal, 2015; Palla & Lenggenhager, 2014). Incorporating motion simulators may also be beneficial since the corresponding peripheral vestibular signals can be more carefully controlled relative to other artificial stimulation techniques (Lopez et al., 2012). These devices also offer closer perceptual and semantic correspondence between the incoming vestibular and visuospatial inputs (e.g. applying otolith stimulation via rotational or linear simulators for tasks involving linear representations of mental space; Palla & Lenggenhager, 2014) and could therefore encourage further integration of vestibular signal content within visual memory representations. Continued research such as the above is needed to move closer towards finding the most effective stimulation protocols. Such efforts are worthwhile since they may enhance current understanding of the psychological role of the vestibular system and improve the likelihood of therapeutic benefit in neurological patients (Harvey & Kerkhoff, 2015).

Additional insights into underlying mechanisms of vestibular-memory effects might also be gained from the application of neuroimaging techniques. For example, MRI could be used to ascertain whether the visuospatial memory impairments described in Chapter 1 were accompanied by atrophy to the vestibulo-cortical network (e.g. reduced activity at the hippocampus/ temporoparietal junction), thus supporting a direct pathway. Although Chapter 4 incorporated electrophysiological measures as an indicator of neurological outcome, alternative EEG analyses (e.g. increased electrode sites with more targeted regional analyses; Wilkinson et al., 2012) or MRI might enable better inferences as to whether any CVS-related effects were accompanied by broad scale changes in cortical arousal or more targeted brain activations. Finally, fMRI could be incorporated into the experiments of Chapter 5 to

investigate whether the same brain areas that were active when encoding a crossmodal visual-vestibular pairing were reintegrated at retrieval- as within the other sensory modalities (Hamilton, 1859; Thelen & Murray, 2013). Note that the potential benefits of the above suggestions would need to be weighed against any potential costs to participant comfort and research resources.

Conclusion

This thesis has evidenced a connection between the vestibular and memory systems whereby vestibular dysfunction induces visuospatial memory impairment, and artificial vestibular stimulation can under certain conditions facilitate visuospatial working memory, visual search and explicit recall. The previous chapters provide evidence to suggest that this connection cannot be explained away by comorbid symptomology or age-related decline and does not simply occur via generic arousal mechanisms. Moreover, the thesis shows that vestibular signals may make a more specific contribution to memory at the level of an individual representation by marking one visual event (particularly spatial locations) from another. These findings have potentially profound implications for managing patients with vestibular dysfunction, neuropsychiatric deficits (e.g. TBI, acquired brain injury, Parkinson's disease) and amnesia.

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Appendix A

SEM Analyses from Chapter 2.

SEM results for the remaining balance tests. Neither the VAS, VSS_VS nor the DHI mediated the relationship between age and visuospatial memory performance (see Table A.1).

Table A.1
Results from SEM Analyses Examining the Contribution of Vestibular Dysfunction to Cognitive Impairment Over and Above Normal Age-Related Change.

Measure	Model Fit	Total	Direct	Indirect
VAS	$\chi^2(25, N = 95) = 20.38, p = .73$	-0.54**	-0.55**	0.01
DHI	$\chi^2(25, N = 95) = 24.88, p = .47$	-0.54**	-0.55**	0.01
VSS_VS	$\chi^2(25, N = 95) = 22.53, p = .61$	-0.53**	-0.53**	-0.004

*p<.05, **p<.01.

Model fit for the SEMs involving posturography (balance platform). The basic model (age, balance platform, visuospatial memory) provided poor fit for the observed data as indicated by the significant chi-square test [$\chi^2(51, N = 95) = 99.34, p<.001$]. However, the root mean squared error of approximation (RMSEA= .099) and the comparative fit index (CFI= 0.91) indicated mediocre and good fit to the data respectively (Hooper, Coughlan & Mullen, 2008). Given the small sample size and relative complexity of the model, this model fit was deemed acceptable and the model was interpreted further.

Chi-square difference tests could be used to compare the model fit of the nested models involving the psychiatric and fatigue variables (where the additional direct path between the balance platform and visuospatial memory was added) using the following procedure:

$$\chi^2 \text{ diff} = \chi^2 S - \chi^2 L \text{ and } df \text{ diff} = df S - df L$$

"S" denotes the less complex/ smaller model with fewer parameters to estimate and therefore more degrees of freedom, whereas "L" denotes the more complex/ larger model with more parameters and therefore fewer degrees of freedom. This χ^2 diff-value is distributed with *df*diff degrees of freedom and can be checked manually for significance using a χ^2 table (Werner & Schermelleh-Engel, 2010). If balance function only interacts with cognition indirectly then the additional path between balance function and visuospatial memory should not improve the fit.

While the direct path significantly improved the fit of the model involving the psychiatric variables, the effect missed significance within the fatigue model (see Table A.2). These findings compliment the results presented in Chapter 2 where the direct path retained significance within the psychiatric mediator model (β= -0.27, p<.05) but just missed significance in the fatigue mediator model (β= -0.23, p=.05). These results partially support

the hypothesis (psychiatric model). The relatively small sample sizes recruited here may have prevented any further direct vestibular-cognitive effects from being revealed.

Table A.2

Chi-Square Difference (χ^2) Tests between Mediation Models Which Freely Estimated or Controlled for the Direct Pathway between Posturography and Visuospatial Memory.

Model	**Estimates of Fit**	**χ^2 Difference tests**
Psychiatric Indirect	$\chi^2(79, N = 95) = 125.08, p = .001$	125.08 - 120.08 = 5. The addition of the direct path significantly improved model fit ((>3.841 critical χ^2 difference for 1 *df*).
Psychiatric Indirect & Direct	$\chi^2(78, N = 95) = 120.08, p = .002$	
Fatigue Indirect	$\chi^2(79, N = 95) = 140.35, p < .001$	140.35 – 136.90 = 3.45. The addition of the direct path did not significantly improve model fit (<3.841 critical χ^2 difference for 1 *df*).
Fatigue Indirect & Direct	$\chi^2(78, N = 95) = 136.90, p < .001$	

Appendix B

Individual Patient Case Histories from Chapter 3.

This section summarises the key clinical features of each participant that completed the study. This information was gathered from medical records that were made available to the researcher as well as through interviews with the participant and their carers. These histories include the original GCS classification scheme (where available), as well the clinical guidelines of "mild, moderate and severe TBI" (see Granacher, 2015 for a breakdown of each category). However, it should be noted that the evaluation of TBI is constantly evolving beyond these simple classifications (Manley & Mass, 2013). Efforts have therefore been made to provide a more detailed history which includes structural imaging findings and the participants' most disabling symptoms.

Removed to protect patient privary – contact researcher.

Results Tables for the Analyses of Reliable Change from Chapter 3.

Table B.1

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 01.

Cognitive Test	Discrepancy	*z*	*p*	Point estimate of abnormality (%)	95% CI
PAL					
Baseline_4weeks	0.86	0.12	0.91	45.38	36.24, 54.72
Baseline_8weeks	-0.14	-0.02	0.99	49.27	40, 58.56
Baseline_Follow-up	0.86	0.12	0.91	45.38	36.24, 54.72
SWM_S					
Baseline_4weeks	-2.35	-0.53	0.60	30.02	23.07, 37.54
Baseline_8weeks	1.65	0.37	0.71	35.65	28.34, 43.36
Baseline_Follow-up	-2.35	-0.53	0.60	30.02	23.07, 37.54
SWM-E					
Baseline_4weeks	-0.03	-0.003	0.99	49.88	40.41, 59.36
Baseline_8weeks	17.97	1.66	0.10	5.04*	2.27, 9.14
Baseline_Follow-up	-5.03	-0.46	0.64	32.19	23.73, 41.38
DMS					
Baseline_4weeks	1.18	0.44	0.66	33.21	25.23, 41.80
Baseline_8weeks	0.18	0.07	0.95	47.33	38.61, 56.15
Baseline_Follow-up	2.18	0.80	0.42	21.18	14.55, 28.84
SSP					
Baseline_4weeks	1.75	1.39	0.17	8.37*	1.90, 20.51
Baseline_8weeks	0.75	0.60	0.55	27.59	11.12, 49.05
Baseline_Follow-up	1.75	1.39	0.17	8.37*	1.90, 20.51
OTS					
Baseline_4weeks	0.42	0.34	0.73	36.68	29.27, 44.47
Baseline_8weeks	2.42	1.95	0.05	2.69*	1.08, 5.24
Baseline_Follow-up	1.42	1.15	0.25	12.72	8, 18.52
RTI (ms)					
Baseline_4weeks	17.31	0.41	0.68	34.24	26.67, 42.31
Baseline_8weeks	-105.62	-2.48	0.01	0.74*	0.19, 1.83
Baseline_Follow-up	-26.56	-0.06	0.53	26.69	19.74, 34.38
RVP_hits					
Baseline_4weeks	-9.71	-2.85	0.005	0.26*	0.02, 1.01
Baseline_8weeks	-6.71	-1.97	0.05	2.57*	0.55, 6.74
Baseline_Follow-up	-2.71	-0.80	0.43	21.36	10.23, 35.89
RVP (ms)					
Baseline_4weeks	-34.65	-0.50	0.62	30.80	19.99, 43.04
Baseline_8weeks	-75.87	-1.10	0.27	13.67	7.01, 22.57
Baseline_Follow-up	56.73	0.82	0.41	20.61	11.93, 31.32

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.2

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 02.

Cognitive Test	Discrepancy	*z*	*p*	Point estimate of abnormality (%)	95% CI
PAL					
Baseline_Sham	8.32	1.12	0.27	13.27	7.81, 20.18
Baseline_4weeks	2.32	0.31	0.76	37.78	28.68, 47.42
Baseline_8weeks	4.32	0.58	0.56	28.12	19.96, 37.22
Baseline_Follow-up	1.32	0.18	0.86	42.98	33.55, 52.71
SWM_S					
Baseline_Sham	-1.87	-0.42	0.68	33.84	26.60, 41.56
Baseline_4weeks	3.13	0.70	0.49	24.27	17.80, 31.50
Baseline_8weeks	-5.87	-1.31	0.19	9.62*	5.62, 14.75
Baseline_Follow-up	2.13	0.48	0.63	31.74	24.63, 39.38
SWM-E					
Baseline_Sham	-0.37	-0.03	0.97	48.66	38.51, 58.88
Baseline_4weeks	-4.37	-0.40	0.69	34.43	25.18, 44.43
Baseline_8weeks	-18.37	-1.69	0.09	4.70*	1.99, 8.82
Baseline_Follow-up	-1.37	-0.13	0.90	45.01	35, 55.26
DMS					
Baseline_Sham	-5.15	1.88	0.06	3.13*	1.04, 6.71
Baseline_4weeks	-2.47	-0.91	0.37	18.35	10.61, 27.99
Baseline_8weeks	0.85	0.31	0.76	37.75	26.58, 49.75
Baseline_Follow-up	-4.15	-1.52	0.13	6.61*	2.82, 12.32
SSP					
Baseline_Sham	-0.61	-0.50	0.62	30.88	23.74, 38.60
Baseline_4weeks	-0.61	-0.50	0.62	30.88	23.74, 38.60
Baseline_8weeks	-0.61	-0.50	0.62	30.88	23.74, 38.60
Baseline_Follow-up	-0.61	-0.50	0.62	30.88	23.74, 38.60
OTS					
Baseline_Sham	0.42	0.34	0.73	36.68	29.27, 44.47
Baseline_4weeks	1.42	1.15	0.25	12.72	8, 18.52
Baseline_8weeks	2.42	1.95	0.05	2.69*	1.08, 5.24
Baseline_Follow-up	0.42	0.34	0.73	36.68	29.27, 44.47
RTI (ms)					
Baseline_Sham	23.88	0.55	0.58	29.04	16.94, 43.25
Baseline_4weeks	-31.31	-0.73	0.47	23.47	12.77, 36.71
Baseline_8weeks	34.65	0.80	0.42	21.17	11.14, 33.89
Baseline_Follow-up	-0.94	-0.02	0.98	49.13	34.19, 64.17

RVP_hits					
Baseline_Sham	-1.96	-0.59	0.56	27.94	19.59, 37.30
Baseline_4weeks	-6.96	-2.08	0.04	2.01*	0.65, 4.39
Baseline_8weeks	-1.96	-0.59	0.56	27.94	19.59, 37.30
Baseline_Follow-up	-1.96	-0.59	0.56	27.94	19.59, 37.30
RVP (ms)					
Baseline_Sham	-46.31	-0.68	0.50	24.97	18.41, 32.26
Baseline_4weeks	-6.31	-0.09	0.93	46.33	38.55, 54.21
Baseline_8weeks	43.17	0.63	0.53	26.45	19.75, 33.84
Baseline_Follow-up	-29.60	-0.43	0.67	33.28	26.05, 41.00

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.3

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 03.

Cognitive Test	**Discrepancy**	***z***	***p***	**Point estimate of abnormality (%)**	**95% CI**
PAL					
Baseline_Sham	-3.12	-0.42	0.67	33.72	26.38, 41.55
Baseline_4weeks	4.88	0.66	0.51	25.59	18.90, 33.01
Baseline_8weeks	-7.12	-0.96	0.34	16.94	11.38, 23.49
Baseline_Follow-up	-8.12	-1.10	0.28	13.78	8.80, 19.84
SWM_S					
Baseline_Sham	0.50	0.11	0.91	45.61	36.62, 54.77
Baseline_4weeks	1.50	0.33	0.74	36.96	28.42, 46.01
Baseline_8weeks	0.50	0.11	0.91	45.61	36.62, 54.77
Baseline_Follow-up	1.50	0.33	0.74	36.96	28.42, 46.01
SWM-E					
Baseline_Sham	3.45	0.35	0.73	36.51	28.19, 45.32
Baseline_4weeks	-11.25	-1.04	0.30	15.09	9.49, 21.91
Baseline_8weeks	-2.25	-0.21	0.84	41.79	33.18, 50.71
Baseline_Follow-up	-1.25	-0.12	0.91	45.42	36.65, 54.35
DMS					
Baseline_Sham	2.07	0.76	0.45	22.36	16.13, 29.40
Baseline_4weeks	0.07	0.03	0.98	48.98	41.22, 56.77
Baseline_8weeks	3.07	1.13	0.26	13.02	8.25, 18.86
Baseline_Follow-up	2.40	0.88	0.38	18.92	13.14, 25.61
SSP					
Baseline_Sham	-0.04	-0.03	0.98	48.76	40.74, 56.81
Baseline_4weeks	-0.04	-0.03	0.98	48.76	40.74, 56.81
Baseline_8weeks	0.96	0.79	0.43	21.47	15.21, 28.61
Baseline_Follow-up	-0.04	-0.03	0.98	48.76	40.74, 56.81

OTS					
Baseline_Sham	-1.73	-1.37	0.17	8.72*	3.02, 17.89
Baseline_4weeks	-0.73	-0.58	0.56	28.22	15.01, 44.20
Baseline_8weeks	0.27	0.21	0.83	41.63	25.63, 58.78
Baseline_Follow-up	1.27	1.00	0.32	15.94	6.89, 28.65
RTI (ms)					
Baseline_Sham	-49.79	-1.17	0.25	12.24	7.37, 18.36
Baseline_4weeks	-66.99	-1.57	0.12	5.93*	2.92, 10.19
Baseline_8weeks	-70.89	-1.67	0.10	4.95*	2.31, 8.79
Baseline_Follow-up	-59.52	-1.40	0.17	8.26*	4.47, 13.32
RVP_hits					
Baseline_Sham	1.65	0.49	0.62	31.13	22.88, 40.14
Baseline_4weeks	4.65	1.39	0.17	8.37*	4.40, 13.75
Baseline_8weeks	1.65	0.49	0.62	31.13	22.88, 40.14
Baseline_Follow-up	1.65	0.49	0.62	31.13	22.88, 40.14
RVP (ms)					
Baseline_Sham	-71.65	-1.04	0.30	14.97	8.44, 23.33
Baseline_4weeks	-77.27	-1.12	0.26	13.17	7.15, 21.04
Baseline_8weeks	-71.17	-1.04	0.30	15.14	8.55, 23.54
Baseline_Follow-up	-84.22	-1.23	0.22	11.16	5.78, 18.40

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.4

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 04.

Cognitive Test	**Discrepancy**	***z***	***p***	**Point estimate of abnormality (%)**	**95% CI**
PAL					
Baseline_4weeks	8.83	1.19	0.24	11.81	7.16, 17.63
Baseline_8weeks	-2.17	-0.29	0.77	38.53	30.66, 46.77
Baseline_Follow-up	-3.17	-0.43	0.67	33.51	25.93, 41.61
SWM_S					
Baseline_4weeks	4.13	0.92	0.36	17.89	12.24, 24.49
Baseline_8weeks	2.13	0.48	0.63	31.74	24.63, 39.38
Baseline_Follow-up	2.13	0.48	0.63	31.74	24.63, 39.38
SWM-E					
Baseline_4weeks	13.88	1.28	0.20	10.14	5.90, 15.57
Baseline_8weeks	-14.12	-1.30	0.19	9.77*	5.63, 15.11
Baseline_Follow-up	2.88	0.27	0.79	39.53	31.61, 47.78
DMS					
Baseline_4weeks	-3.86	-1.38	0.17	8.50*	2.35, 19.28
Baseline_8weeks	-7.19	-2.58	0.01	0.58*	0.05, 2.18
Baseline_Follow-up	Disc.				

SSP					
Baseline_4weeks	0.47	0.38	0.70	35.20	23.28, 48.32
Baseline_8weeks	-0.53	-0.44	0.66	33.19	21.58, 46.16
Baseline_Follow-up	-0.53	-0.44	0.66	33.19	21.58, 46.16
OTS					
Baseline_4weeks	-0.12	-0.09	0.93	46.32	38.02, 54.74
Baseline_8weeks	-1.12	-0.90	0.37	18.59	12.57, 25.64
Baseline_Follow-up	-1.12	-0.90	0.37	18.59	12.57, 25.64
RTI (ms)					
Baseline_4weeks	0.22	0.005	0.99	49.82	13, 86.78
Baseline_8weeks	40.65	0.84	0.41	20.28	1.84, 56.78
Baseline_Follow-up	106.37	2.19	0.03	1.56*	0.01, 9.11
RVP_hits					
Baseline_4weeks	-4.38	-1.27	0.21	10.29	3.06, 22.44
Baseline_8weeks	-7.38	-2.15	0.03	1.72*	0.23, 5.41
Baseline_Follow-up	-7.38	-2.15	0.03	1.72*	0.23, 5.41
RVP (ms)					
Baseline_4weeks	-8.05	-0.11	0.91	45.53	22.43, 69.89
Baseline_8weeks	-74.25	-1.04	0.3	15.07	4.03, 33.26
Baseline_Follow-up	353.89	4.95	<.001	0.00*	0.00, 0.001

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.5

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 05.

Cognitive Test	**Discrepancy**	***z***	***p***	**Point estimate of abnormality (%)**	**95% CI**
PAL					
Baseline_Sham	22.40	2.72	0.01	0.38*	0.002, 2.45
Baseline_4weeks	23.40	2.85	0.005	0.27*	0.001, 1.80
Baseline_8weeks	-24.60	-2.99	0.003	0.18*	0.001, 1.23
Baseline_Follow-up	16.40	1.99	0.05	2.44*	0.06, 11.58
SWM_S					
Baseline_Sham	6.11	1.36	0.17	8.85*	4.38, 15.08
Baseline_4weeks	1.11	0.25	0.81	40.28	29.85, 51.25
Baseline_8weeks	3.11	0.69	0.49	24.53	16.07, 34.36
Baseline_Follow-up	4.11	0.91	0.36	18.14	10.97, 26.92
SWM-E					
Baseline_Sham	2.86	0.26	0.80	39.86	22.58, 58.83
Baseline_4weeks	12.86	1.16	0.25	12.46	4.40, 24.92
Baseline_8weeks	19.86	1.79	0.08	3.82*	0.84, 9.85
Baseline_Follow-up	8.86	0.80	0.43	21.32	9.33, 37.42

DMS					
Baseline_Sham	-8.92	-3.11	0.003	0.12*	0.002, 0.72
Baseline_4weeks	-0.59	-0.20	0.84	41.94	17.55, 69.13
Baseline_8weeks	-12.26	-4.27	<.001	0.002*	0.00, 0.017
Baseline_Follow-up	-5.59	-1.95	0.05	2.73*	0.23, 9.79
SSP					
Baseline_Sham	-2.32	-1.89	0.06	3.09*	0.85, 7.25
Baseline_4weeks	-0.32	-0.26	0.79	39.70	25.91, 54.55
Baseline_8weeks	-1.32	-1.08	0.28	14.23	6.66, 24.67
Baseline_Follow-up	-0.32	-0.26	0.79	39.70	25.91, 54.55
OTS					
Baseline_Sham	-1.21	-0.98	0.33	16.54	10.78, 23.44
Baseline_4weeks	-1.21	-0.98	0.33	16.54	10.78, 23.44
Baseline_8weeks	-0.21	-0.17	0.86	43.15	34.75, 51.79
Baseline_Follow-up	0.79	0.63	0.53	26.46	19.26, 34.48
RTI (ms)					
Baseline_Sham	97.10	2.27	0.03	1.28*	0.30, 3.30
Baseline_4weeks	11.10	0.23	0.80	39.81	27.90, 52.48
Baseline_8weeks	10.60	0.25	0.81	40.26	28.30, 52.94
Baseline_Follow-up	50.10	1.17	0.25	12.26	6.12, 20.61
RVP_hits					
Baseline_Sham	-4.01	-1.19	0.24	11.80	6.07, 19.52
Baseline_4weeks	-1.01	-0.30	0.77	38.26	27.21, 50.07
Baseline_8weeks	-3.01	-0.89	0.37	18.65	10.93, 28.21
Baseline_Follow-up	-1.01	-0.30	0.77	38.26	27.21, 50.07
RVP (ms)					
Baseline_Sham	-55.03	-0.81	0.42	21.12	15.03, 28.05
Baseline_4weeks	-54.25	-0.79	0.43	21.45	15.31, 28.42
Baseline_8weeks	62.64	0.92	0.36	18.07	12.40, 24.68
Baseline_Follow-up	-116.55	-1.71	0.09	4.55*	2.15, 8.03

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.6

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 06.

Cognitive Test	**Discrepancy**	***z***	***p***	**Point estimate of abnormality (%)**	**95% CI**
PAL					
Baseline_Sham	13.484	1.81	0.07	3.64*	1.42, 7.18
Baseline_4weeks	26.48	3.56	<.001	0.03*	0.002, 0.12
Baseline_8weeks	30.48	4.10	<.001	0.004*	0.00, 0.02
Baseline_Follow-up	35.48	4.77	<.001	0.0003*	0.00, 0.002

SWM_S					
Baseline_Sham	4.71	1.03	0.30	15.17	6.53, 27.38
Baseline_4weeks	0.72	0.16	0.88	43.81	27.74, 60.70
Baseline_8weeks	3.72	0.82	0.42	20.85	10.06, 34.97
Baseline_Follow-up	-4.28	-0.94	0.35	17.44	7.89, 30.49
SWM-E					
Baseline_Sham	17.83	1.61	0.11	5.52*	1.48, 12.95
Baseline_4weeks	12.83	1.16	0.25	12.46	4.57, 24.50
Baseline_8weeks	13.83	1.25	0.21	10.72	3.71, 21.81
Baseline_Follow-up	3.83	0.35	0.73	36.50	20.39, 54.68
DMS					
Baseline_Sham	-5.58	-2.0	0.048	2.41*	0.40, 7.05
Baseline_4weeks	1.08	0.39	0.70	34.95	17.92, 54.72
Baseline_8weeks	-8.92	-3.20	0.002	0.09*	0.003, 0.46
Baseline_Follow-up	-0.58	-0.21	0.84	41.81	23.68, 61.90
SSP					
Baseline_Sham	-1.18	-0.97	0.36	16.77	10.59, 24.24
Baseline_4weeks	-0.18	-0.15	0.88	44.24	34.99, 53.74
Baseline_8weeks	-1.18	-0.97	0.33	16.77	10.59, 24.24
Baseline_Follow-up	-1.18	-0.97	0.33	16.77	10.59, 24.24
OTS					
Baseline_Sham	-0.39	-0.32	0.75	37.63	29.92, 45.71
Baseline_4weeks	-0.39	-0.32	0.75	37.63	29.92, 45.71
Baseline_8weeks	0.61	0.49	0.63	31.31	24, 39.19
Baseline_Follow-up	3.61	2.90	0.005	0.23*	0.04, 0.69
RTI (ms)					
Baseline_Sham	38.82	0.89	0.37	18.67	8.26, 32.87
Baseline_4weeks	60.82	1.40	0.16	8.22*	2.67, 17.42
Baseline_8weeks	75.82	1.75	0.08	4.19*	1.05, 10.20
Baseline_Follow-up	52.06	1.20	0.23	11.67	4.33, 22.90
RVP_hits					
Baseline_Sham	3.43	1.00	0.32	15.98	5.88, 30.93
Baseline_4weeks	3.43	1.00	0.32	15.98	5.88, 30.93
Baseline_8weeks	7.43	2.17	0.03	1.64*	0.23, 5.13
Baseline_Follow-up	9.43	2.75	0.007	0.36*	0.02, 1.44
RVP (ms)					
Baseline_Sham	407.08	5.95	<.001	0*	0, 0
Baseline_4weeks	178.59	2.61	0.01	0.52*	0.11, 1.43
Baseline_8weeks	-10.77	-0.01	0.99	49.55	40.25, 58.88
Baseline_Follow-up	61.47	0.90	0.37	18.57	12.10, 26.26

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.7

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 07.

Cognitive Test	Discrepancy	*z*	*p*	Point estimate of abnormality (%)	95% CI
PAL					
Baseline_Sham	15.21	2.05	0.04	2.13*	0.80, 4.33
Baseline_4weeks	5.21	0.70	0.48	24.17	17.74, 31.35
Baseline_8weeks	3.21	0.43	0.67	33.28	26.11, 40.93
Baseline_Follow-up	-5.79	-0.78	0.44	21.81	15.65, 28.80
SWM_S					
Baseline_Sham	-4.35	-0.97	0.33	16.65	11.21, 23.05
Baseline_4weeks	-1.35	-0.30	0.76	38.17	30.74, 45.93
Baseline_8weeks	-4.35	-0.97	0.33	16.65	11.21, 23.05
Baseline_Follow-up	1.65	0.37	0.71	35.65	28.34, 43.36
SWM-E					
Baseline_Sham	-15.67	-1.45	0.15	7.54*	4.11, 12.12
Baseline_4weeks	-4.67	-0.43	0.67	33.36	26.11, 41.11
Baseline_8weeks	7.33	0.68	0.50	24.98	18.41, 32.30
Baseline_Follow-up	-1.67	-0.15	0.88	43.89	36.15, 51.81
DMS					
Baseline_Sham	-0.51	-0.19	0.85	42.51	34.56, 50.69
Baseline_4weeks	-0.51	-0.19	0.85	42.51	34.56, 50.69
Baseline_8weeks	1.16	0.43	0.67	33.54	26.06, 41.55
Baseline_Follow-up	1.16	0.43	0.67	33.54	26.06, 41.55
SSP					
Baseline_Sham	0.20	0.14	0.89	44.49	34.14, 55.13
Baseline_4weeks	0.20	0.14	0.89	44.49	34.14, 55.13
Baseline_8weeks	-0.80	-0.55	0.59	29.33	20.37, 39.34
Baseline_Follow-up	-0.80	-0.55	0.59	29.33	20.37, 39.34
OTS					
Baseline_Sham	-3.19	-2.54	0.01	0.63*	0.10, 1.88
Baseline_4weeks	0.81	0.64	0.52	26.08	15.60, 38.51
Baseline_8weeks	-1.19	-0.95	0.34	17.21	9.07, 27.75
Baseline_Follow-up	3.81	3.03	0.003	0.15*	0.01, 0.58
RTI (ms)					
Baseline_Sham	-17.8	-0.42	0.68	33.84	25.76, 42.51
Baseline_4weeks	11.83	0.28	0.78	39.08	30.65, 47.92
Baseline_8weeks	-5.48	-0.13	0.90	44.89	36.19, 53.78
Baseline_Follow-up	-19.81	-0.47	0.64	32.14	24.19, 40.73

RVP_hits					
Baseline_Sham	3.41	1.02	0.31	15.52	9.91, 22.32
Baseline_4weeks	1.41	0.42	0.67	33.73	25.77, 42.27
Baseline_8weeks	3.41	1.02	0.31	15.52	9.91, 22.32
Baseline_Follow-up	4.41	1.32	0.19	9.52*	5.34, 14.98
RVP (ms)					
Baseline_Sham	-67.91	-0.99	0.33	16.27	9.35, 25.00
Baseline_4weeks	-57.99	-0.84	0.40	20.03	12.19, 29.56
Baseline_8weeks	20.78	0.30	0.76	38.15	27.46, 49.56
Baseline_Follow-up	23.50	0.34	0.73	36.65	26.12, 48.00

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Table B.8

Paired t-test Results for the Discrepancy between Observed and Predicted CANTAB Retest Scores for Participant 08.

Cognitive Test	**Discrepancy**	***z***	***p***	**Point estimate of abnormality (%)**	**95% CI**
PAL					
Baseline_Sham	8.24	1.11	0.27	13.45	8.50, 19.50
Baseline_4weeks	-2.76	-0.37	0.71	35.50	27.96, 43.47
Baseline_8weeks	8.24	1.11	0.27	13.45	8.50, 19.50
Baseline_Follow-up	6.24	0.84	0.40	20.10	14.01, 27.11
SWM_S					
Baseline_Sham	3.37	0.75	0.45	22.66	16.32, 29.81
Baseline_4weeks	1.37	0.31	0.76	38.02	30.48, 45.90
Baseline_8weeks	2.37	0.53	0.60	29.88	22.85, 37.5
Baseline_Follow-up	0.37	0.08	0.93	46.73	38.89, 54.67
SWM-E					
Baseline_Sham	10.67	0.98	0.33	16.44	9.81, 24.68
Baseline_4weeks	14.67	1.35	0.18	9.02*	4.55, 15.17
Baseline_8weeks	8.67	0.80	0.43	21.36	13.65, 30.50
Baseline_Follow-up	-2.33	-0.21	0.83	41.52	31.26, 52.23
DMS					
Baseline_Sham	3.00	1.10	0.27	13.61	8.22, 20.34
Baseline_4weeks	1.33	0.49	0.63	31.27	23.10, 40.19
Baseline_8weeks	1.33	0.49	0.63	31.27	23.10, 40.19
Baseline_Follow-up	-0.32	-0.12	0.91	45.33	36.23, 54.62
SSP					
Baseline_Sham	-0.82	-0.68	0.51	25.03	18.52, 32.27
Baseline_4weeks	-0.82	-0.68	0.51	25.03	18.52, 32.27
Baseline_8weeks	-1.82	-1.51	0.14	6.83*	3.64, 11.15
Baseline_Follow-up	-0.82	-0.68	0.51	25.03	18.52, 32.27

OTS					
Baseline_Sham	0.07	0.05	0.96	47.81	39.89, 55.80
Baseline_4weeks	-0.93	-0.75	0.46	22.75	16.37, 29.96
Baseline_8weeks	2.07	1.67	0.10	4.95*	2.38, 8.64
Baseline_Follow-up	1.07	0.86	0.39	19.59	13.62, 26.49
RTI (ms)					
Baseline_Sham	-7.70	-0.18	0.86	42.85	34, 51.97
Baseline_4weeks	-1.90	-0.05	0.96	48.23	39.19, 57.33
Baseline_8weeks	-45.57	-1.07	0.29	14.36	8.85, 21.16
Baseline_Follow-up	-36.87	-0.87	0.39	19.44	12.93, 27.10
RVP_hits					
Baseline_Sham	1.30	0.39	0.70	34.97	23.76, 47.26
Baseline_4weeks	-0.70	-0.21	0.84	41.81	29.85, 54.37
Baseline_8weeks	2.30	0.68	0.49	24.76	15.29, 35.97
Baseline_Follow-up	2.30	0.68	0.49	24.76	15.29, 35.97
RVP (ms)					
Baseline_Sham	-39.90	-0.58	0.57	28.27	16.65, 41.95
Baseline_4weeks	-44.86	-0.65	0.52	25.91	14.84, 39.22
Baseline_8weeks	-67.88	-0.98	0.33	16.45	8.15, 27.50
Baseline_Follow-up	-59.32	-0.86	0.39	19.66	10.31, 31.64

Note. * denotes a point estimate of abnormality <10%, red indicates an improvement and blue a decline in performance.

Appendix C

Behavioural Results for those participants who showed a CVS-related effect within the n-back Task from Chapter 4.

Participant 01

Accuracy. The analysis revealed significant main effects of Stimulation [$F(1, 784)= 18.96$, $p<.001$, $\eta_{p^2} = .02$] and Load [$F(3, 784)= 32.06$), $p<.001$, $\eta_{p^2} = .11$], but not Session. Since a significant three-way interaction was absent analyses investigated any two-way interactions involving the Stimulation variable.

The Stimulation x Load interaction was significant [$F(3, 784)= 4.92$, $p<.05$, $\eta_{p^2} = .02$] and post-hoc comparisons first examined whether any differences had emerged between the Stimulation conditions. In line with the hypothesis, accuracy was significantly improved during the active CVS recordings (2-back M=0.95; 3-back M= 0.79) relative to the pre-CVS recordings (2-back M= 0.75; 3-back M= 0.66) for the higher loads (2-back $t(198)= -4.11$, $p<.001$; 3-back $t(198)= -2.07$, $p<.05$). No significant differences were observed under the 0 or 1-back (all ps>.16). Load effects were also explored within each Stimulation condition. During the pre-CVS recordings the anticipated decrement in accuracy was observed as Load demands increased between the 0-back (M= 1.0), and the 2 (M= 0.75) and 3-back (M= 0.66) respectively; as well as between the 1-back (M= 0.93) with the 2 and 3-back respectively. The largest discrepancy occurred between the 0 and 3-back load levels [$t(198)= 7.14$, $p<.001$]. Loads 2 and 3, and loads 0 and 1 did not differ from each other (all ps>.21). During the active CVS recordings accuracy appeared to have reached stable ceiling levels on the 0 (M= 0.98), 1 (M= 0.99) and 2-back (M= 0.95), such that accuracy was only significantly decreased for the 3-back load (M= 0.79). The 3-back differed from all other loads, this decrease was greatest between the 3 and 1-back levels, $t(197)= 4.72$, $p<.001$. These results suggest that performance on the higher n-back loads was improved after active CVS. No other significant main effects or interactions were present (all ps>.12).

Participant 02

Reaction time. Significant main effects of Stimulation [$F(1, 301)= 6.12$, $p<.05$, $\eta_{p^2} = .02$] and Load [$F(2, 301)= 18.62$, $p<.001$, $\eta_{p^2} = .11$] emerged from the 2 x 2 x 3 ANOVA (0-back analysed separately). The main effect of Session and the three-way interaction were both absent. However, since a significant Stimulation x Load interaction was present [$F(2, 301)= 3.49$, $p<.05$, $\eta_{p^2} = .02$] further post-hoc tests were completed.

Comparisons first examined whether RTs differed between the Stimulation conditions under each Load. In line with the hypothesis, responses on the 3-back were shorter during active CVS (M= 668ms) relative to the pre-CVS recordings (M= 822ms), [$t(47)= 3.26$, $p<.001$], no effects of Stimulation were present within the 1 and 2-back loads (all ps>.42). Post-hoc tests then examined the effects of Load within each Stimulation condition. During the pre-CVS recordings RTs were shortest during the 1-back (M= 725ms) Load, which was performed significantly more quickly than the 2-back Load (M= 822ms) [$t(133)= -4.02$, $p<.001$], no other comparisons reached significance (all ps>.07). RTs within the active CVS recordings tended to lengthen with increasing Load, but then decreased again at the 3-back (M= 668ms) which was responded to at a similar speed as the 1-back (M= 705ms) (p= .91). All other comparisons were significant (all ps<.001), with the largest discrepancy occurring between the 2 (M= 862ms) and 3-back Loads (M= 668ms) [$t(61)= 5.15$, $p<.001$]. These

effects suggest that responses were shorter during the active CVS recordings for the 3-back Load. However, it remains unclear whether this effect reflects an improvement in performance, or participant resorting to a guessing strategy given that accuracy responses did not show the same trend. No other significant main effects or interactions were present (all *p*s>.09).

Participant 03

Accuracy. Significant main effects of Stimulation [$F(1, 784)= 5.49$, $p<.05$, $\eta_{p^2} = .01$], Load [$F(3, 784)= 152.36$, $p<.001$, $\eta_{p^2} = .37$] and Session [$F(1, 784)= 23.11$, $p<.001$, $\eta_{p^2} = .03$] were all revealed. Since a three-way interaction was absent, analyses examined any two-way interactions involving the Stimulation variable.

Accuracy responses were influenced by a significant Stimulation x Load interaction [$F(3, 784)= 5$, $p<.05$, $\eta_{p^2} = .02$] and post-hoc comparisons first examined whether any differences were present between the Stimulation conditions under each n-back Load. Contrary to the hypothesis, performance on the 3-back condition was improved during the pre-CVS recordings ($M= 0.56$), relative to the active CVS recordings ($M= 0.38$), $t(198)= 2.58$, $p<.001$. No other differences were present between the Stimulation conditions (all other *p*s>.46). Post-hoc tests also examined differences between the n-back loads within each Stimulation condition. During the pre-CVS recordings all n-back loads were performed with similarly high levels of accuracy (all *p*s>.16), except the 3-back ($M= 0.56$) condition which was performed less accurately (all *p*s<.001). The largest discrepancy occurred between the 3 ($M= 0.56$) and 0-back, where performance was at ceiling ($M= 1.00$), $t(198)= 8.820$, $p<.001$. During the active CVS recordings the number of correct responses for the 2 ($M= 0.88$) and 3-back ($M= 0.38$) loads was significantly different from all other loads (all *p*s<.02), with the strongest effects relating to the performance drop during the 3-back load relative to the 0 and 1 back loads ($M= 1.00$) (both $t(198)= 12.71$, $p<.001$). These results suggest that performance on the 3-back Load was performed less accurately relative to the other loads across the study and did not appear to improve in response to CVS. No other significant main effects or interactions were present (all *p*s>.39).

Reaction time. Significant main effects of Stimulation [$F(1, 637)= 28.58$, $p<.001$, $\eta_{p^2} = .04$] and Load [$F(3, 637)= 75.04$, $p<.001$, $\eta_{p^2} = .26$] were observed. Since the main effect of Session and the three-way interaction were both absent, analyses therefore examined any two-way interactions involving the Stimulation variable.

Response times showed a significant Stimulation x Load interaction [$F(3, 637)= 19.14$, $p<.001$, $\eta_{p^2} = .08$]. Post-hoc analyses first explored whether there were any differences between the Stimulation conditions at each n-back Load. RTs differed between the Stimulation conditions across all loads except the 0-back ($p=.89$). During the 1 and 3-back conditions RTs were shorter during the active CVS recordings (1-back $M= 553$ms; 3-back $M= 697$ms) relative to the pre-CVS recordings (1-back $M= 712$ms, 3-back $M= 1049$ms), the effect was greatest at the 3-back load (1-back $t(194)= 5.24$, $p<.001$; 3-back $t(83)= 5.36$, $p<.001$). Conversely during the 2-back condition, RTs were longer during the active CVS recordings ($M= 911$ms) relative to the pre-CVS recordings ($M= 824$ms), $t(170)= -1.84$, $p<.05$. Comparisons next explored whether any effects of Load were present within each Stimulation condition. During the pre-CVS recordings, RTs differed across all n-back loads (all *p*s<.01), and were significantly longer as load increased. The largest discrepancy occurred between the 0 ($M= 551$ms) and 3-back ($M= 1049$ms) loads, $t(146)= -13.82$, $p<.001$. During the active CVS recordings RTs were similar between the 0 and 1-back loads ($p= 1.00$) but all other loads differed from one another (all *p*s<.013). Here, the largest discrepancy

occurred between the 0 (*M*= 546.04ms) and 2-back (*M*= 911ms) loads [*t*(182)= -11.22, *p*<.001], where RTs were shortest and longest respectively. RTs were changed across the study sessions but these fluctuations did not show a consistent decrease in response speed during CVS. No other significant main effects or interactions were present (all *p*s>.21).

Participant 06

Reaction time. The analysis revealed significant main effects of Stimulation [*F*(1, 675)= 30.72, *p*<.001, η_{p^2} = .04], Load [*F*(3, 675)= 72.36, *p*<.001, η_{p^2} = .24] and Session [*F*(1, 675)= 31.57, *p*<.001, η_{p^2} = .05]. A three-way interaction was also observed [*F*(1, 675)= 6.63, *p*<.001, η_{p^2} = .03] and further post-hoc comparisons were therefore completed to follow-up Stimulation x Session effects within each Load.

A Stimulation x Session interaction was present within the 2 [*F*(1, 174)= 9.09, *p*<.05, η_{p^2}= 0.05] and 3-back loads [*F*(1, 163)= 8.01, *p*<.05, η_{p^2}= .05] only (all other *p*s>.36). Comparisons between the Stimulation conditions showed that RTs were significantly shorter after four weeks CVS (*M*= 746ms) relative to the baseline (*M*= 936ms) under the 3-back [*t*(74)= 4.99, *p*<.001], but not the 2-back Load (*p*=.51). Conversely, RTs on the 2-back were shorter after eight weeks CVS (*M*= 660ms) relative to the sham recording (*M*= 792ms) [*t*(87)= 3.77, *p*<.001], but remained stable under the 3-back (*p*=.07). Post-hoc tests examining the effects of Session revealed that RTs remained stable between the baseline and sham recording on the 2-back (*p*=.91), but were unexpectedly decreased within the 3-back between the two pre-CVS sessions (baseline *M*= 936ms; sham *M*= 772ms), *t*(75)= 4.25, *p*<.001. RTs were then reduced between the recordings taken after four (*M*=817ms) and eight weeks CVS (*M*= 660ms) on the 2-back [*t*(87)= 4.76, *p*<.001], but remained stable under the 3-back (*p*=.32). Within both the 2 and 3-back loads, RTs were shorter during one of the active CVS sessions relative to one of the pre-CVS sessions. However, the effect on the 3-back appeared to onset during sham stimulation, indicating that this facilitation was not driven by CVS alone. No other significant main effects or interactions were present (all *p*s>.11).

Participant 08

Reaction time. The analysis revealed significant main effects of Stimulation [*F*(1, 664)= 88.93, *p*<.001, η_{p^2}= .12] and Load [*F*(3, 664)= 17.48, *p*<.001, η_{p^2}= .07], but not Session. Since a Stimulation x Session x Load interaction was absent from the analysis, two-way interactions involving the Stimulation variable were explored.

RTs were influenced by a significant Stimulation x Session interaction [*F*(1, 664)= 17.40, *p*<.001, η_{p^2}= .03]. Post-hoc tests first examined whether any differences were present between the Stimulation conditions (within each Session). In line with the hypothesis, RTs were significantly shorter during the recording taken after four weeks CVS (*M*= 437ms) relative to the baseline (*M*= 492ms), *t*(339)= 3.47, *p*<.001. Similarly, RTs were also shorter after eight weeks CVS (*M*= 377ms), relative to the sham recording (*M*= 520ms), *t*(337)= 10.39, *p*<.001. Post-hoc tests between sessions also revealed that RTs had remained stable between the baseline and sham recordings (*p*=.65), but were decreased between the recordings taken after four (*M*= 437ms) and eight (*M*= 377ms) weeks of CVS, where they were shortest, *t*(349)= 4.49, *p*<.001. Responses were shorter during the active CVS recordings across both sessions, consistent with a CVS induced facilitation of RTs. No other significant effects or interactions were present (all *p*s<.08).

ERP plots for those participants who failed to show a CVS-related effect within the n-back Task from Chapter 4.

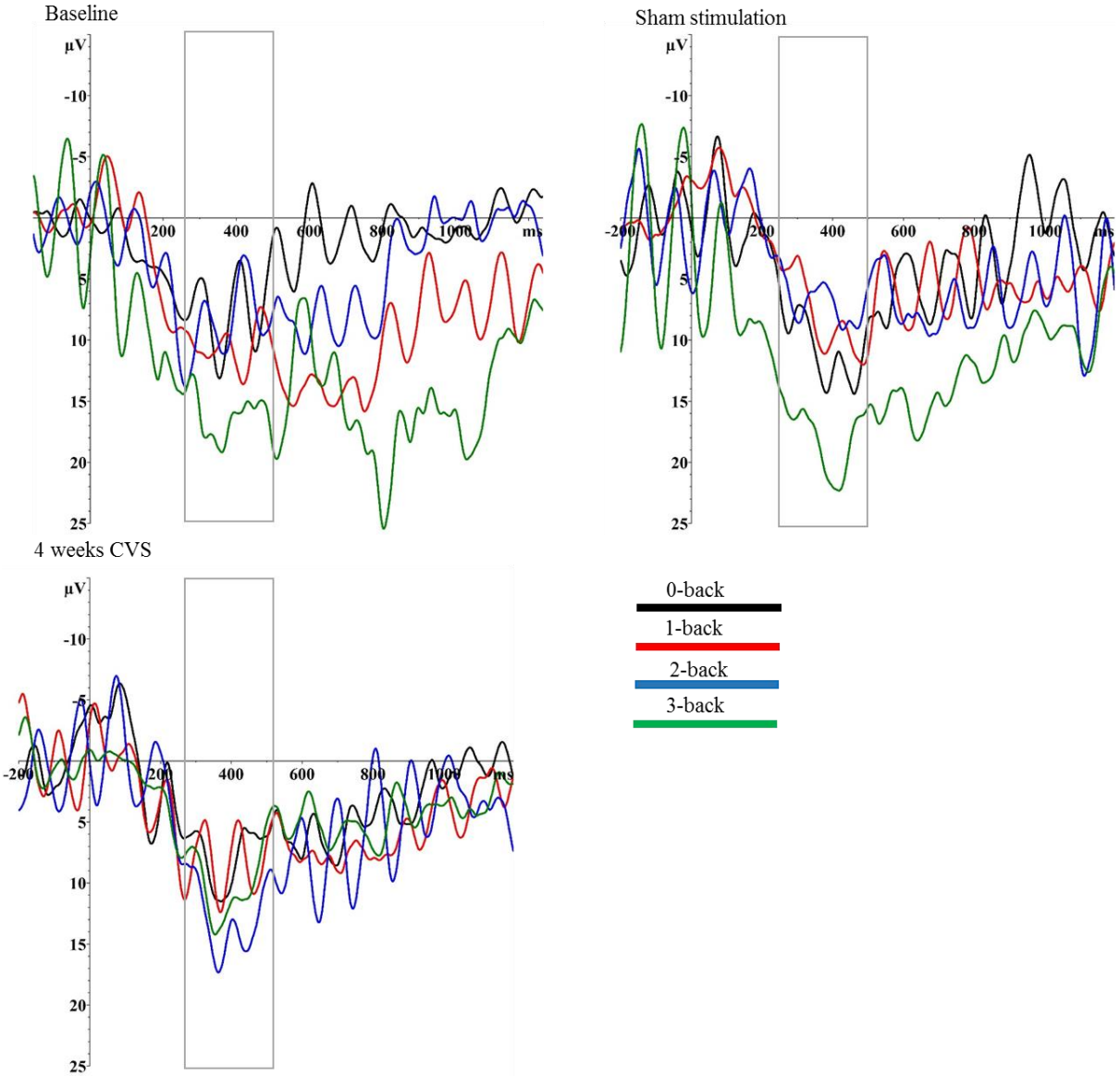

Figure C.1. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the three EEG recordings, at the Pz electrode in participant 05.

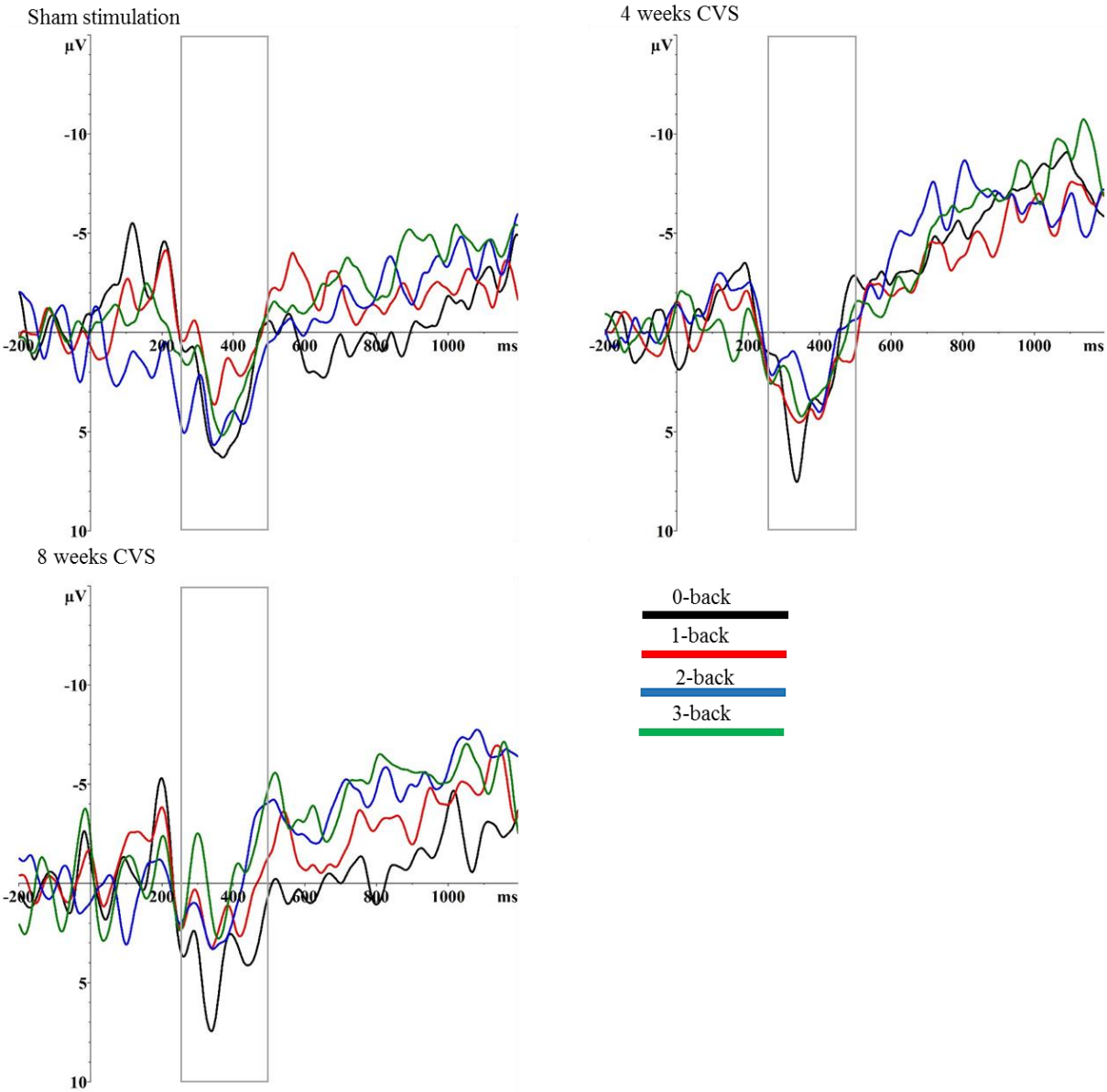

Figure C.2. Grand average ERPs at stimulus onset for correctly answered target n-back trials, across for the three EEG recordings, at the Pz electrode in participant 06.

Appendix D

Experiment 1 Reaction Time Analysis.

Correct RT trials were first filtered for outliers using a *z*-score correction (see Chapter 4 statistical analysis section). Note that any RT effects in this experiment should be interpreted with caution given the unconventional three button press.

Object recognition. Responses where participants correctly identified the Object as old or new were included in the analysis. The remaining filtered trials were then entered into an Object x Stimulation ANOVA. Neither the main effect of Stimulation [$F(2, 46)= 0.23$ $p=.80$, $\eta_p^2=.10$] nor Object [$F(1, 23)= 1.33$ $p=.26$, $\eta_p^2=.06$] reached significance, the two-way interaction was also absent [$F(2, 46)= 0.05$ $p=.96$, $\eta_p^2 =.002$].

Source recognition. Trials where participants correctly placed an object within its encoded Location (left, right) were included in the analysis. The remaining filtered data was then entered into a Location x Stimulation ANOVA. Significant main effects of Stimulation [$F(2, 46)= 0.21$, $p=.81$, $\eta_p^2= .01$] and Location [$F(1, 23)= 0.07$, $p=.79$ $\eta_p^2=.003$] were both absent. Although a significant two-way interaction was present [$F(2, 46)= 3.98$, $p<.05$, $\eta_p^2= .15$], post-hoc comparisons completed to interrogate the interaction failed to show any further significant differences (all *p*s>.91).

Experiment 4 Early Priming Effects

Priming effects (indicative of implicit memory) are likely to be stronger during earlier trial repetitions (Manelis et al., 2011), since block repetitions towards the end of the study may have been influenced by learning effects. To investigate whether any stronger priming effects were present before learning had potentially taken place, responses from the first five trial blocks only (maximum of 30 data points) were also analysed.

No significant main effects (Image $F(2, 48)= 0.25$, $p>.05$, $\eta_p^2=.01$; Location $F(1, 24)= 2.67$, $p>.05$, $\eta_p^2= .10$), nor a two-way interaction ($F(2, 48)= 0.03$, $p=.97$, $\eta_p^2= .001$) emerged within the RT data during these early trial blocks. Figure *D.1* shows that although insignificant, the results followed a similar pattern to the previous RT analysis whereby responses to the GVS Location were facilitated.

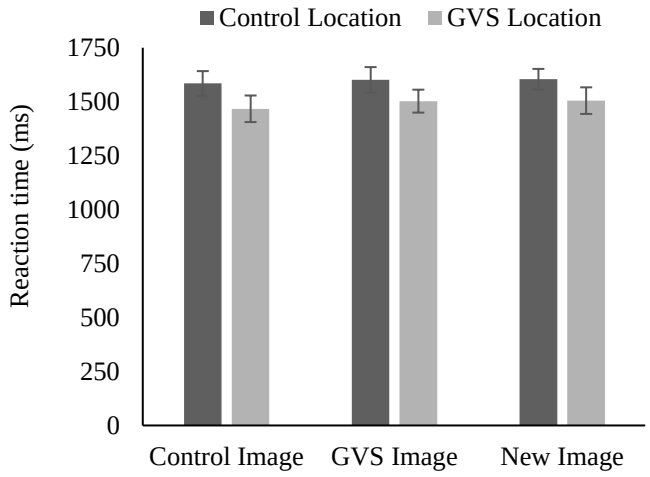

*Figure D.*1. RT and accuracy data for the six key comparisons during blocks 1-5.

Experiments 1-4 Self-rated Perceptions of GVS Sheet.

Participant ID:

Please help us to understand your perceptions of the stimulation that you received.

Q1.) How strong was the sensation of the stimulation?

a.) Could not feel anything at all

b.) Slight sensation, but unsure if it was the result of the stimulation

c.) Felt a definite sensation of being stimulated

d.) Strong feeling of being stimulated

e.) Currents were too strong, stimulation was overpowering

Q2.) What did the stimulation feel like?

a.) A brief pulsating sensation behind the ears?

b.) A continuous sensation or wave of activity behind the ears?

Q3.) How often did you notice the stimulation?

Q4.) Did you notice any patterns in the stimulation?

Thank you for your feedback.