Vestibular Influences on Neuropsychological Outcomes in UK Military Veterans with Mild Traumatic Brain Injury

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Declaration

The research presented in this thesis was conducted at the School of Psychology, University of Kent and at UK Combat Stress treatment centres, whilst the author was a full-time postgraduate student. The author received a Kent Health PhD Studentship Award from the University of Kent to support this research. The theoretical and empirical work presented is original work completed by the author under the supervision of Professor 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.

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Abstract

The epidemiology and treatment of mild traumatic brain injury (mTBI), along with its co-morbid symptoms, has previously received little attention in UK military samples. In US military veterans, mTBI is among the most frequently seen and challenging of conditions to arise as a consequence of the conflicts in Iraq and Afghanistan. mTBI has been shown to represent a complicated and particularly harmful polymorbid condition when accompanied by PTSD and depression, resulting in poor life outcomes. Symptoms of dizziness are one of the most common comorbid symptoms of mTBI and PTSD. In fact, the symptomology of mTBI and PTSD share many distinct features that can also be seen in patients with vestibular disorders. This is perhaps unsurprising given the diffuse nature of the ascending vestibular pathways. Despite this anatomical feature, vestibular influences in mTBI have yet to be explored in UK military veterans. To this end, this thesis first aimed to determine if vestibular disturbance influenced the neurobehavioural and affective symptoms of mTBI. A further line of investigation examined if the vestibular pathways can be artificially modulated using galvanic vestibular stimulation (GVS) to ameliorate some of these symptoms.

Chapter 1 of this thesis describes the main features of mTBI in both the UK and US military, outlining the classification/current diagnostic criteria, mechanisms of injury and co-occurring cognitive, psychiatric symptoms of mTBI. It will be argued that mTBI commonly occurs in military samples as a result of blast exposure, and is particularly difficult to diagnose and treat. Chapter 2 will illustrate that both blunt and blast mTBI frequently result's in damage to the vestibular system and thereon assesses the potential contributions of vestibular dysfunction to the chronic symptoms of mTBI. Drawing on previous intervention studies from civilian samples, it will illustrate how the vestibular system may provide a novel pathway to treat mTBI. Chapter 3 reports results from an epidemiological study of 162 UK military veterans which show that 72% of the sample reported one or more mTBI in their lifetime. Vestibular disturbance affected 69% of these individuals and was most frequently seen in those who had sustained both blunt and blast injuries. Mediation analysis indicated that when PTSD, depression and anxiety were accounted for, vestibular

disturbance was directly associated with increased neurobehavioural symptoms and functional disability. These findings indicate that vestibular disturbance is common particularly after combined blunt and blast head injuries and is singularly predictive of poor long-term mental health and functional disability.

In light of the newfound association between vestibular disturbance and mTBI, the remaining chapters sought to establish if and how artificial vestibular stimulation can remediate aspects of mTBI. To help determine whether to target positive or negative symptoms, in Chapter 4 I sought to determine if GVS could induce either long-term potentiation (LTP) or depression (LTD) type effects, in neurologically healthy individuals up to 24hours post stimulation. The results showed that in participants who demonstrated cortical hyperexcitability at baseline, GVS induced a significant LTD type effect at 24hours post-stimulation. This indicated that conditions such as anxiety and PTSD, which are associated with cortical hyperexcitability, should be targeted. In Chapter 5 a small proof of concept study evaluated the efficacy of GVS in treating current symptoms of anxiety in 5 UK military veterans. The results showed that state symptoms of anxiety were exacerbated at 24hours post active GVS, which although further introduces a link between the vestibular system and anxiety in mTBI, did not support therapeutic application of GVS. In Chapter 6, the general discussion concludes that, vestibular disturbance is predictive of poor long-term mental health and therefore needs to be routinely screened and treated. Further studies are also needed to establish how to yoke the novel effects of GVS on cortical excitability observed here for treatment of mTBI symptoms.

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Chapter 1

The Epidemiology and Chronic Sequelae of Mild Traumatic Brain Injury in Military Personnel

Epidemiology of mTBI in the UK and US Military

Between the periods of 2001 to 2014 the Ministry of Defence (MOD) deployed 281,990 British military personnel to the Iraq and Afghanistan conflicts (Ministry of Defence, 2014). Traumatic brain injury (TBI) was a major contributor to fatalities accounting for 42% of British casualties killed in combat between 2006 and 2007 (Hodgetts et al., 2007). These fatalities may represent the tip of the iceberg because, historically, 15 to 20% of combat related injuries have been shown to occur above the clavicles (Champion et al., 2003). mTBI has been characterised as a signature injury of US troops in the recent Iraq and Afghanistan conflicts. Eighty-five per cent of deployment related TBIs in US troops were mild in severity (MacGregor et al., 2010), with an estimated prevalence ranging between 15% (Hoge et al., 2008) and 23% (Terrio et al., 2009). However, the prevalence of mTBI is not uniform between countries. In the UK, armed forces estimated incidence rates fall between 3.2% and 13.5% (Hawley et al., 2014; Jones et al., 2011; Rona et al., 2012). Several factors may help explain this discrepancy between US and UK estimates, such as the greater reliance on self-report rather than medical records in the US, and the shorter deployment periods of UK soldiers (6 months compared to 12-18 months for US personnel). Nonetheless, the narrow time widow of deployment may not capture the effects of mTBI and might be better understood by evaluating mTBI within the context of lifetime exposure.

Classification and definition of mTBI

TBI has been described as having two phases. The first involves neuronal injury as a direct result of the traumatic event; this has been defined as the 'primary (immediate) injury'. The primary injury is a result of the energy transfer to the brain at the moment of injury, and its severity partly reflects the amount of energy transferred. The second later phase is defined as secondary (delayed) and can be caused by multiple neuropathologic processes that can continue for weeks post insult (Gentleman, 2008; Granacher, 2015).

Classification of TBI severity is determined by levels of consciousness, typically this is measured using the Glasgow Coma Scale (GCS) which provides a global index of brain function (*see Table 1.1*). Brain injury is classified as severe when the GCS score is < 3-8, moderate 9-12, or mild 13-15 (Teasdale, 1979). Although the GCS is internationally accepted as a global index of brain function, its efficacy in predicting severity is greater for moderate and severe TBI than mTBI, as the vast majority of mTBI patients can present with normal to near normal GCS scores within hours of injury (Granacher, 2015). A more sensitive case definition and severity index of brain injury for mTBI has been developed by the US Department Defense and Department of Veterans Affairs screening programs (DOD/VA) which is consistent with national surveillance definitions (Faul, Wald & Coronado, 2010; Management of Concussion/mTBI Working Group, 2009) (*See Table 1.2; Table 1.3*). It should be noted that this definition criteria also defines the events of TBI. The American Congress of Rehabilitative Medicine (ACRM) also include duration of posttraumatic amnesia (PTA) as a marker of TBI severity and short-term prognosis. (Feinstein et al., 2002). However, duration of PTA frequently goes unobserved in a combat arena, and this measure (when potential observers may be fighting for their own lives or be injured) has not been a reliable marker for predicting severity of impairment in mTBI cases (Borg et al., 2004).

Table 1.1. GCS Classification Criteria

Type of response		Score	Description
Eye opening	Spontaneous	4	Open with blinking at baseline
	To speech	3	Opens to verbal command, speech or shout
	To pain	2	Opens to pain not applied to face
	None	1	No response
Motor	Obeys commands	6	Can process instructions and respond
	Localises pain	5	Powerful movement to pain stimulus
	Withdrawal	4	Withdraws from pain stimulus
	Abnormal flexion	3	Abnormal (spastic) flexion, decoriticate posture
	Extension	2	Extensor (ridged) response, decerebrate posture
	None	1	No response
Verbal	Oriented	5	Oriented to person (knows identity), to place (knows where he or she is)
	Confused	4	Confused but able to answer questions
	Inappropriate	3	Intelligible speech (shouting swearing) incoherent conversation
	Incomprehensible	2	Moaning and groaning; no recognisable words
	None	1	No response

(Teasdale, Murray, Parker & Jennett, 1979).

Concussion, a term used often to describe mild head injury, refers to the specific event that may or may not be associated with persistent symptoms or structural brain injury. Predominantly, concussion/mTBI results in a full recovery (Ponsford et al 2002). However, 15% to 20% of patients who sustain a mTBI can present with symptoms that persist beyond the typical recovery period of three months, a chronic condition known as post concussion syndrome (PCS) (Bazarian et al.,

2001; Marshall et al., 2012; Ryan et al., 2003). However, the DSM-5 no longer recognises PCS as a diagnostic label as the eitiology of PCS is poorly understood and instead suggests neurocognitive disorder as a result of TBI (American Psychiatric Association, 2013).

Table 1.2. DOD/VA Definition of Traumatic Brain Injury

DOD/VA Definition of Traumatic Brain Injury
A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: • Any period of loss of or a decreased level of consciousness (LOC) • Any loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA]) • Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.) (Alteration of consciousness/mental state [AOC]) • Neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient • Intracranial lesion.

(Management of Concussion/mTBI Working Group, 2009)

Defining the neuropathology associated with persistent cognitive deficits in mTBI is problematic. Frequently, no abnormalities are apparent from MRI scans (Hughes et al., 2004). Clinical screening of mTBI months or weeks after concussive events is also particularly difficult in military populations, not least because acute signs of concussion might overlap with symptoms of disassociation which can result from acute stress (Hodge et al., 2008). Frequently

mTBI can go undiagnosed particularly when there is an absence of blast exposure, PTSD, depression and substance abuse.

Table 1.3 DOD/VA Severity of brain injury stratification

Criteria	**Con/mTBI**	**Moderate**	**Severe**
Structural imaging	Normal	Normal/abnormal	Normal/abnormal
Loss of consciousness	0-30 Minutes	>30 mins, <24 hrs	>24 hrs
Alteration of consciousness /Mental state	A moment up to 24 hrs	>24hrs	Severity based on other criteria
Posttraumatic amnesia	≤1 Day	> 1 And 7 days	> 7 Days
GCS (best available score in first 24 hrs)	13-15	9-12	3-8

(Management of Concussion/mTBI Working Group, 2009)

Blast and Blunt Brain Trauma

Injuries sustained from blast munitions are not a new phenomenon. Previously, the symptoms from blast exposure were referred to as "*shell shock*", a term used to describe soldiers who were rendered incapable of fighting for some period following blasts. Historically, there was considerable debate as to whether this was due to a physical or psychological reaction to multiple explosions (King & Hattendorf, 1997; Kinch et al., 2018). Along similar lines, an individual killed without evidence of bodily injury might have been described as suffering from the "wind" of the injury. Death due to blast is well documented yet research of closed brain injury survivors is limited (Warden, 2006). The reasons for this are not clear, however, factors such as life-threatening wounds during mass casualty events may cause a potential overlook of blast mTBI as all available medical assets are required to save lives.

In present day battlefields, the use of improvised explosive devices (IEDs) has increased the risk of TBI. Repeated deployments and high rates of blast exposure have made a significant contribution to high prevalence rates of mTBI and PTSD. Potentially hundreds of thousands (at least 30% of US troops) have suffered a mTBI as a result of IED blast waves in Afghanistan and Iraq (Glasser, 2007; Hodge et al., 2007; Hodge et al., 2008). The US DOD (2017) reported that since 2001 more than 2 million service personnel have been deployed in operational theatres and approximately 400,00 have reported TBI, the vast majority of which were mild in nature. Blast exposure was the most common mechanism of injury in this population (Hodge et al., 2008, Masel & DeWitt, 2010). During Operation Herrick the MOD reported that injuries to the head and neck equated to just under a fifth of the injuries sustained by UK armed forces in Afghanistan. However, the most frequent mechanism of battle injury was explosive munitions, which accounted for 52% of 2,201 of these injuries (Ministry of Defense, 2014).

Chen et al., (2013) suggests that the exposure of blast kinetic energy to the human body from IEDs can be transferred into hydraulic energy in the cardiovascular system, which in turn can cause rapid physical movement and volumetric blood surge. This can move through the blood vessels from the ‘high-pressure body cavity’ to the ‘low-pressure cranial cavity’ and result in damage to the cerebral blood vessels in the blood brain barrier (BBB). Blast injuries like this have been suggested to cause large-scale cerebrovascular insults and BBB damage, and might be the cause of non-impact blast induced brain injury including TBI and post-traumatic stress disorder (PTSD).

The repercussions of blast overpressure trauma are significant and it has been suggested that blast TBI is unique from other forms of TBI because the nature of diffuse interaction of the pressure wave with the brain leads to a complex cascade of events that effects neuronal cell bodies, axons,

glial cells and blood vessels (Duckworth et al., 2013; Granacher, 2015). This is a result of the initial, rapid up-rise from the blast, followed by a longer delay in the shock wave that reaches a negative inflection point before returning to baseline. This process is a specific profile pressure-time curve known as the “Freidlander curve”.

A great deal of controversy surrounds the aetiology, course and treatment of persistent somatic, cognitive and behavioural symptoms that can result from blast induced mTBI (Hodge et al., 2009; Peskind et al., 2009; Sigford et al., 2009). It is important to acknowledge that blasts can cause both physical and psychological trauma; it is also accepted that blast exposed personnel frequently meet the acute mTBI criteria set by the ACRM (Key et al., 1993). The term mTBI is associated with subtle cognitive deficits, headaches, dizziness, tinnitus, sleep disruption, daytime fatigue, irritability and other symptoms that can persist for months or years post blast-induced acute mTBI (Peskind et al., 2009). It is not yet clear if the chronic symptoms seen in acute mTBI are due to structural or functional brain damage as many of these symptoms except for headache are correlated to PTSD and depression (Fear et al., 2008; Schneiderman et al., 2008; Turgoose & Murphy, 2018). The aforementioned data would argue against a neurobiological basis for blast related acute mTBI symptoms because psychological and motivational factors are also thought to play an important role in the persistence of these symptoms (Armistead-Jehle et al., 2018; McCrea, 2008). Yet, many clinicians are convinced that acute mTBI is real, albeit subtle brain damage (Ruff et al., 2008; Sigford et al., 2009; Schneiderman et al., 2008). Moreover, veterans with a diagnosis of mTBI, PTSD and depression have been shown to be more likely to have multisensory impairment if they had deployment related mTBI and both blast and non-blast mTBI (Pogoda et al., 2012).

Current diagnostic tests involving CT or MRI scans are neither sensitive nor specific enough to identify individuals who have sustained mTBI (Belanger et al., 2007; Dash et al., 2010). However, evidence is beginning to emerge that suggests blast induced mTBI might have a neurobiological basis for persistent mTBI symptoms. It is possible that in vivo characterisation of traumatic axonal injury using diffusion tensor imaging (DTI) may shed light on the neuropathology associated with mTBI (Miller et al., 2016). DTI can identify microscopic tissue damage and examine the white matter tracts. MacDonald et al., (2010) utilised DTI to investigate the neuropathology of blast related injury within 90 days of insult in 63 US military personnel diagnosed with mTBI. Compared to 21 controls, abnormalities in this group were consistent with traumatic axonal injuries. None of the 63 subjects with blast related mTBI had detectable intracranial injury from CT scans. Yet, there were marked DTI abnormalities in this group in the middle cerebellar peduncles ($p < .001$) the cingulum bundles ($p = .002$), and in the right orbitofrontal white matter ($p = .007$). Follow-up DTI scans 6 to 12 months post enrolment were performed on 47 subjects with mTBI and revealed persistent abnormalities that were consistent with evolving injuries. Blast-related mTBI also represents a neuropsychiatric spectrum disorder that clinically overlaps with chronic traumatic encephalopathy (CTE) a condition associated with repetitive concussion injury in athletes (Collins et al., 2013).

CTE was originally reported by pathologist Harrison Martland (1928), who described the condition as ‘punch drunk’ as it occurs in boxers after repetitive blunt mild brain injuries. CTE is a progressive neurodegenerative disorder that is characterised by the accumulation of hyperphosphorylated tau protein that begins focally and then spreads to involve most of the central nervous system (Mckee et al., 2009). CTE is clinically associated with symptoms of irritability, impulsivity, aggression, depression, progressive affective lability, executive dysfunction, memory

disturbances and suicidal ideation. The onset of CTE typically occurs 8 to 10 years after experiencing repetitive mTBIs (Collins et al., 2013; Mckee et al., 2012). With advance cases, more severe neurological changes occur to include dementia, gait and speech abnormalities and Parkinsonism. In the late stages of disease, the condition is often mistaken for Alzheimer's or frontotemporal dementia (Gavett et al., 2010).

There is a great deal of controversy surrounding the diagnosis of CTE because it is unclear whether CTE reflects a progressive neurodegenerative disease or whether it reflects the aging process superimposed by neurological injury (or both) (Iverson et al., 2015). The disease is characterised by both McKee et al., (2013) and Omalu et al., (2011) as tau pathology uniquely situated in the sulci and superficial cortical layers which is unlike tau pathology in age related Alzheimer's disease. However, the microscopic neuropathology evidenced in these samples is diverse and non-specific. Mc Kee et al., (2013) suggest that p-tau immunoreactive astrocytic tangles are a defining feature of the disease yet other seminal research from Omalu et al., (2011) reported that these features were not present. It should also be noted that the criteria for CTE are particularly encompassing in that any localized phosphorylated tau can constitute CTE. A critical review by Iverson et al., (2015) suggests that this would explain why all subjects who have been examined to date demonstrate the stigmata of CTE. Furthermore, the clinical features of CTE are not evidenced in how these small amounts of tau pathology can cause complex changes in behaviour (Solomon, 2018). Closer scrutiny to determine the extent of which neuropathology is causally related to these clinical features is required, nonetheless, concussion in sports has been of international concern since at least 2001 (Granacher, 2015).

Despite the aforementioned controversy, it is now widely accepted that athletes who have a history of sustaining repeated concussion such as American football players are at risk of long-term changes to brain structure and or function, slower recovery, increased risk of future seizures and CTE (Bailes et al., 2013). Participating in sports is seen as important to the welfare and operational effectiveness of personnel serving in the UK Armed Services (www.Army.MOD.UK, 2016). Sports form a large part of the military lifestyle and may also contribute to an increased risk of sustaining more than one concussion; particularly in those who play contact or collision sports such as boxing or rugby. Currently, there are no statistics available on the prevalence rates of sports related concussion or proportions of blunt versus blast mTBIs in the UK or US military. However, post-mortem brains obtained from a case series of US military veterans who had committed suicide and were known to have blast exposure and mTBI showed the same neuropathology that has been observed in young American football players who had sustained repeated mTBIs and also committed suicide (Goldstien et al., 2012). The repeated nature of mTBI may constitute a significant risk for military personnel not only from blast exposure, but from blunt force trauma. Sports, combat training and road traffic accidents are likely to be commonly seen mechanisms of injury. In civilian populations blunt TBI accounts for a significant burden of healthcare worldwide. In the US (2002-2006) approximately 1.7 million TBI-related hospitalizations, emergency department (ED) visits, and deaths were recorded each year, with 1.4 million treated and released after ED care, 275,000 hospitalised and discharged alive, and 52,000 deceased (Faul et al, 2010). The proportionate prevalence of TBI is likely to be greater in military compared to civilian settings. Further exploration of the incidence of blunt/blast mTBI over lifetime is required to determine the influence of mTBI over the course of aging. Many military personnel may be at greater risk of neurodegenerative conditions as a result of repeated mTBI.

Long-term Symptoms of mTBI

Long-term post concussive symptoms following mTBI can include a combination of somatic, sensory, affective and cognitive symptom clusters (King et al., 2012). However, these symptoms are not specific to mTBI, and overlap with several other disorders such as depression, generalised anxiety disorder, PTSD, substance use disorders and everyday complaints like headache (Carlson et al., 2011; Cooper et al., 2015). Moreover, analysis of mTBI patients has found that a previous history of affective or anxiety disorders (including PTSD), being female, a higher IQ and pain is a significant predictor of acute mTBI (Bryant & Harvey, 1998). PTSD, in particular, has been widely suggested as more strongly related to persistent mTBI symptom reporting than the severity or mechanism of neurological insult (Hodge et al., 2008; Schneiderman et al., 2008; Lange et al., 2013; Polusny et al., 2011) Although neurobehavioural disorders such as depression and PTSD commonly occur after combat, the presentation of such disorders in those with head injury may result in the enduring symptoms of mTBI being left undiagnosed. Therefore, a multidimensional approach should be applied for diagnosis (Halbauer et al., 2009).

Somatic and Sensory Symptoms

Axonal shearing as a result of mTBI can result in several types of sensory deficits, which should be independently evaluated (Halbauer et al., 2009). Symptoms of dizziness are almost universally present in mTBI; hearing loss is also frequently present due to blast exposure (these factors will be outlined in detail in Chapter 2) (Szczupak et al., 2016; Fausti et al., 2009). Olfactory dysfunction and disorders of taste are common and often arise as a result of blunt force injury causing damage to the nasal epithelium, the cribriform plate and the olfactory bulb (de Kruijk et al, 2002). Among combat veterans with mTBI, severity of PTSD and olfaction impairment has been linked to increased number of LOC episodes (Ruff et al., 2012). Olfactory dysfunction not

only cause changes to smell and taste, but can also affect motivation, emotion and memory as the three branches of the olfactory bulb project to the basil forebrain and medial temporal lobe limbic areas.

Visual disturbances are also quite common in mTBI. Alteration in visual function in individuals with blast related mTBI has been frequently reported (Brahm et al., 2009; Goodrich et al., 2013; Magone et al., 2013). For example, Magone et al., (2014) reported that 68% of patients who reported a history of blast induce mTBI still suffered from visual complaints when assessed at 16 to 91 months post injury. Symptoms can include abnormal saccades, pursuit and fixation issues that can impact on reading and spatial perceptual deficits. Additionally, anomalies of light sensitivity such as photosensitivity and photophobia can occur (Kapoor & Ciuffreda, 2002). Blast related TBI may be accompanied by involvement of the visual system through optic nerve injury or cerebral injury (Armstrong 2018; Gilmor et al., 2016; Taber et al., 2006). Eye movement dysfunction is reported in approximately 90% of patients suffering a concussion or blast injury (Armstrong 2017).

Headache is one of the most common symptoms following mTBI affecting between 32% to 91% of individuals (Hodge et al., 2008; Hoffman et al., 2011). Fatigue has been shown to be a significant independent predictor of headache severity (Bomyea et al., 2016) and whilst PTSD may mediate some TBI physical health symptoms, brain injury has been shown to correlate independent of psychological disorders with chronic pain (Nampiaparampil, 2008). Furthermore, Ruff et al., (2008) showed that veterans with neurological impairment as a result of mTBI were more likely to suffer from headaches, features of migraine, more severe pain and more frequent headaches when they have been exposed to more explosions.

Affective Symptoms

PTSD is caused from physical and/or emotional trauma, and has many symptoms that overlap with those of mTBI (DSM-5, 2013). Much like mTBI, PTSD can result in grey and white matter damage via stress related pathologies of neuroinflammation, oxidative damage and excitotoxicity (Kaplan et al., 2018). The association between mTBI and PTSD is strong, with 43% of US soldiers whom experienced a mTBI with loss of consciousness (LOC) meeting the criteria for PTSD diagnosis (Hodge et al., 2008). However, 9.1% of soldiers with no mTBI met the criteria for PTSD. Frequently, the symptoms of PTSD can have a delayed onset and many soldiers are more likely to develop symptoms after their return home.

As classified by the DSM-5, PTSD is induced by a hypersensitive response to threat and includes intrusive symptoms such as reoccurring memories, nightmares, dissociation, persistent distress, numbing, impulsivity, aggression and avoidance (DSM-5, 2013). PTSD is also considered a disorder of memory organisation and may involve intrinsic, non-declarative amygdala-based memory processing systems and extrinsic, declarative, hippocampal-based memory processing systems. Typically, patients present with intrusive memories, fragmented autobiographical and trauma related memories, deficits in declarative memory and a presence of traumatic related amnesia (Elzinga & Bremner, 2002). The association between PTSD, anxiety and memory is not necessarily a conflict, but an indication of the involvement of several interrelated brain systems. PTSD is thought to arise from malfunctioning within the ventromedial prefrontal cortex (VMPFC) and this malfunctioning is suggested to increase vulnerability and fear sensations as the VMPC modulates the amygdala, a brain region known for processing fear of anxiety (Delgado et al., 2008).

PTSD has been identified as a risk factor to violent behaviour and is linked to a range of negative outcomes including an increased risk of anti-social conduct (Elbogen et al., 2012). MacManus et al., (2013) conducted a study based on criminal records that showed 11% UK military personnel who had been deployed to the Iraq and Afghanistan conflicts have a criminal record for violent conduct. Violent conduct was particularly prevalent in men aged 30 years or younger accounting for 20% of 521 service personnel. Negative affect is seen frequently in veterans with PTSD anger and irritability, alcohol and substance abuse are common placed and often related to committing crime also (Elbogen et al., 2012).

Veterans with PTSD are also at greater risk neurodegenerative conditions such as Alzheimer's disease and vascular dementia in later life (Greenberg et al., 2014). TBI can cause neurodegeneration in many brain structures, notably the hippocampus, cortex, and thalamus. PTSD has also been linked to decreased hippocampal volume (Hall et al., 2008; Mooney & Haas, 1993); and there has been much debate as to whether PTSD can damage the hippocampus via stress effects or whether some individuals with a small hippocampus are more likely to develop PTSD (Bremner et al., 2008). It has also been argued that mTBI may damage hippocampal connections sufficiently to prime the system for PTSD. On a related note, LOC following mTBI is a known risk factor for the future development of PTSD (Mayou, Black & Bryant, 2000).

Depression is an especially debilitating problem in veterans and post-mTBI. Prevalence rates range from 18.5% to 61% (Jorge et al., 1993; Jorge et al., 1993; Jorge et al., 2004; Kreutzer et al., 2001; Seel & Kreutzer, 2001). This large range has been attributed to the overlap of depression with other mTBI symptoms such as poor concentration, irritability, fatigue and sleep disturbances. It is

important to elucidate whether the symptoms of depression are the emergence of a major depressive disorder or are especially related to mTBI, as suicide can be an outcome of psychiatric illness particularly depression (Halbauer et al., 2009). It has been suggested that TBI is likely to put individuals at even greater risk of suicide; individuals with TBI have a three- to four-fold increase in committing suicide, an increase in suicide attempts of 18%, and increased suicidal ideation of 21% to 22% (Simpson & Tate, 2007). Furthermore, research from the US Army has shown an increasing trend of suicide related events; 67 suicides were reported in 2004, 87 in 2005 and 99 during 2006 (Simpson & Tate, 2007). In contrast, a cohort study of UK Armed service veterans investigating suicide rates between 1996 and 2005 found that 233,803 individuals had left the Armed services and 244 died by suicide. This is comparable to that of the general population. However, men who left the Armed services ages 24 years or younger were found to be two to three times at greater risk of suicide than the same age group in the general population (Kapur et al., 2009). That said, research that has explored the association between TBI and suicide attempt has often yielded conflicting results. One of the more definitive studies from Fonda et al., (2016) utilised data evaluations from 273,591 US veterans to quantify the impact of deployment related TBI and psychiatric diagnosis on attempted suicide. Veterans with TBI were shown to be more likely to attempt suicide than those without. Furthermore, the association of TBI with attempted suicide when mediated with psychiatric conditions and PTSD showed an even greater impact and risk of attempted suicide. This indicates that veterans with these co-occurring conditions should be closely monitored.

Cognitive Symptoms

Executive function is heavily reliant on the frontal lobes of the brain and involves complex goal directed behaviours such as decision making, abstract thinking, planning, task switching and

inhibition. These directed behaviours are essential for the organisation of ideas, time management, concept formation, categorisation, insight and judgement (Halbauer et al., 2009). The symptoms that arise from mTBI, PTSD and depression can overlap with deficits seen from executive dysfunction making it difficult to distinguish the underlying drivers of executive dysfunction. Whilst cognitive dysfunction is common complaint in mTBI patients, its nature and prevalence are far from clear due to the inherent difficulties in designing schema for classifying such conditions (Warden et al., 2006). Cognition is neither a single entity nor ability, which makes the measurement and quantification problematic. Cognitive functions are constructs and as such, rigidly constrained by the tools utilized to measure them. This can cause problems as trauma to the central nervous system can be diffuse and does not respect functional boundaries or system classifications which adds complexity to the evaluation process. The degree to which patients may suffer from cognitive deficits following TBI will vary according to the intensity and impact site of injury, the premorbid intellectual status and other factors such as the nature of subsequent treatment and rehabilitation (Linder et al., 1998).

Problems with memory are among the most frequently seen cognitive dysfunction following TBI (Warden et al., 2006). Acute dysfunction is described as post-traumatic amnesia and is generally time limited, with most impairments resolving without intervention within 10 days post-concussion (Sim et al., 2008). Chronic memory impairment following TBI has not been labelled diagnostically. Deficits can persist for years and impact on implicit or nondeclarative memory (which is responsible for automatic priming) and explicit or declarative memory (Halbauer et al., 2009).

If attention is significantly impaired then there can be a direct impact on memory (Chun & Turk-Browne, 2007). Impaired cognition may at first appear to be a disorder of memory, when in fact attention is the primary impairment because if information cannot be encoded then it cannot be stored. Deficits in information processing and attention are considered principal features of mTBI (Frencham et al., 2005). But clinicians often fail to detect attention deficits due to insufficient cognitive loading during clinical examination to make the defects salient (Toyokura et al., 2012). In many patients divided attention deficits do not become apparent until they return to work or ordinary daily function. It has been suggested that a pathophysiological relationship exists between mTBI and attention deficit hyperactivity disorder (ADHD). mTBI symptoms can mimic those of ADHD, however, ADHD cannot be diagnosed in the presence of mTBI as it is primarily recognised as a childhood or developmental condition (Doyle, 2004). Accordingly, a diagnosis of mild neurocognitive impairment is used to capture the symptoms of inattention (Halbauer et al., 2009). Patients typically present with complaints of concentration difficulties, distractibility, difficulty multitasking, and decreased processing speed.

Assessing the cognitive effects of mTBI in combat veterans is challenging due to the multiple factors involved in cognitive impairment and the reliance of self-report measures. The cognitive and physical complaints associated with a history of mTBI are not specific to head injury; symptoms are associated with other psychiatric and medical disorders (Spencer et al, 2010). For instance, the symptoms of chronic pain, depression, and PTSD can impair cognitive functioning independently of the aftereffects of head injury (Vasterling et al., 2005). An investigation on individuals with a history of mild to severe closed head injuries by Gas and Apple (1997) found that self-report of cognitive function was strongly associated with emotional distress on select neuropsychological tasks. Furthermore, Green (1996; 2003) revealed that individuals who had

suffered mild head injury demonstrated substantially higher failure rates on symptom validity tests (SVT) than those with severe head injury. Notably, from this sample of 1,300 patients 30% demonstrated inadequate effort in performance validity test (PVT) as measured by the Word Memory Test.

Veterans who have demonstrated performance below that of normative expectations in self-report neuropsychological assessments and poor effort on SVT tend to be more prevalent in a mTBI sample, particularly when litigation or other compensation is involved (Green et al., 2001). At present, TBI is among the 10 most prevalent US service-connected disabilities for veterans receiving compensation (Department of Veterans Affairs, Veterans Benefits Administration, 2010). Dikmen et al., (2010) showed that symptom reporting following TBI was significantly related to age, gender, pre-injury alcohol abuse, pre-injury psychiatric history and severity of TBI. There is also some evidence that poor PVT performance is more prevalent in individuals with a dual diagnosis of mTBI and PTSD who are seeking compensation (Greiffenstein & Baker, 2008; Mittenberg et al., 2002). A medical symptom validity test (MSVT) failure rate of 58% was observed in a sample in which PTSD was at 91% and depression 69% (Armistead-Jehle, 2010). In contrast, a much lower failure rate of 20% was observed in veterans with mTBI who had lower rates of PTSD 44% and depression 15% (Armistead-Jehle & Hansen, 2011). In other samples of veterans with mTBI, higher rates of poor performance validity have been observed in those who have co-morbid psychiatric diagnosis in comparison to those without (Lange et al., 2012). Therefore, it is imperative to note that the diagnosis of mTBI, PTSD and various clinical diagnoses based on self-reported symptoms and history could be susceptible to potential exaggeration of symptoms.

On a more positive note, PVT failure has been shown to occur in a relatively small percentage of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) veterans when tested in research settings. Base rate performance in this sample of veterans showed a rate of poor effort 5.6% which is significantly lower than previous reports in clinical or forensic settings (Clark et al., 2014). This highlights the importance of context in which evaluations are carried out when considering the prevalence of malingering.

Treatment

Given the vast array of symptoms that accompany mTBI, treatment is currently approached on a predominantly individual basis, with various pharmacological and neuropsychological interventions. There are currently no specific treatments available for mTBI symptoms recommended by the Cochrane review. Research interventions to treat the enduring symptoms of mTBI have produced mixed results often using poor methodology and there is no professional consensus to support an effective treatment (Prince & Bruhns, 2017). Early intervention in the acute phase of mTBI typically involves education of PCS, reassurance and education on the expectation of a full recovery and guidance on rest and gradual resumption of typical activities (Prince & Bruhns, 2017). The National Institute for Health and Care Excellence (NICE) guidelines have suggested that there is some suggestion of patient education approaches being beneficial in the early stages of injury (Snell et al., 2018).

Drug treatments for chronic cognitive impairments in TBI have been reviewed by Cochrane (Dougall & Agrawal, 2015). However, results showed that there were no differences between drugs modafinil, the experimental drug (-) OSU6162, atomoxetine, rivastigmine and placebo on cognitive function. The hormone progesterone has been suggested to reduce brain damage if given

shortly after TBI and is typically used for more severe brain injuries (Wright et al., 2007;2014; Xiao et al., 2008). Nonetheless, the Cochrane review found no evidence of progesterone reducing mortality or disability in patients who have sustained a TBI (Ma et al., 2016). Cognitive rehabilitation for attentional deficits or cognitive behavioural therapy (CBT) for the symptoms of depression and anxiety along with psychotherapeutic support are frequently integrated treatment options (Prince & Bruhns, 2017).

The treatment approaches for PTSD recognize that this disorder is a complex, dynamic entity rather than a unidimensional set of symptoms. It is, therefore, often the case that a combination of cognitive behavioural therapy (CBT), psychotherapy and psychopharmacotherapy are utilized to suit the patient's individual needs (Wilson, Freidman & Lindy, 2012). According to the Cochrane review (2009), no single treatment has however proven effective as a cure for veterans with PTSD. The review instead suggests that the risk of suicide, drug and alcohol abuse is in fact increased (Bisson & Andrew, 2007; Hyman et al., 2012).

Fatigue is also a common symptom in patients with TBI and whilst fatigue and lethargy may be symptoms of depression, they may exist as separate entities and be directly related to the brain injury (Cantor et al., 2008). The neurobiology of depression remains unclear. However, there is a relationship that exists between serotonin and norepinephrine systems and selective serotonergic reuptake inhibitor (SSRIs) medications, that have been shown to benefit patients with depression. However, few studies have evaluated the efficacy of SSRIs in treating TBI related depression. Statistically, sertaline has been shown to significantly reduce psychological distress, anger and aggression, which are also symptomatic of mTBI (Fan, Uomoto & Katon, 2000).

The management of persistent mTBI symptoms and its accompanying comorbid disorders is a challenge to health care providers. These individuals represent a complicated poly-morbid population that are not suited to typical NHS standard of care models that target one diagnosis at a time. Enduring symptoms in one domain can thwart rehabilitative progress in other domains (Vanderploeg, Belanger & Curtiss, 2000). There is, therefore, a pressing need to understand the factors that influence mTBI symptoms so that appropriately targeted care can be provided.

In summary, the neuropsychiatric and cognitive symptoms that can accompany mTBI are multifaceted and the underlying drivers of symptoms remain unclear. Understanding the factors that influence these symptoms and the functional outcome for veterans is of real importance to provide targeted care and assessment. The combination of current depressive disorder, PTSD and military mTBI has been suggested to represent a significant clinical phenotype (deployment trauma factor) that increases the risk of not only disability but also other clinical issues such as substance abuse (Lippa et al., 2015). In the next chapter I propose that the ambiguity of mTBI can be partly addressed by looking at the relationship between mTBI and the vestibular system, I will later suggest that rehabilitation may be enhanced by utilizing the vestibular system as a novel treatment pathway.

Chapter 2

The Vestibular System and mTBI

"*It is easy to underrate the importance of a sensory system whose receptors are buried deep with the skull and of whose performance we are not usually aware"* (Wilson and Melvill Jones, 1979. *p*1)

Introduction

In Chapter 1 mTBI was described as a clinal phenotype that causes significant disability to military veterans (Lippa et al., 2015). However, the drivers of long-term disability are far from clear. Here I suggest that one possible driver of mTBI symptoms is vestibular pathology. Exposure to blast can be a significant risk factor in sustaining damage to the inner ear. In line with this, auditory dysfunction has become the most prevalent individual US service-connected disability, with compensation payments of more than 1 billion dollars per year (Fausti et al., 2009). In fact, explosive munitions accounted for 74.4% of US military wounded in action cases in the Iraq and Afghanistan conflicts (Belmont et al., 2012). Rupture of the tympanic membrane has been considered as an indicator of blast intensity and potential underlying primary blast injury (Elder & Cristian, 2009). Perhaps unsurprisingly, accumulating evidence suggests that blast wave trauma and secondary head injury can cause damage to the peripheral (and central) vestibular system (Lien and Dickman 2018; Szczupak et al., 2016). The long-term impact of blast injuries are still not fully appreciated and the late sequelae from repeated blast exposure often goes unrecognised, frequently because vestibular assessments are not routinely performed. But the likely prevalence of inner ear injury, coupled with the wide behavioural impairment that we know from civilian studies accompanies vestibular damage, raises the possibility that some sequelae of mTBI are vestibular in origin.

Vestibular Pathology as a Driver of mTBI Symptoms

The cognitive and psychiatric symptoms that result from mTBI reflect likely damage to both cortical and sub-cortical structures within the brain (Scherer & Schubert, 2009). But specific mechanisms are elusive, and one that has received little attention is the vestibular system. Individuals with mTBI commonly report changes in their ability to maintain balance, posture and gait. In the acute phase of mTBI, symptoms of dizziness have been shown to be the second most commonly reported symptom with 11.5% of soldiers developing persistent problems post deployment (Terrio et al., 2009). Concurrent injuries to the auditory system as a result of acute blast trauma and TBI accounted for one-quarter of all injuries among US marines during OIF through 2004, and were the most common type of injury (Fausti et al., 2009). Exposure to blast waves can affect both gas and fluid filled structures of the middle/inner ear and has resulted in significantly greater rates of vestibular injury, hearing loss and tinnitus than non-blast related TBI, affecting 60% of these patients (Lew & Guillory, 2007; Fausti et al., 2009). Secondary, blunt trauma from blast can be sustained by way of impact to the back of the head after falling or being hit by a projectile which can also induce vestibulopathy. In addition to inner ear damage, white matter abnormalities and defuse axonal injury have been observed in the cerebellum, thalamus and ventral posterior cerebral cortex in mTBI patients presenting with vestibulopathy (Furman et al., 2000). In a long-term study of untreated patients with mTBI, vertigo was shown to persist in 59% of patients five years post injury (Berman & Fredricson, 1978). Patients with mTBI who present with symptoms of dizziness and imbalance often experience a slower recovery and are less likely to return to work than patients without dizziness (Chamelian & Feinstein, 2004).

Meta-analysis of individuals with non-complicated mTBI (which can be defined as having no intercranial abnormality) (Iverson et al., 2012), has shown that sensorimotor and physiological changes in balance can last beyond the typical recovery time of concussion effecting gait, motion and oculomotor tasks (Galea et al., 2018). Moreover, persistent postural instability has been observed up to 7 years post injury in US veterans (Pan et al., 2015). A considerable number of blast-trauma patients with vestibular injury may have been misdiagnosed due to the lack of assessment criteria for this population and logistical testing difficulties with polytrauma patients.

Disorders of imbalance following mTBI can result from peripheral vestibular disturbance such as benign paroxysmal positional vertigo (BPPV), perilymph fistula syndrome (PFS), central nervous system trauma to the brain stem and or cerebellum, post-traumatic vestibular migraine and spatial disorientation. BPPV spells typically last for less than a minute at a time and cause a sensation of falling or light-headedness that is provoked by movement of the head. Frequently, patients with traumatic BPPV present with lateral canal deficits. However, the posterior semi-circular canal is the most commonly affected by the stray otoliths which cause BPPV (Szczupak et al., 2016). PFS arises as a result of an abnormal opening (most commonly at the round or oval window) or by rupture of the fluid-filled membranous labyrinth (Glasscock et al., 1992; Szczupak et al., 2016). Fluid leaks from the inner ear to the middle ear cavity. PFS occurs frequently from blast wave trauma or scuba diving depressurization with difficult to diagnose dizziness and is frequently accompanied by sensorineuronal hearing loss and tinnitus. Direct trauma to the brain stem and/or cerebellum causes complaints of imbalance with standing and walking, and occasionally true complaints of vertigo (Shepard et al., 2013). Post-traumatic vestibular migraine can cause 50% of migraine headaches and individuals often report episodic vertigo with periods of unsteadiness (Lempert et al., 2012). The most common and difficult balance disorder seen after head injury is

spatial disorientation which results in individuals feeling continually unsteady (Hoffer et al., 2004).

Central vestibular disorders are more likely than peripheral disorders to cause chronic imbalance and are frequently associated with other neurologic symptoms (Miedaner et al., 2005). Lesions along the vestibular pathways extend from the vestibular nuclei in the medulla oblongata to the ocular motor nuclei and integration centres in the pons and rostral midbrain, and thereon the thalamus, and multisensory vestibular cortex areas in the temporal cortex (Dieterich, 2006). The vertigo symptoms that arise from central vestibular damage can present in various syndromes that typically present with ocular motor, perceptual and postural manifestations (Dieterich, 2006). There is however a large overlap in the duration of episodes between central and peripheral disorders and a detrimental association with quality of life measures (Grimby & Rosenhall, 1995). Dizziness can be accompanied by postural instability and the fear of falling has been shown to have a direct link to low self-esteem (Tinetti & Powel, 1993). Patients with uncompensated vestibular hypofunction can have functional limitations such as the inability to walk in the dark, cross streets rapidly, or stand on a moving bus.

The relationship between blast exposure, mTBI and damage to the vestibular system is relatively well established and persistent dizziness, vertigo, clumsiness and imbalance symptoms have frequently been shown to occur (Hodge et al., 2008; Pogoda et al., 2012; Terrio et al., 2009). Additionally, 50% of blast exposed soldiers experiencing symptoms of dizziness have been observed to have abnormal nystagmus (Scherer et al., 2011). Diffuse axonal injury occurs when shearing, stretching or traction on small nerves leads to impaired axonal transport, focal axonal swelling and possible axonal disconnection (Hurley et al., 2004; Mendez et al., 2005). This

pathophysiologic process can be evident from blast, blunt and mixed mTBI and may further contribute to comorbid dizziness and vestibular pathology in cases of secondary and tertiary effects of blast. Furthermore, BPPV, PFS, and vascular or central lesions are commonly implicated as causes of vestibular pathology after head trauma (Scherer & Schubert, 2009). Although the diagnosis of mTBI alludes to a mild deficit, the reality for many patients who suffer from this condition has been shown to be debilitating particularly when accompanied by PTSD and depression (Lippa et al., 2015). However, the effects of imbalance in mTBI, cognition, affect, functional status and long-term outcome have not been properly examined (Pogoda et al., 2012).

The Anatomy and Function of the Vestibular System

The vestibular system constitutes our sixth sense and plays an important role in our everyday life, contributing to a range of functions from motor reflexes to the highest levels of perception and consciousness. Otherwise known as the balance organs of the inner ear, the vestibular sensory organs are located in the petrous part of the temporal bone in close proximity to the cochlea. The vestibular system is comprised of two types of sensors. The two oltolith organs (the saccule and utrical) which provide information about linear acceleration and gravitational pull, and the three roughly orthogonal semicircular canals, which sense angular acceleration and rotational movement of the head (see Figure 2.1) (Angelaki and Cullen, 2008). These sensory organs send signals to the vestibular nerves which concurrently send signals to the neural structures that control eye movements and posture. The vestibular system is primarily proprioceptive in nature, concerned with the maintenance of equilibrium and orientation of the body in space.

Hair cells are a common element in the vestibular semicircular canals, otolithic organs and the cochlea (Highstien, Fay & Popper, 2004). They transform mechanic displacement into electric

energy (Kingma & Van De Berg; 2016) and are comprised of stereocilia and a kinocilium which are embedded within a glutinous mass (see Figure 2.2), overlaid by small calcium carbonate crystals in the otoliths. When the head undergoes either vertical or horizontal acceleration, these crystals move and activate the hair cells transmitting information to the brain stem via the vestibular nerves for perception of motion or tilt.

Figure 2.1. The Peripheral Vestibular System (http://utahhearingandbalance.com/dizziness/balance-and-the-vestibular-system/).

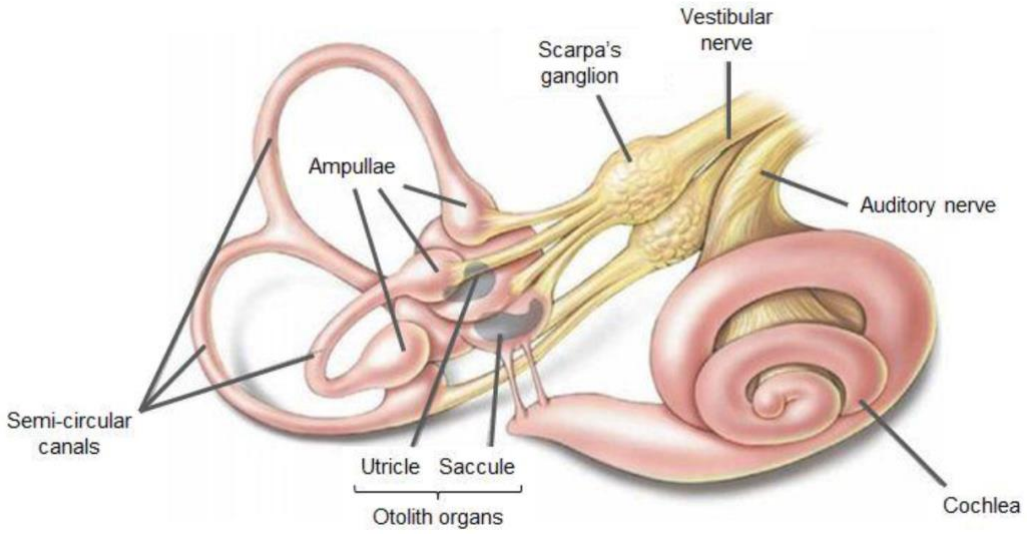
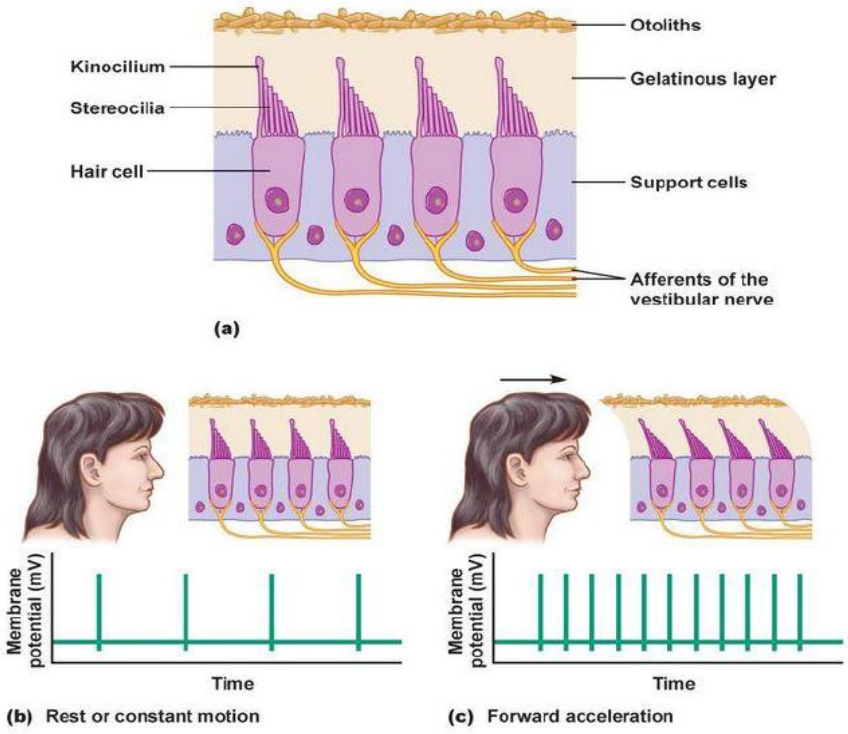


Figure 2.2. Anatomy of Hair Cells within the Otolith Organs:

a) during rest or constant movement; b) the cilia are perpendicular to the cell surface however, move when horizontal acceleration c) is applied (http://droualb.faculty.mjc.edu).



In a similar fashion, the ampullae, the stereocilia and the kinocillum of the hair cells are immersed in a gelatinous mass called the 'cupula'. This is distorted by currents within the endolymph induced by movement in the fluid that fills the canals and ampullae. Accelerations in the cupula bend the cilia causing these hair cells to increase their firing rate (vestibular afferents continuously fire even when the body and head are at rest and motionless). Signals from the semicircular canals and the otolith organs are complementary, such that their combined activation is necessary to encode the vast range or physical motions experienced in day to day life (Angelaki and Cullen, 2008).

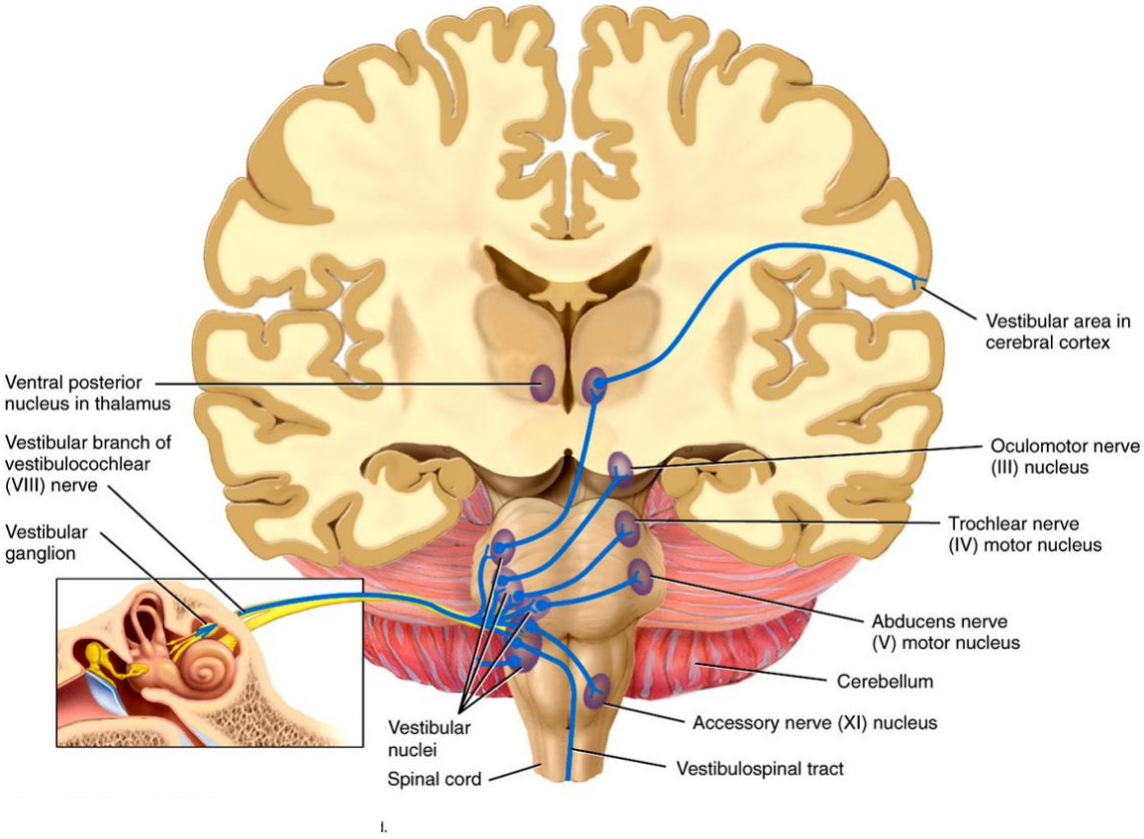
At the central level, the vestibular system is highly convergent and multimodal. Visual/vestibular and proprioceptive/vestibular interactions occur throughout the central vestibular pathways sending signals that are vital for gaze and postural control. The influence of angular and linear forces is pervasive and a continuous flow of vestibular signals extends throughout the central nervous system. These signals are integrated with processes related to arousal, wakefulness, vision, audition, somatosensation, movement, digestion, cognition, learning and memory (Highstein, Fay & Popper, 2004).

The diversity of vestibular anatomy is evidenced by its widespread connectivity. The vestibular system is unique in that many second-order sensory neurons in the brain stem are also premotor neurons; the same neurons that receive afferent inputs send direct projections to motoneurons (see Figure 2.3). This streamlined circuitry is advantageous in eliciting short reaction times. For example, the latency period for the vestibular ocular reflex, in which head movement is compensated by an eye rotation to keep retinal images stable, occurs in 5-6ms (Highstein, Fay & Popper, 2004).

As seen in *Figure 2.3* the 1st order sensory neurons of the vestibular pathways project from the hair cells in the vestibule and the semicircular canals to the cell bodies of the vestibular ganglion and then to the vestibular branch of the vestibulaocochlear (VIII) nerve. The vestibular nerve projects to the ipsilateral complex of four major vestibular nuclei in the dorsal part of the pons and medulla. The vestibular nuclei is where the 1st order sensory neurons synapse with 2nd order sensory neurons ‘interneurons’.

Figure 2.3. Ascending and Descending Pathways of the Vestibular System

(http://theimgpic.pw/Vestibular-tracts-Vestibular-Disorders-t-Neuroscience.html)



The 2nd order sensory neurons in the vestibular nuclei integrate signals from the vestibular organs with those from the spinal cord, cerebellum and visual system. Projections then continue on to the 3rd order sensory neurons in the ventral nuclei of the thalamus, the oculomotor nuclei, the reticular centres occupied with skeletal movement, spinal centres occupied with skeletal movement and the vestibulocerebellum. The 3rd order sensory neurons in the ventral thalamus send axons to synapse with neurons in Broadmann's area 2V and 3a of the primary somatosensory cortex and the cortex.

A Relationship between the Vestibular System, Cognition and Affect

A growing number of studies indicate that damage to the vestibular system can not only affect neuropsychiatric function, but present in a manner that is much like PTSD and mTBI (Fausti et al., 2009). Since the first century, medical literature has linked vestibular disorders to psychiatric symptoms such as panic disorder, anxiety and depression (Asmund et al., 1998; Balaban, 2001; 2011; Eagger et al., 1992; Best et al., 2008; Preuss et al., 2014; Yardley et al., 1998). More recently, a study conducted by Harber et al., (2016) showed that PTSD severity was positively associated with dizziness severity in 50 US military veterans with a PTSD diagnosis. Dizziness handicap scores were three times worse in veterans with PTSD compared to those of the control group. Patients with vestibular disorders also report higher rates of depersonalisation derealisation symptoms which include difficulty focusing attention, thoughts seeming blurred and disassociation (Sang et al., 2006 Cheyne and Girard, 2009); Agoraphobia is also particularly common in patients with vestibular disorders (Eagger et al., 1992; Gazzola et al., 2009; Guidetti et al., 2008).

In many cases, these psychiatric complaints are accompanied by cognitive disorder. In a large-scale survey of 20,950 adults from the US population, Bigelow et al., (2015) reported that 8.4% of participants self-reported symptoms of vestibular vertigo. These individuals were eight times more likely than those without vestibular disorders to have serious difficulty in concentrating or remembering; and were four times more likely to have activity limitations as a result. These individuals were also three times more likely to suffer from depression, anxiety and panic disorder. Interestingly, patients with PTSD frequently describe symptoms such as dizziness, disorientation and/or extreme discomfort in environments such as supermarkets, shopping malls and stadiums. Typically, these individuals comment on trying to avoid being in such environments. These

manifestations are classified as an anxiety disorder, but they are also characteristic of patients with visual vertigo or space motion discomfort (Jacob et al., 2009). More recently Smith et al., (2018) provided further support for this cognitive/psychiatric association from 101 patients with a neurotological diagnosis. 50% suffered from reduced visuospatial short-term memory, 60% and 37% exceeded cut-off on the Beck Anxiety and Depression Inventories and fatigue was also shown as particularly problematic affecting 78% of the sample. Research from Lahmann et al., (2017) echoes these findings, with approximately 50% of 547 vestibular patients also meeting a psychiatric diagnosis. To add to this, there is also a growing body of evidence to demonstrate a broad range of cognitive impairments that result from vestibular dysfunction including: learning disability, deficits in memory, executive function, attention, apraxia, motivation and visuo-spatial ability (Black et al., 2004; Byl, Byl & Rosenthal, 1989; Candidi et al., 2013; Grimm et al., 1989; Grabher et al., 2011; Guidetti et al., 2008; Mast et al., 2014; Risey et al., 1990). It is feasible and quite probable that the association between vestibular dysfunction and affective symptoms has a connection with observed cognitive deficits that accompany vestibular disorders (Balaban et al., 2001; 2002; Staab, 2006). Indeed Smith et al., (2018) has demonstrated that memory loss is not mediated by affective symptoms, but is instead directly associated to vestibular injury. Together, and most importantly, these studies illustrate that affective and cognitive symptoms attributed to mTBI and allied psychiatric disorders may be partly vestibular in nature.

Could Treating the Symptoms of Imbalance help relieve symptoms of mTBI and PTSD?

In the UK, treatment for balance and dizziness disorders currently requires referral to an neuro-otologist. Evaluation of balance and gait is often made using the Dizziness Handicap Inventory, caloric irrigation of the of the external auditory canal, optokinetic testing, administration of the Dix-Hallpike test, posturography, and/or centre of mass movement testing (Basford et al., 2003).

Attaining the neuro-otological history is imperative to determine the correct course and management of the specific balance and dizziness disorder. For example, the treatment of PFS frequently requires surgery to repair labyrinth rupture and to prevent fluid leaks from the inner ear to the middle ear (Grimm et al., 1985). The Epley repositioning manoeuvre is commonly used to treat BPPV which moves calcium carbonate crystals from the semicircular canals in to the utricle. Individuals who have stable vestibular function yet continue to present with symptoms when provoked by head motion, in the absence of visual or altered somatosensory cues, may benefit from vestibular rehabilitation therapy (Shepard et al., 2013). Therapeutic vestibular exercise which is designed to restore a normal vestibular ocular reflex may be effective in treating a unilateral vestibular deficit. By contrast, individuals that have bilateral vestibular loss are typically the hardest to rehabilitate. Nonetheless, the symptoms of many forms of imbalance are to some degree treatable (Balaban, Jacob and Furman, 2011).

Preliminary evidence has started to emerge to suggest that treatments traditionally used to treat imbalance disorders may hold therapeutic value in treating the broader symptoms of mTBI and PTSD. Carrick et al., (2015) investigated the efficacy of a novel brain and vestibular rehabilitation (VR) treatment that aimed at treating PTSD. In this sample, all 75 subjects had suffered combat related TBIs and fell in the severe category of the Clinician Administered PTSD Scale (CAPS). The VR treatment involved gaze stabilization exercise, off axis whole body rotation, visual pursuit and visual saccadic eye movements to novel targets. Each subject received three sessions of VR treatment five days a week for two weeks. Pre vs. post treatment CAPS scores revealed a 36% improvement of PTSD symptoms. Similarly, in a series of four case studies by Keffelgaard et al., (2015), patients with mTBI received eight weeks of individually modified VR exercises. Here three out of the four patients showed reduced self-perceived disability, improved quality of life

reduced psychological destress and improved performance-based balance. This reduction in symptoms was still evident at three months follow-up. Although promising, it should be noted that these studies were underpowered and lacked formal trials methodology.

Could Artificial Stimulation of the Vestibular System using Galvanic Vestibular Stimulation Provide a Practical Treatment Approach for mTBI?

Artificial stimulation of the vestibular nerves via thermal current, using a procedure known as caloric vestibular stimulation (CVS), or electric current using galvanic vestibular stimulation (GVS) has been shown to remediate a number of cognitive and affective symptoms; including, pain, episodic migraine, schizophrenia, bipolar disorder, Parkinson's disease, prosopagnosia, aphasic syndrome, minimally conscious state, and hemi-spatial neglect (Black et al., 2016; Dodson 2004; Ramachadran et al., 2007; Vanzan et al., 2017; Wilkinson et al., 2013; 2014; 2016). This suggests there is significant potential to modulate cognitive and affective functions seen in mTBI (Stephan et al., 2005; 2009; Bense et al., 2001), from a stimulation process that has been described as similar to the stimulation that arises from natural head movement. Some of these studies indicate that the effects can be long-term, Wilkinson et al., (2014) demonstrated that as little as one 25min session of GVS with ~1mA Direct Current (DC) could elicit an amelioration of inattention symptoms in patients with hemi-spatial neglect for up to four weeks. Of particular note, one active session of GVS was enough to show a carry-over of comparable efficacy to ten. Producing a median improvement of 20% on Barthel Index scores most notably in continence, bathing and transfer subscales. In an unpublished follow-up study, I re-assessed 28 of the 52 participants at 1 to 3 years post GVS, and found that the ameliorating effects of GVS were still evident (Denby & Wilkinson, 2014[unpublished]). Along similar lines, Schmidt et al., (2013) showed lasting improvements in tactile extinction using GVS at 84 days post stimulation on 12 patients with right

hemisphere lesions; and Wilkinson, Podlewska & Sakel, (2016) revealed carry over effects at five months post CVS in a patient with Parkinson's disease, who showed clinically relevant improvements in motor symptoms, cognition, depression and fatigue.

GVS is a technique that was traditionally used to probe the role of the vestibular system in autonomic motor control (Fitzpatrick & Day, 2004). The procedure activates the vestibular nerves via low amplitude electrical currents that are delivered to the mastoid processes using self-adhesive, rubber electrodes. A subsequent change in the vestibular nerve afferent firing rates occurs upon stimulation, which via basil forebrain/brainstem projections throughout the central thalamus and hypothalamus (Lopez, Blanke & Mast, 2012), elicits a variety of compensatory responses in distal frontal-parietal and striatal networks associated with arousal and goal-directed behaviour (Philips, Ladoucer & Drevets, 2008). GVS has been shown to be safe, easy to administer and has less side effects than the traditional method of stimulating the vestibular system using caloric irrigation. Caloric irrigation involves injecting cold water into the ear canal and is known to cause side effects of pain, vertigo, nausea and nystagmus during irrigation making it a messy and unpleasant procedure (Utz, et al., 2011; Wilkinson et al., 2010; Wilkinson et al., 2014; Zubko et al., 2013).

The mechanisms of GVS promoting clinically relevant change are still unclear. However, GVS has been associated with the release of a number of neurotransmitters including serotonin (Ma et al., 2007), histamine (Horii et al., 1993), acetylcholine (Ma et al., 2007; Goldstien et al., 2007) and GABA (Samoudi et al., 2012; Sailesh & Mukkadan, 2013). Early studies have illustrated that both place cell and theta rhythm could be modulated by vestibular stimulation (Gavrilov. 1995; Wiener et al., 1995). The pathways through which vestibular signals reach the hippocampus is yet to be

fully elucidated. Nonetheless, electrical stimulation of one labyrinth has been shown to evoke field potentials and single unit activity in both the unilateral and contralateral CA1 region (Hicks 2004; Horri et al., 2004). Both CVS and GVS have been shown to enhance short-term memory (Batchtold et al., 2001) and a reduction of mean reaction times to recall of faces (Wilkinson et al., 2008). DC GVS has also been shown to promote the release of GABA in the substantia nigra (Samoudi et al., 2012) and GABAergic inhibition controls the activity of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the bodies response to stress (Sailesh & Mukkadan, 2013). Reciprocally, this involves regulating the production of corticotropin releasing hormone (CRH) neurons in the hypothalamus which sends signals to release adrenocorticotropic hormone (ACTH), then triggering the release of cortisol from the adrenal gland (Mody and Maguire, 2012). Most notably, CVS in vestibular dysfunction has been shown to activate hippocampal formation which inhibits the stress axis (Vitte et al., 1996). Furthermore, controlled swaying evoked vestibular stimulation has been shown to decrease salivary cortisol levels in elephants (Markia et al., (2008), new born infants (White-Traut, 2009) and (N = 240) neurologically healthy adults who also showed a reduction in stress levels, blood pressure and pulse rate (Archana et al., 2016).

Brain imaging research indicates that GVS can induce diffuse cortical and subcortical activations to the hippocampus, basil ganglia, thalamus and motor cortex (see Chapter 4, Bense et al., 2001; Bucheret al., 1998; Deutschlander et al., 2002; Dieterich et al., 2003; de Waele et al., 2001; Fasold et al., 2002; Lobel et al1998; Stephan et al., 2005; Suzuki et al., 2001). For example, Stephan et al., (2005; 2009) utilised functional magnetic resonance imaging (fMRI) to determine if DC or alternating current (AC) GVS would mediate different activation sites within the vestibular cortex and to identify an optimal waveform with respect to perception. As can be seen in (*Figure 2.4*) there was haemodynamic evidence of both DC and AC GVS evoking wide spread activation

changes in blood oxygenation level-dependent (BOLD) responses. AC GVS was shown to induce greater BOLD responses than DC (Stephen et al., 2005; 2009).

Figure 2.4. Activation Maps Indicating the Effects of DC and AC GVS (Stephan et al., 2005; 2009)

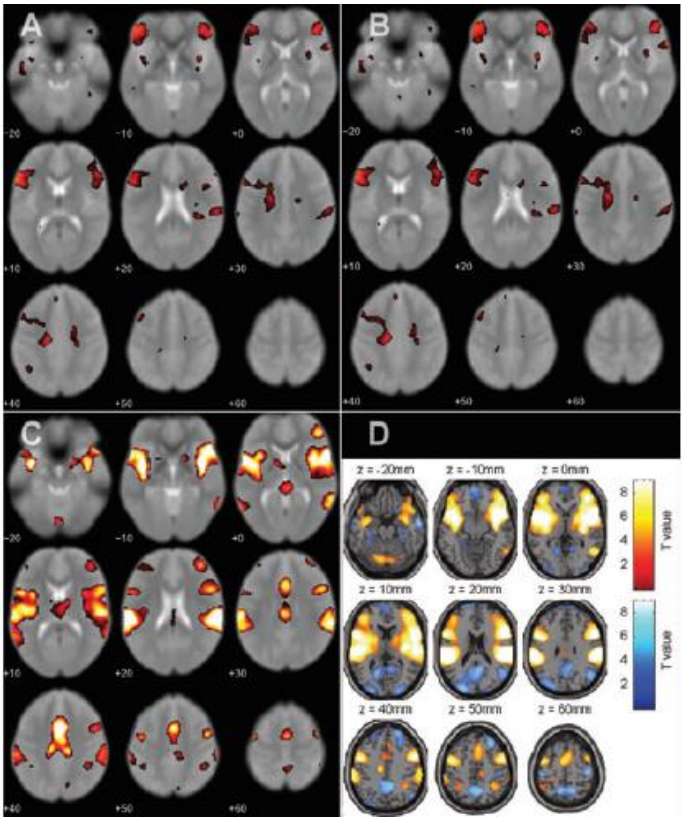


Figure 2.4 (A) Effects of persistent response to DC-GVS (model 1). (B) Effects of persistent response to DC-GVS (model 2) indicate the same response as pattern of activation as model 1. (C) Effects of transient responses to switching DC-GVS on and off. (D) The effects of AC GVS.

The link between GVS and GABA noted above is particularly interesting because GABA uptake has been shown to regulate cortical excitability via cell type-specific tonic inhibition which is linked to long-term potentiation (LTP) and long-term depression (LTD) (Semyanov, Walker and Kullmann, 2003). LTP is the enduring enhancement of synaptic connection, while the

complementary process LTD causes reduced transmission of synaptic connections. Both of these processes can cause structural modification of neuronal connectivity which are important underlying mechanism of learning and memory process (Bliss & Cooke, 2011; Hebb, 1949; Monte –Silva et al., 2013) and are therefore relevant to neuro-rehabilitation.

Different forms of LTP/LTD have been defined as dependent on the duration of the excitability enhancements. Early LTP/LTD is discerned from late by excitability alterations lasting for more than three hours, and showing an increase or decrease in synaptic weight and strength of postsynaptic potentials (Monte-Silva et al., 2013; Rioult-Pedotti et al., 2000). In the present context the effects of GVS on GABA coupled with its lasting clinical and strong effects on BOLD response, may imply that GVS can manipulate synaptic strength and potentially a powerful neuromodulator in mTBI.

Chapter 2 Summary and Research Questions

Inner ear injury and the symptoms of imbalance are common sequelae of mTBI in military personnel (Fausti et al., 2009; Terrio et al., 2009). Damage to the inner ear as a result of blast waves or by way of secondary head injury has been shown to negatively impact vestibular function (Fausti et al., 2009). In this Chapter it has been suggested that sensory, cognitive and affective symptoms that can arise from mTBI closely resemble symptoms of common vestibular pathology. This may imply that some of the symptoms of mTBI are vestibular in origin. Yet while the symptoms of imbalance are often noted, the presence of an underlying vestibular diagnosis is often missed because screening is not carried out.

This thesis aims to develop understanding of how the vestibular system interacts with the long-term symptoms of mTBI, both as a driver of symptoms and a novel treatment modality. The extent to which symptoms of imbalance influence mTBI is still unclear and further exploration of this relationship is required if we are to develop potential treatments for mTBI and provide appropriate care pathways for military personnel and veterans in the future.

To explore the relationship between the vestibular system and mTBI, Chapter 3 examines the lifetime prevalence of mTBI and the neuropsychiatric outcomes of 162 UK military veterans. Mediation analysis was also used to assess the direct impact of vestibular disorder in neurobehavioral function and general disability; independent of co-morbid psychiatric symptoms. A further aim was to for the first time determine if vestibular disturbance was more frequently seen in blunt, blast or blunt + blast injuries.

In Chapter 4 I assess if GVS can affect cortical excitability up to 24hours post stimulation which is a precursor of long-term synaptic change. The neurological sequela of mTBI that are targeted will depend on the pattern of excitability observed. If GVS can be shown to reduce cortical excitability then I will target anxiety symptoms which are associated with cortical hyper-excitability (Bunse et al., 2014; Centonze et al., 2005). However, if GVS increases motor cortex excitability then symptoms of information slowing and reduced arousal would seem a better target (Heart & Kwentus, 1987; Monte-Silva et al, 2013; Wilkinson et al., 2008). The results from this Chapter informed Chapter 5 in which 6 UK military veterans were recruited to establish if excitability changes seen in Chapter 4 modulated their behavioural symptoms as predicted.

Chapter 3

Vestibular Disturbance as an Influence on the Chronic Symptoms of Mild Traumatic Brain Injury in UK Military Veterans

Introduction

During the conflict in Iraq and Afghanistan, the proportion of head and neck wounds in US soldiers were higher than those experienced in World War II most (75%) were due to blast munitions (Owens et al., 2008). Explosive munitions were also the most frequent mechanism of battle injury for UK service personnel during Operation Herrick and accounted for 52% of 2,201 injuries sustained. Just under a fifth of these reported injuries were to the head and neck (Ministry of Defence, 2014). The dynamics of blast waves are characterized by shock displacement waves that can cause implosion and pressure changes in the inner ear. This coupled with noise levels that exceed 185dB can rupture the tympanic membrane in approximately 50% of adults (Chandler & Edmond, 1997). Tympanic membrane perforation has been identified as a marker of concussive brain injury and should raise a high index of suspicion for concomitant neurologic injury (Xydkis et al., 2007). Given the proximity of the vestibular and hearing organs, it is likely that many veterans with hearing loss will also have vestibular loss. However, the role of the vestibular system in mTBI has previously received little attention. This Chapter aims to address this issue and further develop the evidence presented in Chapter 2 that suggests the vestibular system may be an influence on the affective, cognitive and sensory symptoms experienced from chronic mTBI.

Of particular interest, is the distinct overlap in neurobehavioural and psychiatric symptoms that accompany vestibular disfunction, mTBI and PTSD. Previous research on UK military personnel

deployed to Iraq has indicated that the symptoms of post-concussion syndrome (PCS) are difficult to distinguish from those of psychological trauma. It has been suggested by Fear et al., (2011) that the symptoms of PCS are not specific and that trying to distinguish between physical and psychological trauma being the cause of PCS, could be fraught with hazards. Predominantly this is because individuals who demonstrate PCS symptoms frequently have not suffered neurological insult, but have experienced psychological trauma. This, coupled with the fact that vestibular disturbance is not routinely assessed in military personnel, raises the possibility that symptoms of vestibular origin may wrongly be attributed to mTBI or psychiatric disturbance. Furthermore, as mTBI is not routinely screened during deployment in the UK armed forces, it is likely that the prevalence of mTBI is much higher than current estimates suggest.

There is an emerging consensus that the effects of mTBI sustained during deployment might be better understood by evaluating mTBI within the context of lifetime exposure. Research from McGlinchy et al., (2016) provided a comprehensive evaluation of lifetime incidence of TBI in US military veterans. This revealed that 72% of 294 US veterans had sustained one or more TBI in their lifetime. 40% had sustained more than one TBI and almost half 48% had suffered a military related TBI. Of these individuals who reported military TBI, 42% experienced one or more blast related TBI and 31% were mild grade injuries. Military TBI by blunt force mechanism was seen in 35% of the sample. Furthermore, almost two thirds 64% of these veterans had a current PTSD diagnosis, 28% had depressive disorder and 16% had substance abuse/dependence issues. Sleep disturbance was particularly problematic affecting 79% of veterans and in general terms the sample were shown to suffer from multiple psychical and psychiatric conditions that required a comprehensive approach to characterize. A less comprehensive study of 123 UK military veterans seeking psychiatric support for mental health difficulties revealed a prevalence rate for TBI of 63%

(Murphy et al., 2015). However, this study reported no relationship between TBI and PCS, but significant associations between reporting TBI, depression, problems with anger and an increased risk of experiencing mental health difficulties. This relationship is supported by research from Orlovska et al., (2014) who reviewed the medical records of 113,906 civilians with head injuries and showed that individuals were four times more likely to develop a mental health illness following TBI.

Following mTBI, 15 to 20% of individuals present with neurobehavioual symptoms that are enduring (Bazarian et al., 2001; Marshall et al., 2012; Ryan et al., 2003). Soldiers often report physical sensory, cognitive and behavioural emotional changes (Pogoda et al., 2012). As evidenced in Chapters 1 and 2 symptoms such as headache, fatigue, sleep disorder, dizziness, amnesia, slowed information processing, executive dysfunction, depression and anxiety are commonly seen in mTBI and PTSD (Cassidy et al., 2017; Herbert et al., 2018; Harber et al., 2016). Furthermore, recent research has started to indicate that vestibular pathology affects neuropsychiatric function in a manner that is akin with on-going mTBI symptoms (Bigelow & Agrawal, 2015; Smith & Zheng, 2013; Hitier et al., 2014). Sustained-in-combat mTBI is frequently accompanied with bodily trauma and PTSD, which makes the drivers of neuropsychiatric impairment unclear.

Dizziness is one of the most commonly seen symptoms of mTBI, yet, information on balance deficits in military veterans is sparse. Symptoms of dizziness and imbalance are the second most commonly reported in acute concussion (Hodge et al., 2008; Terrio et al., 2009). Post deployment, 11.5% of soldiers report vestibular symptoms that are persistent (Pogoda et al., 2012) that also have a greater likelihood worsening at three months post injury, than other mTBI symptoms

(Laborey et al., 2014). Frequently, symptoms that effect balance can go undetected in a seminal paper from Grimm et al., (1985), he postulates that of 102 patients suffering with perilymph fistula syndrome, all cases were as a result of TBI or whiplash and these individuals had been injured months if not years before their diagnosis.

There is a strong relationship between balance disorders, cognitive and affective symptoms and many of which share a distinct overlap with those symptoms seen in mTBI and PTSD (Herbert et al., 2018; Harber et al., 2016). This may be partly attributed to the shared neurochemical features of the ascending vestibular afferents and limbic arousal systems (Balaban et al., 2011) a network which is also associated with migraine headache (Balaban et al., 2011). Combined these findings indicate the complexity of vestibular disorder influencing gravitational and head-centred frames of reference that can compromise many brain processes. This may provide indication of vestibular function independently influencing neurobehavioural and functional outcomes of military mTBI and PTSD. Either way, it is probable that military veterans are at substantial risk of vestibular dysfunction.

To investigate the influence of vestibular disturbance in mTBI this study first needed to establish the lifetime prevalence of mTBI in UK military veterans and the relative presence of chronic vestibular disturbance in relation to blunt, blast or blunt+blast mTBI. Whilst all of these mechanisms can lead to vestibular pathology it is not yet clear which if any mechanism constitutes the greatest risk of vestibular disturbance. Comparatively, auditory dysfunction in US military TBI shows a strong association with blast TBI (Lew & Guillory, 2007). Hearing loss affected 62% of veterans with blast mTBI and tinnitus 38%; while in the non-blast group only 44% suffered hearing loss and 18% suffered tinnitus (Lew & Guillory, 2007). A second key aim of the current study

was to establish the impact of vestibular disturbance on neurobehavioural symptoms and general disability which is commonly seen in both mTBI and vestibular disorders. To do this mediation analysis was employed to determine if vestibular disturbance could independently influence these outcomes irrespective of the psychiatric mediators of PTSD, depression and anxiety symptoms.

Methods

Participants

162 participants were recruited for study - see Table 3.1 for their demography and military background. Of this sample 137 participants were recruited from a 6week programme of in-patient psychiatric treatment at one of three *Combat Stress* treatment centres in the UK, and the remaining 25 participants were recruited from drop-in counselling sessions at the *Portsmouth Veterans Outreach* Centre. Veterans seeking psychiatric support were recruited due to their poor life outcomes and greater likelihood of vestibular dysfunction that can accompany psychiatric disturbance. Individuals were eligible if over 18 years old, retired from the UK armed forces, and willing to consent to study participation. Potentially eligible participants were approached shortly after their treatment/counselling session and asked if they would be willing to conduct a survey aimed at assessing the frequency and nature of head injury in military veterans. They were advised that the survey was would take approximately 40minutes to complete and involved answering questions on a hand-held iPad. Favourable ethical opinions from the University of Kent School of Psychology and Combat Stress research ethics review panels were given prior to study commencement.

Procedure

Following written informed consent, participants completed the survey in a quiet corner room accompanied by the experimenter. The survey comprised a number of validated, standardised self-report assessments presented serially using the on-line survey software *Qualtrics*. These assessments were administered using iPads in the order in which they appear below and were preceded by questions about demographic background and military service. Participants were told that they could take breaks throughout the survey as needed.

Self-Report Measures

Demographics and Military Background

Demographics were attained relating to military service branch, length of service, number of deployments to a war zone (this included deployments to Northern Ireland during conflict). Information relating to experience of active service, current vocational/relationship status, gender and age were obtained. Additionally, questions related to alcohol and drug consumption were included. All demographic questions were self-reported and not verified measures.

Traumatic Brain Injury assessment

To determine participants lifetime history of TBI, The Ohio State TBI Identification Method (OSTIM) was administered (Corrigan & Bogner, 2007). This is a gold standard self-report assessment that probes hospitalisation as a result of TBI, method of injury via blunt or blast mechanisms and age at the time of injury. Additional questions were added to the test battery from the Boston Assessment of TBI-lifetime (BAT-L) that determined proximity of individuals to blast TBI (Fortier et al., 2014).

Classification of TBI

Classification of TBI severity was determined by the US Department of Defense and Department of Veterans Affairs screening definitions (Management of Concussion/mTBI Working Group, 2009). mTBI classification included a loss of consciousness (LOC) of 0 to 30minutes and/or an alteration of consciousness or mental state for a moment up-to 24hours post injury, and/or a presence of post-traumatic amnesia lasting less than one day. Moderate TBI was defined by a LOC for more than 30minutes and less than 24hours. Severe TBI was categorized as a LOC lasting more than 24hours.

Neurobehavioural Symptoms

The Neurobehavioral Symptom Inventory (NSI) (Cicerone and Kalmer, 1995) was administered to access current severity of postconcussive symptoms. This 22-item self-report questionnaire is validated to quantify the severity of commonly seen neurobehavioural symptoms and is comprised of three subscales that probe affective, somatic sensory and cognitive complaints (King et al., 2012). Affective symptoms comprise of fatigue, sleep, anxiety, depression and irritability. Somatic sensory symptoms include dizziness, balance, hearing, vision, changes in taste/smell, appetite and numbness. Cognitive symptoms comprise memory, decision making and slowed thinking. These three subscales have been shown to hold a high degree of internal consistency for affective (r = 0.91), somatic sensory (r = 0.88) and affective (r = 0.91) symptoms. The internal consistency of total NSI scores (r = 0.95) is excellent, and the NSI has also been shown to have good external validity relative to probable TBI (r = 0.41), PTSD (r = 0.67), depression (r = 0.64) and generalized anxiety disorder (r = 0.65).

Vestibular Disorder

The Vertigo Symptom Scale Long form (VSSL) is a 22-item self-report questionnaire that can be used to quantify vertigo severity and somatic anxiety symptoms. The VSSL has been shown to be a good pre. vs. post therapy measure with both subscale scores showing excellent test-retest reliability (a = >.90), excellent internal consistency (a = >0.8) and moderate to excellent construct validity (r = 0.45 to 0.97) (Yardley et al.,1992).

PTSD

PTSD symptoms were assessed using the PTSD Checklist for DSM-5 (PCL-5) (Weathers et al., 2013). This 20-item self-report questionnaire probes the 20 DSM-5 symptoms of PTSD and is used for monitoring symptom change, making a provisional diagnosis and as a screening tool. The PCL-5 has demonstrated good internal consistency (a = .96), and test-retest reliability (r =.84) in US military veterans (Bovin et al., 2016).

Depression and Anxiety

The Kessler Psychological Distress Scale (K10) was administered to determine symptoms of depression and anxiety (Kessler & Mroczek, 1992). This validated measure has been shown to be sensitive in detecting depression (a = 0.69), PTSD (a = 0.69) and panic disorder (a = 0.71) (Spies et al., 2009).

Daytime Sleepiness

The Epworth Sleepiness Scale (ESS) was utilized to measure the propensity for subjects to sleep during the daytime (Johns, 1991). This is a well validated measure with good internal consistency

(a = 0.73 and 0.86) (Kendzerska et al., 2014). This measure is able to distinguish control subjects from patients with sleep disorders (Johns, 1992), and is widely used in the field of sleep medicine.

Headaches

The Headache Impact Test (HIT-6) is a six-item questionnaire that rates the severity of pain and the impact of headaches on functional outcomes (Yang et al., 2011). HIT-6 has good internal consistency (a = 0.89), test retest reliability (a = 0.80), and high relative validity coefficients discriminating across diagnostic and headache severity groups (a = 0.82 and 1.00) (Kosinski et al.,2003).

Disability

The World Health Organisation Disability Assessment Schedule II short version (WHODAS 2.0) was used to determine levels of functional disability (Üstün, 2010). The WHODAS 2.0 is comprised of six subdomains, understanding and communicating, getting around, self-care, getting along with people, life activities and participation in society. This is a well validated measure shown to have good test re-test reliability and stable factor structure in TBI (Soberg et al., 2012) and non-TBI samples (Strauss et al., 2006). It has also been suggested by DSM-5 that the WHODAS 2.0 is a suitable tool for disability assessment in clinical settings (American Psychiatric Association, 2013).

Symptom Validity

To examine possible symptom exaggeration on self-report measures we employed the Memory Complaints Inventory (MCI) (Green, 2004). The MCI is a computerised inventory of memory problems that compares a person's subjective everyday memory problems objectively with those

from diagnostic comparison groups. The measure is a 58-item questionnaire that has been shown to have excellent reliability (a = 0.92) (Green, 2004).

Statistical Analysis

Summary statistics were calculated for the demographic, TBI and co-morbid characteristics of the sample. Participants with missing data were excluded from analysis (see Table 3.3). Chi-square analyses were then applied to compare the relative frequency of vestibular disturbance reported by participants with blunt, blast, or blunt+blast (i.e. both blunt and blast) who self-endorsed mTBI. For the purpose of the chi-square analysis, participants who reported dizziness symptoms more than 3 times per year in VSSL scores were classified as suffering from a vestibular disturbance (or dysfunction) while those who reported symptoms either never or only 1-3 times per year were classified as not suffering from a vestibular disturbance these group differences were later confirmed via independent sample *t*-tests. As vestibular function can deteriorate with age, I first utilized linear regression to determine if age was associated with vestibular disorder. Mediation analyses (Hayes, 2013) were then conducted on scores provided by those who endorsed mTBI to determine if the severity of their vestibular symptoms (as measured by the VSSL total score) independently contributed to the broad profile of postconcussive symptoms (as measured by the NSI), disability (WHO-DAS 2.0) and headaches (HIT-6) when depression, anxiety and PTSD were taken into account as mediators. The mediation analysis was also used to interrogate the relationship between vestibular symptoms and each of these mediators, and between these mediators and each of the outcome variables (NSI, HIT-6 and WHO-DAS 2.0). Finally, the analysis allowed me to assess the combined association (i.e. total effect) of the predictor and mediator variables on the outcome measures.

Post hoc exploratory analysis helped clarify the outcomes of the main NSI mediation analysis. A sensitivity analysis was conducted in which the mediation analysis was re-run on the adjusted NSI total score scores after the 3 items on the NSI that relate to imbalance/unsteadiness were removed. This was carried out to determine if the observed association partly reflected the fact that both questionnaires probe several common balance symptoms. To estimate the extent to which the observed relationship between VSSL and NSI scores reflect vertigo and balance factors as opposed to autonomic and anxiety-related factors, two other modified versions of the original NSI mediation analysis were run; the first replaced the VSSL total score with the VSSL vertigo-balance subdomain score while the second replaced the VSSL total score with the autonomic-anxiety subdomain score. Participants with missing data were excluded from analysis. All inferential analyses were computed using SPSS 24.

Results

Overview of Sample Characteristics

Please see Table 3.1 for the sample demographic and clinical characteristics, Table 3.2 for the lifetime history and prevalence of mTBI and Table 3.3 for the co-morbid neuropsychiatric symptoms. The mean age of the group was 46.6 years (standard deviation =9.3) which was mostly male and had been deployed to a war zone an average of 4 times. Seventy two percent of the sample reported a lifetime history of one or more mTBIs (M age = 24.4, SD = 10.52) of these 74% of injuries resulted in visiting an A&E department or acute military medical facility. 49% reported that they had periods in their lives where they had sustained repeated mTBIs. As shown in Table 3.3, the majority reported neuro-behavioural and neuro-psychiatric symptoms including vestibular impairment, headache, daytime sleepiness, PTSD, and depression/anxiety. The average WHODAS score was 20.49 (*SD* = 10.70), which is worse than approximately 90% of the general international

population (Andrews et al., 2009). Seventy-three participants (50%) indicated that they drank alcohol regularly, consuming a weekly average of 20.91 units (SD = 20.37) (alcohol units defined by the UK Department of Health). Most of the sample had never used recreational drugs (*n* = 118). Evidence of symptom exaggeration measured by the MCI was evident in 51% of the mTBI sample; (*n* = 110) participants with one or more mTBI completed the MCI, (*n* = 56) failed to meet our cut off score of <40%. The mean MCI score was 39.59 (*SD* = 19.82).

Table 3.1 Sample Demographic (*n* = 162).
Parenthesised values show standard deviation. *M* = mean.

	n		*n* or *M (SD)*
Males	151	Part-time student	2
Females	11	Unemployed	53
Relationship Status		Retired	32
Married	92	**Military Service Branch**	
Divorced	39	Royal Navy	23
Single	29	Army	123
Widowed	2	Royal Airforce	11
Vocational Status		Royal Marines	6
Full-time employment	55	**Armed Service History**	
Part-time employment	19	Mean length of Service (years)	12.8 (7.2)
Full-time student	1	Mean deployments to a war zone	3.7 (1.8)

Table 3.2 Lifetime History and Prevalence of mTBI (n=117)

	n		*n*
Lifetime history ≥1mTBI	117	Blunt & Blast	41
		Blast only	17
Hospitalised due to mTBI	82	Blunt only	59
mTBI with LOC	69	**Blast Proximity**	
		0-10 meters	38
Sustained >1 TBI	112	11-25 meters	15
Periods of repeated mTBI	57	26-100 meters	5
		Method of blunt injury	
History of moderate TBI	23	Road traffic	57
History of severe TBI	12	Sports-related	73
No TBI	10	Assault	54

Blast & Blunt mTBI

Sports related mTBI (62%) was the most common method of blunt injury although injuries sustained via road traffic accidents (49%) were also prevalent. The majority of the mTBI sample (81%) indicated that they had been exposed to blast during their military career. 50% sustained one or more blast mTBIs, and 53% of this sub-group reported 3 or more blast mTBIs. Of these blast mTBIs, 38 were sustained within a proximity of 0-10meters, 15 within 11-25 meters and 5 within 26-100 meters. 47% (n=8) of participants in the blast only category reported vestibular disturbance, 59% (n=35) reported vestibular disturbance in the blunt only category, and 83% (n=34) reported vestibular disturbance in the blunt and blast category. Chi-square analysis indicated a significant association between mechanism of injury and the presence of vestibular disturbance $\chi_2(2) = 9.70$, $p = .008$. Interpretation of the 2x2 contingency tables (using a bonferonni corrected alpha =0.017) indicated no significant difference between the observed frequencies of vestibular disturbance following blunt or blast ($\chi_2(1) = 1.46$, $p = .223$). However, the frequency of

vestibular disturbance was significantly greater for blunt+blast compared to blast ($\chi_2(1) = 9.19$, p =.006) and marginally greater for blunt+blast compared to blunt ($\chi_2(1) = 5.61$, p =.018). Group differences in VSSL scores between the presence or absence of vestibular disturbance were later confirmed via an independent sample *t*-test which indicated significantly $t(111) = -7.812$, p = <.001 higher mean VSSL scores in the presence group (M = 48.08, SD = 19.91) than absence group (M = 18.63, SD = 11.13).

Table 3.3 Frequency of Comorbid Symptoms in mTBI Sample

Comorbid Symptoms	*n*	%	missing cases
PCS (NSI)	89	77.4	2
Vestibular (VSSL)	78	69.0	4
PTSD (PCL-5)	100	88.5	4
Depression/anxiety (K10)	104	92.9	5
Daytime sleepiness (ESS)	59	52.7	5
Headaches (HIT-6)	79	70.5	5

Mediation analyses

Multiple linear regression was first conducted to identify which test variables were statistically associated with vestibular impairment and could therefore be included in the mediation analysis (see Tables 3.4.a/3.4.b/3.4.c). This showed significant associations ($p<0.01$) between vestibular disturbance and all variables (coefficient scores ranged from 0.5 to 0.8) except sleep. Age was also added to this regression but did not show a statistically significant association so was not carried forward. Mediation analysis were then conducted using Hayes (2013) PROCESS macro for SPSS, which bias-corrects the sample by bootstrapping a sample of 10,000 using 95% confidence

intervals. Coefficients were considered statistically significant at $p < .05$. Three mediation analysis were applied to determine if the severity of vestibular impairment, as defined by the VSSL, imposed a direct effect on neurobehavioural symptoms (NSI), headache (HIT6) and disability (WHODAS) independent of mediators PTSD (PCL-5), depression and anxiety (K10).

Table 3.4.A Correlation Matrix for Model 1 Multiple Linear Regression Analysis (Outcome Variable NSI) (*N*=113)

	NSI		VSSL		PCL-5		K10	
NSI			*r* = .69	*p* = <.001	*r* = .65	*p* = <.001	*r* = .66	*p* = <.001
VSSL	*r* = .69	*p* = <.001			*r* = .54	*p* = <.001	*r* = .44	*p* = <.001
PCL-5	*r* = .65	*p* = <.001	*r* = .54	*p* = <.001			*r* = .79	*p* = <.001
K10	*r* = .66	*p* = <.001	*r* = .44	*p* = <.001	*r* = .79	*p* = <.001		

Table 3.4.B Correlation Matrix for Model 1 Multiple Linear Regression Analysis (Outcome Variable HIT6) (*N*=112)

	HIT6		VSSL		PCL-5		K10	
HIT6			*r* = .51	*p* = <.001	*r* = .49	*p* = <.001	*r* = .54	*p* = <.001
VSSL	*r* = .51	*p* = <.001			*r* = .55	*p* = <.001	*r* = .45	*p* = <.001
PCL-5	*r* = .49	*p* = <.001	*r* = .55	*p* = <.001			*r* = .78	*p* = <.001
K10	*r* = .54	*p* = <.001	*r* = .45	*p* = <.001	*r* = .78	*p* = <.001		

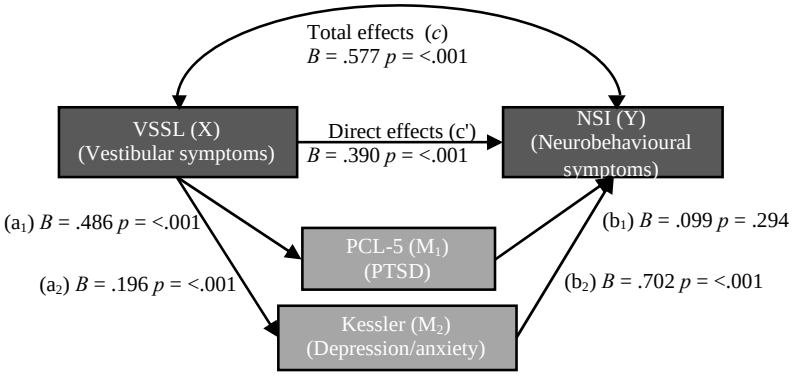
Table 3.4.C Correlation Matrix for Model 1 Multiple Linear Regression Analysis (Outcome Variable WHODAS) (*N*=111)

	WHODAS		VSSL		PCL-5		K10	
WHODAS			*r* = .60	*p* = <.001	*r* = .63	*p* = <.001	*r* = .68	*p* = <.001
VSSL	*r* = .60	*p* = <.001			*r* = .55	*p* = <.001	*r* = .45	*p* = <.001
PCL-5	*r* = .63	*p* = <.001	*r* = .55	*p* = <.001			*r* = .78	*p* = <.001
K10	*r* = .68	*p* = <.001	*r* = .45	*p* = <.001	*r* = .78	*p* = <.001		

As can be seen in Figures 3.1, 3.2 and 3.3, the VSSL scores exerted a direct effect on the NSI, HIT-6 and WHO-DAS 2.0 scores independently of the psychiatric mediators in all three

mediation models. There was also a significant association between VSSL score and the psychiatric mediators of depression, anxiety (K10) and PTSD (PCL-5) (see a_1 and a_2 pathways in figures 3.1, 3.2 and 3.3). As expected, depression and anxiety was strongly associated with outcome in all three mediation models (see b_2 in figures), although PTSD symptoms showed no significant influence (see b_1 in figures). While VSSL scores directly affect NSI scores, they showed no effect when combined with PTSD scores within the indirect pathway a_1*b_1. In contrast, when combined with PTSD scores within the indirect a_2*b_2 pathway, VSSL scores were significantly associated with NSI scores. Finally, there was a significant total effect across all three mediation analyses, indicating that vestibular symptoms are significantly associated with outcome both independently and in conjunction with the psychiatric mediators.

Figure 3.1 Mediation analysis NSI (n=113)



Indirect effects a_1*b_1 B = .048 BootULLCI = -.0369 BootULCI = .1335

Indirect effects a_2*b_2 B = .138 BootULLCI = .0549 BootULCI = .2569

Figure 3.2 Mediation analysis HIT 6 (*n* = 112)

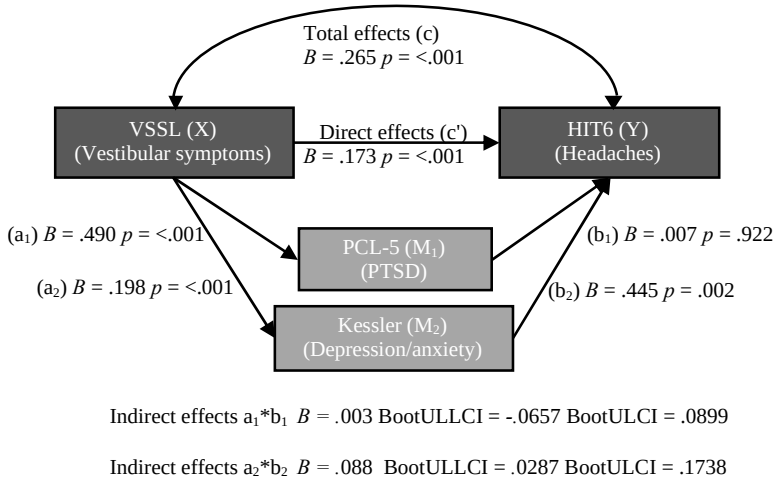
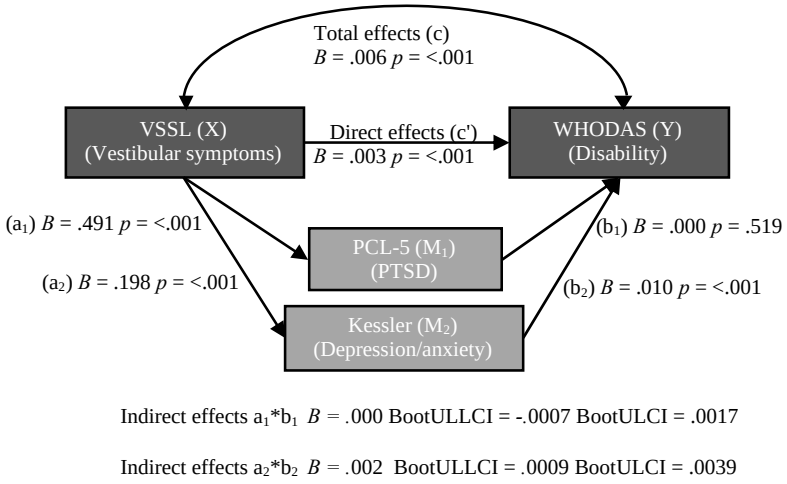


Figure 3.3 Mediation analysis WHODAS (*n* = 111)



Exploratory Analysis

Sensitivity analysis indicated that both the direct and indirect effects of VSSL scores on the NSI remained significant after the 3 dizziness-related items on the NSI were removed (see Table 3.5a.) Likewise, the pattern of statistical significance remained unchanged when the mediation

analysis was re-run after replacing the VSSL total scores with first the VSSL vertigo subdomain scores and then the VSSL anxiety-related scores (see Table 3.5b).

Table 3.5.A Exploratory mediation analysis (Outcome variable: NSI dizziness questions removed)

	Total Effects	Direct Effects	Mediator	Indirect Effects	LCI	UCI
VSSL	*B* = .50	*B* = .311	PCL-5	*B* = .055	-.016	.130
	P = < .001	*P* = < .001	Kessler	*B* = .134	.055	.245

Table 3.5.B Exploratory mediation analysis (Outcome variable: NSI)

	Total Effects	Direct Effects	Mediator	Indirect Effects	LCI	UCI
VSSL*(vestibular)*	*B* = .773	*B* = .540	PCL-5	*B* = .092	.017	.222
	P = < .001	*P* = < .001	Kessler	*B* = .139	.015	.343
VSSL *(anxiety)*	*B* = 1.129	*B* = .767	PCL-5	*B* = .100	-.109	.287
	P = < .001	*P* = < .001	Kessler	*B* = .268	.038	.496

Discussion

This study provided a systematic evaluation of how vestibular disturbance can both directly and in conjunction with co-occurring psychiatric symptoms, influence neurobehavioural symptoms and general disability. It is the first study of its kind to retrospectively assess the lifetime history of mTBI in help seeking UK military veterans and to evaluate their current comorbid symptoms and levels of disability. The findings revealed that more than two thirds of the sample 72% had sustained one or more mTBIs in their lifetime which is a much higher than previous estimates of mTBI in UK soldiers on deployment or studies that used less detailed lifetime assessments. This estimate is, however, in line with that of US military veterans, where 71.7% of (n =274) had a lifetime history of mTBI (McGlinchey et al., 2016). 58% of mTBIs in this sample involved a LOC and 49% reported periods in their life where they had sustained repeated mTBIs. Many veterans 70% reported that their head injuries resulted in visits to A&E departments or military medical facilities. Most commonly blunt injuries were due to sports and road traffic accidents. Both of

these mechanisms were reported by over half of the mTBI sample, with individuals reporting they sustained one or both of these types of injury.

Much like veterans in the US, exposure to blast constituted significant health problems for UK military veterans; 81% of the current study sample reported exposure to blast, 50% of who reported concussion and 53% of this subgroup reported blast mTBI on three or more occasions. The repeated nature of blast mTBI seen here could pose a substantial potential risk factor for neurodegenerative disease and chronic traumatic encephalopathy (Khachaturian et al., 2014; Goldstein et al., 2012; Omalu et al., 2011). The majority of blast injuries 80% were within the proximity of 10 meters, which has been associated with decreased connectivity of the bilateral primary somatosensory and motor cortices (Robinson et al., 2015). Both of these brain regions receive vestibular input and play a role in differentiating self from object motion (Hitier et al., 2014). Improper functioning across any of these systems can lead to a loss of balance and/or postural instabilities, gait abnormalities, vertigo and dizziness (Basford et al., 2003; Brandt et al., 2014; Hillier et al., 1997). Cerebellar diffusion-tensor imaging abnormalities have also been observed in individuals who present with vestibular symptoms following mTBI, which is indicative of injury to the central vestibular system (Alhilali et al., 2014). Research into blast trauma is complicated by other coexisting conditions. Blasts not only increase the risk of secondary blunt head injuries but can also incur psychological consequences such as PTSD; which can also independently affect brain structure and function (DePalma et al., 2005).

Consistent with the high prevalence reported in other military samples, 69% reported symptoms consistent with a chronic vestibular disturbance. A presence of vestibular disturbance was highly prevalent across the all categories of blunt 59%, blast 47% or blunt+blast 83% mTBI. Chi-square analysis confirmed that vestibular impairment was more frequently seen in the blunt+blast mTBI

category. Recently, research from Walker et al., (2018) has revealed that repetitive mTBI is more strongly associated with balance disturbances. Notably, these US veterans who had combat exposure showed no significant difference in imbalance between blast versus non-blast comparisons. This coupled with our own findings may indicate that it is repeated nature of mTBI rather than blast mTBI alone, that is most harmful in terms of vestibular impairment.

Over the longer-term, more than three quarters of those who sustained mTBI 77% reported persistent post-concussive neurobehavioural symptoms, headaches affected 70% and daytime sleepiness 52% of the sample. Depression and anxiety symptoms were severe effecting 93% of veterans and respectively PTSD 88%. Alcohol consumption exceeded current UK government guidelines of 14 units per week (Department of Health, 2016), and WHODAS scores indicated that general disability fell within the bottom 10% of the general international population (Andrews et al., 2009). Together these data highlight significant, long-term care needs in help-seeking UK military veterans with a self-reported history of mTBI.

Comorbid psychiatric symptoms of depression, anxiety and PTSD cannot only exacerbate the symptoms of mTBI (Lippa et al., 2015; Porter, Stien & Martis, 2018), but particularly in the case of PTSD make diagnosis difficult. Partly this is due to the symptoms of mTBI often not being specifically related to neurological insult but psychiatric disturbance (Fear et al., 2014; Green et al., 2001). This is the first study to endorse these detrimental effects in a UK military sample and demonstrate via mediation analysis that the symptoms of dizziness independently contributed to disability and neurobehavioral status. Mediation analysis also showed indirect influences of depression and anxiety symptoms on those of mTBI but failed to do so for PTSD. This is perhaps surprising as most participants reported severe PTSD symptoms and therefore produced too little

variability for the correlation to reach statistical significance. Given the overlap between PTSD and vestibular symptoms, correlations between these two factors were unsurprisingly strong. However, it would be unwise to postulate that the vestibular system provides causality for mTBI symptoms partly because the relationship between psychiatric and vestibular disturbance is reciprocal. Nonetheless, exploratory analysis revealed the direct effects of vestibular disturbance in mTBI symptoms held when mediation analysis included only the vertigo subdomain scores from the VSSL and not the anxiety-related symptoms. This provides support for symptoms of an underlying vestibular deficit influencing mTBI, rather than vestibular induced psychiatric deficits, which are difficult to differentiate from primary psychiatric deficits. That said, the predictive strength of balance dysfunction in mTBI seen here could comprise a particularly harmful combination along with PTSD, depression and anxiety when considering the significant total effects of mediation analysis and it would be reasonable to assume that vestibular dysfunction play's a key role in influencing the neurobehavioural symptoms of mTBI.

The clinical presentation of the current sample reflects a striking comparison to civilians diagnosed with vestibular impairment who present with similar cognitive and affective symptoms (Smith et al., 2018). This study demonstrates the pervasive influence of the vestibular system on cognition and affect rather than only influencing low level autonomic motor control as was traditionally thought. The findings from this study highlight a need to more closely examine vestibular disorder and provide appropriate treatment interventions.

There are a number of methodical considerations that limit the current study conclusions. As mTBI and vestibular disorder are not routinely screened for in the UK military, our data needed to be collected via self-report measures rather than clinical examination. All veterans were help seeking

and receiving psychiatric support so whilst high in clinical need they may not be representative of the broader veteran community. The psychiatric profile of these veterans may go some way to explaining the high number of MCI failures. In particular, depressed mood has been shown to significantly effect decreased performance on measures of memory (Gervais et al., 2008). It is plausible to assume that psychiatric symptoms distorted perception of actual memory impairment. There is also a growing body of research that demonstrates within the confines of neurological testing, that effort accounts for more variance in memory test scores, than neurological insult (Green et al., 2001; Armistead- Jehle et al., 2012). Furthermore, symptom exaggeration in one modality can infer exaggeration in other modalities such as cognition and balance (Armistead-Jehle et al., 2017). This sample was representative of veterans receiving help for combat related psychiatric complaints. This therapeutic process causes veterans to revisit painful memories which can cause significant distress and exacerbate symptomology, this could be a potential cause of symptom exaggeration. The MCI results from this study however, should be considered cautiously, as the study design does not allow the underlying motivations for malingering and psychological dissociation to be separated. Moreover, the statistical outcomes from mediations analysis were consistently significant even when separate analysis was run between pass and fail MCI groups.

In conclusion, the long-term mental health of UK military veterans with a history of mTBI has been shown to be directly influenced by vestibular disturbance. Although the symptoms of dizziness are common in this population, vestibular function is not routinely assessed so veterans are often not referred to a neuro-otologist. Future research should aim to investigate the benefits of mandatory vestibular screening. Secondly, given the pervasive influence of the vestibular system, efforts should be directed into testing if the vestibular system can be harnessed for therapeutic effect. In the next Chapter I will evaluate the potential contribution of GVS as a

treatment modality and will later assess the potential benefits of GVS as a treatment for veterans with mTBI in Chapter 5.

Chapter 4

The Effects of Galvanic Vestibular Stimulation on Cortical Excitability

Introduction

Artificial stimulation of the vestibular system has been shown to ameliorate a number of neurological conditions such as Parkinsonism (Wilkinson et al., 2016; Yamamoto et al., 2005), prosopagnosia (Wilkinson, Kilduff, McGlinchey & Milberg, 2005), episodic migraine (Wilkinson et al., 2017) and hemi-spatial neglect (Wilkinson et al., 2014). A randomised control trial (RCT) by Wilkinson et al (2014) applied galvanic vestibular stimulation (GVS) to 52 patients with hemi-spatial neglect which resulted in the lasting amelioration of symptoms at four weeks post stimulation. A 28% mean improvement in the behavioural inattention test (BIT) and an increase of 20% in in median Bartel Index scores (functional capacity) were observed. These clinically relevant improvements were evident regardless of whether participants received one, five or ten sessions of GVS and contrast to results of other neuromodulation techniques such as transcranial magnetic stimulation (TMS) for which even repeated sessions of stimulation do not seem to induce lasting therapeutic effects from neglect (Brighina et al., 2003; Fregni et al., 2006). Interestingly, a follow-up study of the Wilkinson et al., (2014) trial showed that remediation of neglect symptoms was still evident up to three-years post-stimulation in the 28 participants that I was able to re-assess (Denby & Wilkinson, 2014[unpublished]). Only 12 out 28 participants still had evidence of residual neglect, but their improvements in neglect symptoms post GVS were still evident after three-years, demonstrating long-term therapeutic gain.

Currently, the underlying therapeutic mechanism of effect for GVS is unknown. However, one possible hypothesis, derived from the lasting effects described above is the induction of long-term

neuroplastic change. Further evidence of the effects of GVS can be found in neuroimaging literature. Haemodynamic evidence from functional magnetic resonance imaging (fMRI) research has shown perfuse cortical and subcortical activations as a result of GVS. Activation changes in blood oxygenation level-dependent (BOLD) responses have been observed in the posterior insula and retroinsular regions, anterior insula and inferior/middle frontal gyrus, superior temporal gyrus, tempro-parietal cortex, precentral gyrus (frontal eye field), basil ganglia, thalamus, anterior cingulate gyrus, parahippocampal gyrus and hippocampus, the supplementary motor area and cerebellar crus I (superior semilunar lobe), and vermal lobule VII (folium and tuber of vermis) (Bense et al., 2001;Bucheret al., 1998; Deutschlander et al., 2002; Dieterich et al., 2003; de Waele et al., 2001; Fasold et al., 2002; Lobel et al1998; Stephan et al., 2005; Suzuki et al., 2001). Deactivations during vestibular stimulation have been seen in the central sulcus and postcentral gyrus, the occipital and fusiform gyri and the praecuneus (Besnse 2001; Stephan et al., 2005). Evidence from these studies is reliant on BOLD signal changes in blood flow, which is limiting as it is still unclear how these hemodynamic changes relate to the functional role of activations (Crosson et al., 2010). Nonetheless, the aforementioned data do suggest that GVS is causing widespread activations which as mentioned is a pre-marker of synaptic plasticity in human brain in vivo (Badawy, Loetscher, Macdonell & Brodtmann, 2012).

One simple way to indirectly probe for neuroplastic change is to measure motor cortex excitability which has been identified as a necessary pre-requisite for neuroplacticity. Neuroplastic change is prompted by long term potentiation (LTP) or long-term depression (LTD). Both processes cause an enduring change in the quality and quantity of synaptic connections, and are candidate mechanisms that occur during Hebbian learning (Hebb, 1961; Bliss & Cooke, 2011). LTP is a form of activity-dependent plasticity defined as an enduring enhancement of synaptic transmission

that outlasts a stimulation period (Bear, 1995). Conversely, LTD demonstrates a reduction in synaptic efficiency that continues post stimulation. High-frequency stimulation protocols have been used to induce LTP in vivo whereas, low frequency trains of electrical stimulation (1Hz) have been shown to induce LTD (Kemp & Manahan-Vaughn, 2004; Heynen, Bear and Abraham, 1995), with effects shown to last for a year in rats (Bliss & Gardner-Medwin, 1973). A number of molecular mechanisms that occur at the synapse underlie LTP and LTD. LTP and LTD are most often induced in Glutamatergnic synapses on the postsynaptic neuron. Hippocampal LTP and LTD both involve *N*-methyl-D-aspartate (NMDA) receptors (Nowak et al., 1984). However, LTD in the cerebellar cortex may be induced by activation of gamma-aminobutyric acid (GABA) receptors at Purkinje cell synapses (Ito & Kano, 1982).

Indirect evidence of changes in cortical excitability in humans that reflect LTP-and LTD-like plasticity have also been observed as a result of non-invasive brain stimulation. Both transcranial direct stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have been shown to change cortical excitability beyond the period of stimulation protocols (Berardelli et al., 1998; Fritsch et al., 2010). Low frequency (<1 Hz) rTMS can reduce cortical excitability in a manner suggestive of LTD (Chen et al., 1997; Ziemman, 2004) whereas, high frequency rTMS (>5Hz) can increase cortical excitability (Di Lazzaro et al., 2012; Ridding & Rothwell, 2007). Likewise, 1mA of continuous tDCS for 13minutes has been shown to induce LTP for up to 24hours post stimulation (Monte-Silva et al, 2013).

LTP and LTD have a potentially important role in clinical neuroscience because a variety of neurological conditions arise from reduced or excessive synaptic drive. In the present context, it is possible that GVS might induce LTP which may affect negative symptoms, or instead induce LTD,

in which positive symptoms might be affected. Evidence of excessive synaptic drive can be seen in individuals with PTSD and anxiety disorders who have been shown to exhibit cortical hyperexcitability (Centonze et al., 2005; Machado et al., 2011). Other neuromodulation techniques such as slow wave rTMS have been shown to influence excessive synaptic drive in a manner suggestive of LTD (Chen et al., 1997; Ziemman, 2004). In patients with PTSD rTMS has reduced right-side cerebral metabolism up to one-month post post-stimulation (McCann et al., 1998), reduce activity in the hypothalamic pituitary-adrenocortical system (Post & Keck 2001) and remediate PTSD and anxiety symptoms (Hoffman & Cavus, 2002; McCann et al., 1998). It is difficult to determine if GVS has induced either LTP or LTD type effects in the neglect patients from the Wilkinson (2014) RCT as these patients demonstrated improvements in both positive and negative symptomology. However, by understanding more about either forms of induction in GVS it might be possible to target specific neurological symptoms in mTBI.

The Current Investigation of the effects of GVS on LTP/LTD induction

I used two different methods to determine if GVS can be associated with LTP or LTD. The first method examined involuntary finger movements via measurement of motor evoked potentials (MEP) which are induced via single pulse transcranial magnetic stimulation (TMS) to the motor cortex. In contrast, the second method I utilised examined the effects of GVS on motor related cortical potentials (MRCP) as measured by the Bereitschaftspotential (BP). These measurements of motor cortex excitability are based on voluntary finger movements (Shibasaki & Hallet, 2006). Both the MRCP and MEP experiments employed an experimental paradigm that probed motor cortex excitability at five time points up to one-hour post-stimulation and at 24hours post stimulation to detect enduring change.

Unfortunately, and despite considerable effort to learning new technical skills in EEG, in Experiment 3 I found no effects of GVS on the BP at any time point up to 24hours post GVS in 40 neurologically health participants. As a result, I was not able to utilise the BP as a marker of neuroplastic change. For brevity, the results from this experiment have therefore not been included in this thesis. Instead, I only report the effects of GVS on TMS induced MEPs which did provide useful insight. A brief summary of Experiment 3 is provided later in this Chapter to outline the technical issues that I experienced.

Experiment 1: The Effects of Subsensory GVS on Motor Evoked Potentials

The measurement of cortical plasticity via MEPs provides a novel opportunity to identify a potential mechanism of effect in GVS. Previous research has demonstrated that 10mins of low amplitude ~ .35mA subsensory alternating current (AC) GVS is well tolerated and can influence cognitive processes involved in audio-motor synchronisation and beat perception (Scmidt-Kassow, Wilkinson, Denby & Ferguson, 2016). I therefore chose to use this amplitude in Experiment 1. If effective this may lend itself to a low power portable GVS device that individuals could use at home. As is convention I employed the use of TMS to induce an MEP. MEPs arise as a result of single pulse TMS activating motor cortical output cells and evoking a descending volley in the cortical spinal tract (Vallence & Ridding, 2013). Changes in MEP amplitudes can be compared pre and post GVS between both active and sham stimulation groups to determine if an excitability change has occurred and the conditions for LTP/LTD induction have been established.

Methods

Participants

Seventy participants were recruited via the University of Kent research participation scheme in exchange for course credits. Prior to participation each participant completed the TMS screening process for eligibility. Participants could only receive TMS if they were not under the effects of any acute or chronic and potentially interfering pharmacological treatments (i.e. antianxiety medication), alcohol or substance use. All individuals were free of any self-reported neurological or psychiatric conditions, metal plates or surgical clips in the skull and had no skin abrasions behind the ears. Participants provided informed consent and were fully debriefed at the end of the study. Full ethical approval was obtained from the University of Kent school of Psychology research ethics committee.

Design

The experiment employed a within-subjects design with pre-post measures repeated over time. The dependent variable (DV) was MEP amplitude and the independent variable (IV) of Time comprised six levels, which measured 25MEPs at baseline and 0, 5, 10, 15 and 30 minutes post-stimulation. The between-subjects factor IV Stimulation comprised Active or Sham GVS.

Galvanic Vestibular Stimulation

A Neuroconn DC stimulator was used to deliver 0.35mA of subsensory alternating current (AC) at a frequency of 1000Hz for 10minutes to the mastoid processes via 5.1cm x 10.2cm rubber self-adhesive electrodes with the anode left and cathode over the right mastoid. The skin was prepared prior electrode placement using surgical wipes and Nuprep gel to ensure low impedance. Sham

stimulation involved the same preparation however, the stimulation device remained out of sight and turned off. Participants were informed that they might receive either active or sham stimulation and asked at the end of the experiment if they noticed and sensations from the stimulation or side effects such as, induced yaw, pitch or roll.

Monitoring of Motor-Cortical Excitability

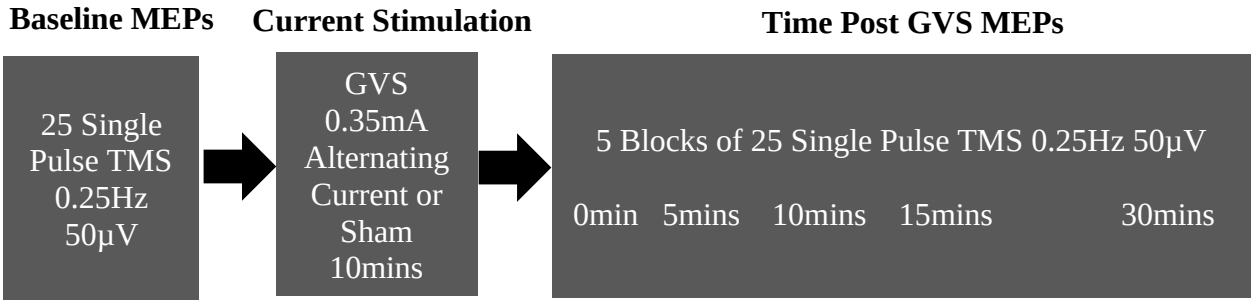
TMS-elicited MEPs were recorded to measure excitability changes of the representational area of the left abductor digiti minimi (ADM). I employed a Brain Products Power MAG Stimulator with a (diameter of one winding = 90mm, peak magnetic field = 2T) figure of eight coil to deliver single pulse stimulation. The coil was placed at a 45° angle from the skull midline with the handle pointing backwards. Surface EMG from the left ADM was recorded with (28mm x 20mm) self-adhesive Ag/AgCl duck foot electrodes (Ambu® Neuroline 710), placed in a belly-tendon montage. Participants were asked to rest their left arm on an arm rest and to allow their hand to be flaccid in a resting state. I employed a BrainAmp EMG amplifier (Brain Products, GmbH, Gilching, Germany) for the EMG recordings. To determine the representational hot spot for the ADM on the scalp, I utilised a segmentation window on Brain Vision recording software. This allowed us to observe the largest MEP measurement of the ADM when a TMS pulse was fired. When the hot spot had been located, I marked the cap worn by participants with a sticker to allow some precision when locating the ADM throughout each of the experimental blocks.

Two Psychopy version 2 (Peirce, 2007) scripts were developed for baseline and post GVS. The scripts sent binary code triggers to control the firing of TMS pulses at 0.25 Hz on 25 separate occasions in each experimental block. The binary code triggers were also used to time lock MEPs in EMG recordings to later facilitate accurate analysis.

Procedure

Participants were first administered the TMS screening protocol and informed written consent. Following this, the representational area of the ADM was located and individual motor thresholds were attained to establish the necessary TMS intensity that would elicit and average peak-to-peak amplitude of 1mV in 10 trial pulses over four test blocks. Baseline EMG recordings of 25 single pulse MEPs were then attained followed by 10minutes of ~ .35mA AC GVS at a frequency of 1000Hz or 10minutes of sham GVS. Immediately after this, post stimulation MEP recordings proceeded and were repeated at 5, 10, 15 and 30 minutes post stimulation (*see Figure 4.1*). Participants in both the active and sham stimulation conditions were asked if they noticed any sensations from GVS at the end of the session. If a participant did notice any sensations from stimulation, they were asked if they experienced any symptoms of dizziness. If they answered yes then I would then administer a standardised questionnaire to determine if they experienced rotational effects of role, pitch or yaw. If participants endorsed these effects their data were removed from analysis.

Figure 4.1. Experimental Protocol



Data Analysis and Statistics

Thirty-two participants were excluded from the data analysis; seven participants failed to meet the TMS screening criteria, a further 25 participants were not included in the main experiment due to failure in reliably eliciting MEPs with an average amplitude of 1mA during threshold testing. This resulted in a final sample size of 38 participants, which consisted of 30 females and 8 males (*M* age = 20.42, *SD* = 3.56) comprising 19 in the Active condition and 19 Sham.

Analysis of EMG data included the application of a 50Hz notch filter. Data was then segmented, baseline corrected, peak-to-peak minimum/maximum waveform values obtained and MEP means then calculated using Brain Vision Analyser software (Brain Products, GmbH, Gilching, Germany). Standardised post-stimulation MEPs were computed by normalising MEP amplitudes to baseline intra-individually to measure change from baseline. This process was applied to raw EMG recordings over all time epochs.

All statistical analysis was performed on SPSS version 24. Statistical analysis included a 2x6 repeated measures analysis of variance (ANOVA) 2 (Stimulation: Active vs. Sham) x 6 (Time: Baseline, 0minutes, 5minutes, 10minutes, 15minutes, 30minutes) conducted on mean MEP amplitudes. Subsequent exploratory analysis was also conducted to determine if TMS intensities effected MEP amplitudes, as previous research has shown slow wave rTMS to induce LTD type effects (Chen et al., 1997; Ziemman, 2004), if this took place in the current study it would confound the results. This analysis involved a median split between High and Low TMS intensity in both the Active and Sham groups. The cut offs for this in the Active condition with Low TMS intensity was < 61% and High TMS intensity was > 63%. In the Sham condition a Low TMS intensity was < 67% and High TMS intensity was > 68%. After this median split of High vs. Low TMS intensity

a repeated measures 2x2x6 ANOVA 2 (TMS Intensity: High vs. Low) x 2(Stimulation: Active vs. Sham) x 6 (Time: Baseline, 0minutes, 5minutes, 10minutes, 15minutes, 30minutes). Post hoc comparisons were also examined, all t-tests were Bonferroni corrected ($\alpha = .01$).

Results

None of the participants reported noticing the effects of 'subsensory' GVS. The mean intensity of TMS stimulation used in both active and sham conditions was 62.5% (see Table 4.1 for breakdown of mean TMS intensity across groups). The 2x6 repeated measures analysis of variance (ANOVA) 2 (Stimulation: Active vs. Sham) x 6 (Time: Baseline, 0minutes, 5minutes, 10minutes, 15minutes, 30minutes) showed a significant main effect of Time $F(5,3.54) = 7.06$, $p < .001$, $n_2 = .164$. Post hoc pairwise *t*-tests revealed a significant difference between baseline and 0minutes ($p < .01$); baseline and 5minutes ($p < .01$); baseline and 10minutes ($p < .001$); and baseline and 30minutes ($p < .001$). There were no significant differences between baseline and 15minutes ($p = .035$). The mean MEP values and standard error from pairwise post hoc evaluations over Time can be seen in Table 4.2 which show a trend of increased MEP amplitude from baseline. There was no significant main effect of Stimulation on MEPs $F(1,36) = 1.531$, $p = .224$, $n_2 = .041$ and no significant interactions between Stimulation and Time $F(5,3.538) = .444$, $p = .729$, $n_2 = .012$.

Table 4.1 Mean TMS Intensity for Stimulation

Stimulation conditions	Mean TMS intensity %
Active	61.8
Sham	63.9

Exploratory Analysis

To examine if GVS had a different effect in participants with high versus low TMS intensities a median split was implemented. However, the 2x2x6 repeated measures ANOVA 2 (TMS Intensity: High vs. Low) x 2(Stimulation: Active vs. Sham) x 6 (Time: Baseline, 0minutes, 5minutes, 10minutes, 15minutes, 30minutes) failed to reach significance $F(3.41,518140.89) = 2.18$, $p = .087$, $n_2 = .060$.

Table 4.2. Mean MEP and Standard Error (N =38) over Time

Time	Mean MEPs	Standard Error
Baseline	936.19	77.39
0Minutes	1139.58	89.35
5Minutes	1231.37	125.01
10Minutes	1401.56	150.34
15Minutes	1160.83	131.91
30Minutes	1420.8	157.66

Discussion

My prediction that 10minutes of subsensory GVS would induce change in levels of cortical excitability post stimulation, was not supported. A general trend for increased MEP amplitude from baseline was however evident in both the active and sham stimulation groups. This may be explained by the fact that the mean intensity of TMS in both active 62% and sham groups 64% was high which on the basis of previous rTMS research may reflect increased corticospinal

excitability (Pellicciari, Miniussi, Ferrari, Koch & Bortoletto, 2016; Julkunen, Säisänen, Hukkanen, Danner & Könönen, 2012; Vaseghi et al., 2015). Most importantly, the standard error rates were extremely high, indicating a large variation in MEP amplitudes both within and between participants. In moving forward to Experiment 2 the noise in this data coupled with other methodological issues needed to be assessed before a null hypothesis could be performed.

A key methodological problem in Experiment 1 was that the MEP threshold of 1mA in the ADM was difficult to elicit in a number of participants, which resulted frequently in the need to use high intensities of TMS. For many participants it was not possible to achieve a MEP of 1mA during threshold testing which led to 25 participants being excluded from the main experiment. One of the reasons it was difficult to elicit a response in the ADM was due to it being the smallest muscle in the hand to locate. This made it difficult to accurately ascertain the exact representational hotspot on the cortex with low intensities of TMS. A further difficulty that arose was the large variability in MEP amplitude between single pulse trials, and time blocks. Evidence of this problem can be seen in the high standard error rates, and this may be partially attributed to the high TMS intensities. Another factor responsible for the large variances in MEPs may be due to movement from the participants. This can affect TMS coil positioning which is known to cause large variances in MEP amplitudes (Thickbroom, Byrnes & Mastaglia, 1999; Amassian, Cracco & Maccabee, 1989). As a result of these limitations, the methodological protocol for Experiment 2 needed to be changed. Firstly, to facilitate a reduction in the large variances seen in MEP amplitudes in Experiment 1. Additionally, to increase the period of time that MEP amplitudes were measured so that potential LTP or LTD type effects could be better more accurately evaluated.

Experiment 2: The Effects of 1mA Direct Current GVS on Motor Evoked Potentials

As a result of the methodological issues in Experiment 1, I implemented a number of changes to the methodology of Experiment 2. Rather than stimulating the ADM, I instead targeted the abductor polics brevis (APB) which is the largest muscle in the hand and therefore should be easier to locate in threshold testing. I also utilised a large reclining chair, to allow participants to rest their head and keep their feet raised. This along with the use of a vacuum cushion which was placed around the back of participants necks enabled me to keep them completely still.

The threshold amplitude for MEP was also lowered to 50μV to facilitate use of lower TMS intensities (Yahagi et al., 2003). Additionally, I increased the time line of post GVS MEP measurements to 60minutes post stimulation on day one of testing and included a 24hour post GVS flow-up session. Experiment 1 only probed the first 30minutes of cortical activity post GVS which may have concealed effect; previous studies of animal slice preparations distinguish between early and late phase LTP and LTD with late phase changes appearing only after four hours post-stimulation, and subsequently lasting for days/weeks (Abraham, 2003; Linden, 1998).

Lastly, I increased the amplitude of GVS to ~1mA and utilised direct current (DC). This amplitude and waveform has been shown to have lasting clinical effect (Wilkinson et al., 2014) so hopefully increase the likelihood of inducing and excitability change.

Methods

Participants

Fifty-eight neurologically healthy participants 41 females, 17 males aged 18-52 (*M*= 21.69, *SD* = 5.62) were recruited via the University of Kent research participation scheme in exchange for course credits or via Jobshop where they received a cash payment for participation. Participants were again screened prior to receiving TMS as in Experiment 1. Full ethical approval was obtained from the University of Kent School of Psychology research ethics committee. All participants provided informed consent and were fully debriefed at the end of the study.

Design

As in Experiment 1 a within-subjects pre-post stimulation design was utilised to measure changes in the DV of MEP amplitudes over Time. However, the IV of Time was changed for the current study so that it comprised six levels, that measured 25MEPs at baseline and five subsequent blocks up to 24hours post-stimulation (*see Figure* 4.4). Again, the between subjects IV of Stimulation, was utilized to compare between Active or Sham GVS conditions.

Galvanic Vestibular Stimulation

We utilised a Neuroconn DC stimulator to deliver 25minutes of Gaussian noise bipolar current. Stimulus intensity varied randomly from ~ 0.5-1.5mA with a mean intensity of ~1mA at a frequency of 1000Hz and was delivered to the mastoid processes via 5.1cm x 10.2cm rubber self-adhesive electrodes. As before this bipolar current was delivered with the anode placed on the left mastoid and the cathode on the right. The reduction of GVS electrode impedance levels and protocol for Sham stimulation were carried out as in Experiment 1.

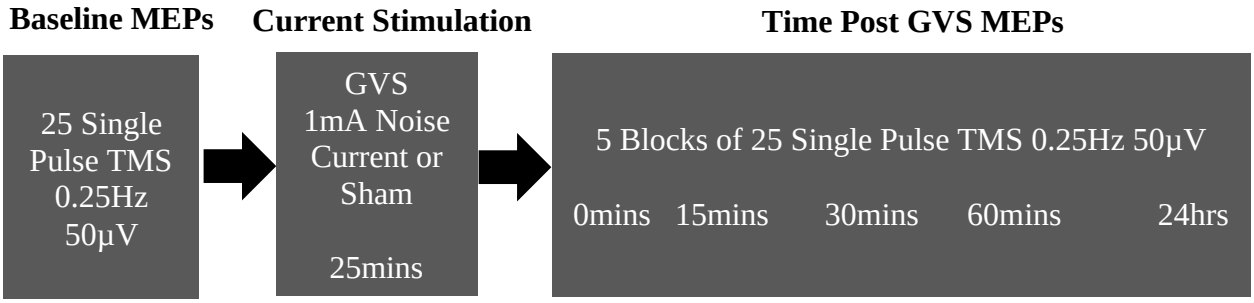
Monitoring of motor-cortical excitability

TMS elicited MEPs were recorded to attain excitability changes of the representational area of the left APB. We employed a Brain Products Power MAG Stimulator with a (diameter of one winding = 90mm, peak magnetic field = 2T) figure of eight coil, to deliver single pulse stimulation. The coil was placed at a 45° angle from the skull midline with the handle pointing backwards. Surface EMG from the left APB was recorded with (28mm x 20mm) self-adhesive Ag/AgCl duck foot electrodes (Ambu® Neuroline 710), placed in a belly-tendon montage. Participants were asked to rest their left arm on an arm rest and allow their hand to be flaccid in a resting state. I utilised a BrainAmp EMG amplifier (Brain Products, GmbH, Gilching, Germany) for the EMG recordings. To determine the representational hot spot for the APB on the scalp, we utilised a segmentation window on Brain Vision recording software. This allowed us to observe the largest MEP measurement of the APB when a TMS pulse was fired. When the hot spot had been located, we marked the cap worn by participants with a sticker to allow us some precision when locating the APB throughout each of the experimental session. Two Psychopy version 2 (Peirce, 2007) scripts were developed for main experiment and follow up session. The scripts sent binary code triggers to control the firing of TMS pulses at 0.25 Hz 25 times in each experimental block. The binary code triggers were also used to time lock MEPs in EMG recordings to later facilitate accurate analysis. All participants were seated in a standard fowlers position slightly tilted back by 45° with their legs supported in a horizontal position by the chair. This was done to help limit movement from participants whilst using TMS so that we could reduce the variability of MEP amplitude between trials. A *MAG&More* vacuum cushion was also used to limit movement of the head during TMS.

Procedure

Participants were first administered the TMS screening protocol and informed written consent. After locating the representational area of the APB, individual motor thresholds were determined by identifying the lowest TMS intensity needed to elicit MEPs with a peak-to-peak amplitude >50μV in three out of five trials. A baseline recording of 25 single pulse MEP was then obtained followed by 25 minutes of 1mA Noise GVS or Sham stimulation. Immediately after GVS, a post-stimulation MEP recording was obtained proceeded by repeated recordings at 15, 30 and 60 minutes post stimulation (*see Figure 4.2*). A follow-up MEP recording was also conducted at 24hours post Active or Sham GVS. Participants in both stimulation conditions were asked if they noticed any sensations from GVS at the end of the session.

Figure 4.2. Experimental Protocol



Data Analysis and Statistics

Eighteen participants were excluded from the data analysis. Four participants failed to pass the TMS safety screening process because they either suffered from episodic migraine or had consumed prescribed neuroactive medication. The subsequent 14 participants were excluded due to insufficient MEP amplitudes during motor threshold testing. Analysis was conducted on the 40 remaining participants 29 females, 11 males aged 18-52 (M= 21.55, SD = 5.93). The sample

comprised 20 participants in both the Active and Sham conditions. Analysis of EMG data comprised the same protocol and equipment as in Experiment 1.

As before statistical analysis included a 2x5 repeated measure ANOVA 2 (Stimulation: Active vs. Sham) x 5 (Time: 0 minutes, 15 minutes, 30 minutes, 60 minutes, 24 hours) with the dependent variable MEP amplitude to investigate changes in cortical excitability post-stimulation. Subsequent exploratory analysis comprised subdividing the sample to High and Low MEPs at baseline groups via a median split to examine differences between participants with prior cortical hyperexcitability and hypoexcitability. This resulted in four groups of 10 participants Active High with a mean baseline MEP amplitude of > 144.200 μV; Active Low with a mean MEP amplitude of < 140.56 μV; Sham High mean MEP amplitude of > 152.78 μV and Sham Low with a mean MEP amplitude of < 138.14 μV. These four factors were then subjected to further analysis which utilised a 2x2x6 repeated measures ANOVA 2 (Stimulation: Active vs. Sham) x 2 (Baseline: High vs Low MEP) x 6 (Time: baseline, 0 minutes, 15 minutes, 30 minutes, 60 minutes, 24 hours). Interaction effects were explored using a two and then one-way ANOVAs with Bonferroni corrected pairwise comparisons applied. Omnibus analysis was considered statistically significant with a *p* value of <.05. If Mauchly's test of sphericity was significant then Huynh-Feldt figures were utilised. All statistical analysis was performed on SPSS version 24.

Results

The mean stimulation intensity for TMS across both Active and Sham Stimulation groups was 54.4% (see Table 4.3). Change from baseline mean MEP amplitudes can be seen in *Figure* 4.5 for both Active and Sham conditions. The repeated measures 2x5 ANOVA examined changes in MEP

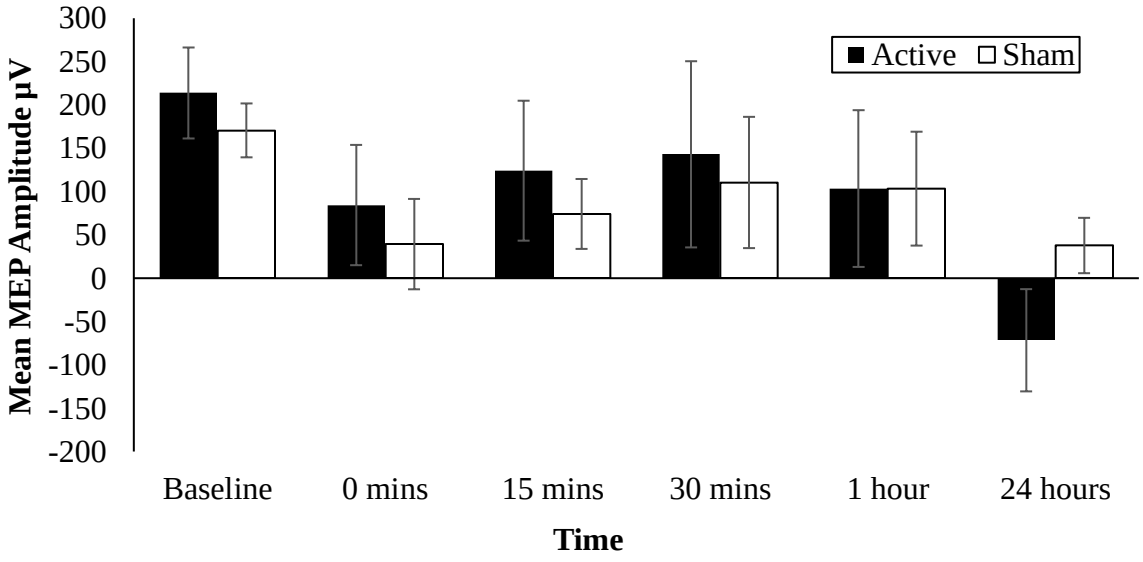
amplitude post stimulation and was comprised of 2 (Stimulation: Active vs. Sham) x 5 (Time: 0 minutes, 15 minutes, 30 minutes, 60 minutes, 24 hours) and showed a significant main effect of Time $F(5, 64336.71) = 3.01$, $p = <.05$, $n2=.073$, however, there was no significant interaction between Stimulation and Time $F(5, 90520.58) = 0.78$, $p = .496$, $n2=.027$.

Table 4.3 Mean TMS Intensity for Stimulation Conditions

Stimulation conditions	Mean TMS intensity %
Active	52.7
Sham	56.1

To explore the main effect of Time a one-way repeated measures ANOVA was conducted and showed a significant effect $F(5, 308712.34) = 3.53$, $p < .05$, $n2=.083$. Pairwise comparisons between baseline and post stimulation time points (Baseline, 0 minutes, 15 minutes, 30 minutes, 60 minutes, 24 hours) indicated a significant reduction in MEP amplitude from baseline at 24hours post stimulation $t(39) = 3.52$, $p < .01$. All other pairwise comparisons to baseline failed to reach significance at 0minutes $p =.361$, 15 minutes $p= 1.00$, 30minutes $p= 1.00$ and 60minutes $p= 1.00$.

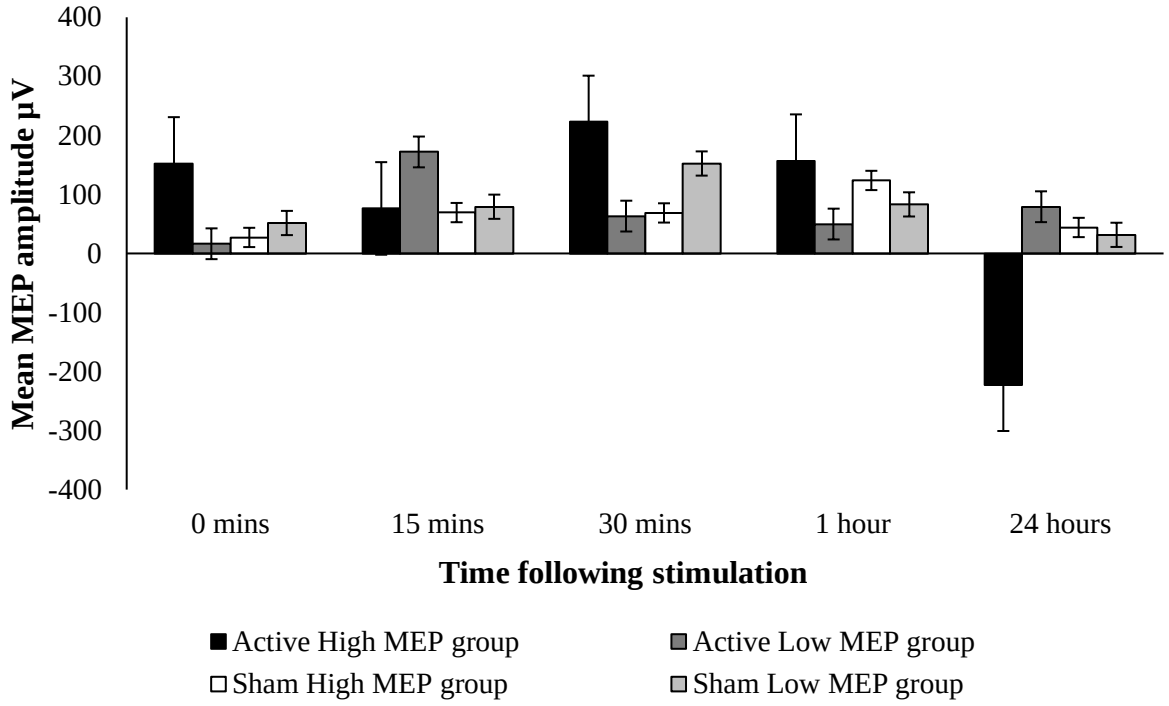
Figure 4.3 Mean Change in MEP Amplitude Over Time in Active and Sham Condition. (with standard error)



Exploratory analyses

To examine if GVS had a different effect between participants with High versus Low baseline MEP amplitude the omnibus ANOVA was re-run after a median split was implemented. Mean MEP amplitudes for all groups across time can be seen in Figure 4.4. Here a significant main effect of Time was evident $F(4, 51519.37) = 3.28$, $p < .05$, n_2=.083 and a three-way interaction between Baseline MEP, Stimulation and Time $F(4, 51519.37) = 3.14$, $p < .05$, n_2=.080, was observed. Two-way interactions between Time and Stimulation $F(4, 51519.37) = 1.13$, p= .346, n_2=.030 along with Time and High/Low MEPS $F(4, 51519.37) = 2.16$, p= .0.76, n_2=.057 failed to reach significance.

Figure 4.4 Mean Change in MEP Amplitude Over Time in all Groups. (with standard error)



To investigate these effects further, separate 2x5 ANOVAs were conducted on the Active and Sham groups. These 2x5 ANOVAs comprised 2 (Baseline MEP: High vs. Low) x 5 (Time: 0 minutes, 15 minutes, 30 minutes, 60 minutes, 24 hours). The Sham Stimulation group 2x5 ANOVA failed to produce a significant effect for Time $F(4, 32263.07) = 0.81$, $p = .49$, $n_2 = .043$ or a significant interaction between Baseline MEP and Time $F(4, 14857.29) = 0.37$, $p = .77$, $n_2 = .020$. Conversely, in the Active group there was a significant main effect of Time $F(4, 194211.39) = 3.03$, $p < .05$, $n_2 = .144$ and an interaction between High versus Low MEPs and Time , $F(4, 256724.91) = 4.01$, $p < .05$, $n_2 = .182$.

To determine the source of this interaction, two separate one-way repeated measures ANOVA were conducted on Active High and Low MEP groups over six levels of Time. The ANOVA for the Active Low baseline MEP group failed to reach significance $F(5, 94627.28) = 1.06$, $p = .35$, $n_2 = .105$. However, in the Active High baseline MEP group there was a significant effect of Time $F(5, 783479.40) = 3.22$, $p = .05$, $n_2 = .263$. Post- hoc tests revealed a significant reduction in MEP amplitude at 24 hours post stimulation $t(9) = 3.42$, $p < .01$ compared to baseline.

Lastly, to determine if this effect was driven by higher TMS intensities in the High MEP at baseline group compared to the other groups, a one-way ANOVA with 4 levels (Group: Active High, Active Low, Sham High, Sham Low) was conducted. No significant effects were evident $F(3, 51.867) = 0.80$, $p = .50$, $n_2 = .063$ indicating that all groups received a comparable TMS intensity (see Table 4.4).

Table 4.4 Mean TMS Intensities for all Groups

Stimulation Groups	Mean TMS intensity %
Active High MEP at baseline	53.7
Active Low MEP at baseline	55.1
Sham High MEP at baseline	51.7
Sham Low MEP at baseline	57.1

Discussion

The aim of Experiment 2 was to test if 25minutes of ~1mA of DC GVS would induce lasting changes in cortical activity. The results initially showed no significant differences in MEP amplitudes between the active group and sham control group. However, subsequent exploratory

analysis, revealed that individuals exhibiting high levels of cortical excitability at baseline showed a significant reduction in cortical excitability 24hours post 'active' GVS. By contrast, low MEPs did not. These reductions are indicative of GVS inducing an inhibitory effect on cortical excitability which is seen as a precursor to LTD-like plasticity in the motor cortex (Vallance & Ridding, 2014). This is the first time that a physiological effect of GVS has been shown to induce such effect.

A potential limitation of the current experiment was the high variability of TMS-elicited MEPs. That said, whilst error margins were still large (see Figure 3.5) they were reduced comparatively from those in Experiment 1 (see Figure 3.2) due to changing the experimental protocol. This limitation is a well reported property of MEPs that can affect the reliability of the technique (Kiers, Cros, Chiappa & Fang, 1993; Ellaway et al., 1998; Darling, Wolf & Butler, 2006). Measures were taken to improve spatial accuracy such as targeting the APB muscle rather than the ADM. However, even the use of functional imaging techniques to guide TMS location have failed to decrease MEP variability, yeilding similar results to that of non-navigated methods (Gugino et al., 2001; Jung et al., 2010). Potentially, MEP variability may be due to less controllable factors in natural excitability fluctuations pertaining to the cortico-spinal tract (Magistris, Rosler, Truffert & Myers, 1998). A further imitation of delivering ~1mA of GVS was that for many participants in the active group a prickling sensation on the scalp was noted over the mastoid processes during stimulation. However, this did not appear to confound the results as as the inhibitory effects of GVS were not evident at 24hours post stimulation, in the sham group with cortical hyper-excitability at baseline.

Experiment 3: The Effects of 1mA GVS on Motor Related Cortical Potentials

In the current experiment I aimed to corroborate the findings of Experiment 2 but employed an alternative method of examining motor cortical excitability by using the Bereitschaftpotential (Shibasaki & Hallet, 2006). I chose this method in the hope that a voluntary hand movement would show less trial variability than the noisy involuntary MEPs evoked by using TMS. The same research design as in Experiment 2 was therefore utilized to hopefully show that the amplitude of the BP would decrease at 24hours post GVS in individuals with cortical hyperexcitability at baseline. As can be seen in the brief experimental summary below, I was however unable to accurately record the BP on sufficient occasions let alone determine if it was modulated by GVS. Two attempts were made to measure it; in the first I utilised passive cup electrodes and was unable to detect a BP at baseline in any of the 12 participants. I suspect that the reason for this was partly due to the misplacement of cup electrodes on the scalp which need to overlie the relevant area of the motor cortex. To address this problem, I made a second attempt in 28 participants to measure the BP by utilising an Easy Cap which makes electrode placement easier.

Methods

Participants

Forty participants were recruited via the University of Kent research participation scheme in exchange for course credits. All individuals were right-handed (confirmed by the Edinburgh Handedness Inventory), free of self-reported neurological conditions, metal plates or surgical clips in the skull and had no skin abrasions behind the ears. Participants provided informed consent

prior to participation and were fully debriefed at the end of the experiment. Full ethical approval was obtained from the University of Kent School of Psychology research ethics committee.

Design

As in Experiment 2 a within-subject's pre-post stimulation design was employed to measure DV changes in MRCPs at baseline and at four subsequent time blocks up to 24 hours post stimulation (*see Figure* 4.4 in Experiment 2). The between-subjects IV 'Stimulation' incorporated the active and sham conditions.

Galvanic Vestibular Stimulation

Both Active and Sham stimulation were carried out in the same way as in Experiment 2; 25miuntes of Gaussian noise, frequency 1000Hz, applied to the mastoid processes in a bipolar, binaural configuration with the anode placed on the left mastoid and the cathode on the right.

Recording Movement-related Cortical Potentials

After preparation of the scalp using sterilization wipes, eight passive cup electrodes were attached using Elefix paste to EEG placements Fz, Cz, Cpz, Pz, C1, C2, C3, C4, using the International 10-20 system with electrodes A1 and A2 linked as references. Disposable (28mm x 20mm) Ag/AgCl duck foot electrodes (Ambu® Neuroline 710) were placed in a bipolar montage over the extensor digitorum muscle of the left forearm to record EMG in the first 12 participants. Subsequent EEG and EMG recordings in the remaining 28 participants utilized the same electrode montage but instead used Easy Cap electrodes to record EEG. Brain Vision Recorder software and a BrainAmp amplifier (Brain Products, GmbH, Gilching, Germany) recorded both EEG and EMG artifacts simultaneously using a band pass filter of 0.05-70Hz for EEG recordings and 20-70Hz for EMG.

Care was taken to inform participants that they should try to avoid unnecessary movement or chewing during EEG/EMG recording to prevent unwanted artifacts.

All analysis was undertaken using Brain Vision Analyser 2.0 (Brain Products, GmbH, Gilching, Germany). Unwanted EEG artifacts were removed off-line upon visual inspection. Averaged, rectified EMG signals were used to trigger back-averaging of EEG epochs set to four seconds (three seconds prior to EMG onset and one second after the EMG signal). The first 500miliseconds of each epoch was baseline corrected and EEG data from 80 trials in each block were averaged to obtain BPs. BPs were quantified using the area under the slope obtained two seconds prior to the EMG onset.

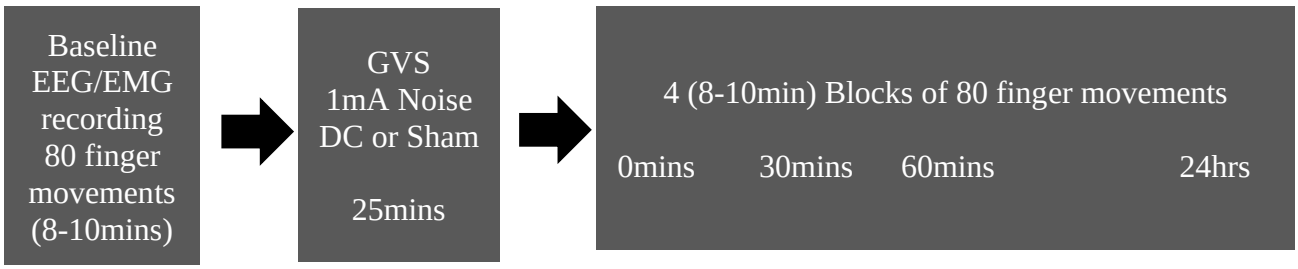
Procedure

After providing informed consent all participants completed the Edinburgh Handedness inventory Oldfield (1971) to confirm that they were right-handed. Participants skin was then prepared with sterilizing wipes to reduce impedance levels and EEG/EMG electrodes were attached. When using the Easy Cap, impedance levels were reduced to below 5kΩ by using a cotton wool stick and abrasive gel.

Participants were then given oral instructions for the motor task which was to make voluntary left middle finger extensions at intervals of approximately five seconds. Participants made these movements at their own pace (no external time cues were provided). A practice session was undertaken for approximately five minutes so that I could monitor their EMG traces for artifacts, ensure that the finger movements were abrupt, and check that complete muscular relaxation occurred between movements to allow later off-line placement of EMG signal markers.

Following practice, the participants were instructed to make 80 finger extensions at 5second intervals during the baseline recordings and then during the later sessions. Participants were fully debriefed upon completion of the testing session at 24hours post-stimulation.

Figure 4.5. Experimental Protocol



Results & Discussion

Despite considerable effort I was unable to produce any data from the first 12 participants that were suitable for statistical analysis. This is because I was unable to attain a BP at baseline when using the passive cup electrodes. After switching to the Easycap, I was able to attain at least some measurement of the BP in 15 of the 28 participants subsequently tested. However, these data were still of a poor quality; of the 80 finger movements made to elicit the BP during each time block, over 25% of trials failed to elicit a BP. As a consequence the data were nosiy and potentially under-powered (see also Luck & Kappenman., 2011). Perhaps unsurprisingly, the ANOVAs performed on these data failed to show any statistically significant effects. As this experiment was conducted towards the end of my PhD, I did not have the time to continue refining the protocol to resolve the technical issues that I faced which, on reflection, partly reflected my lack of experience and the lack of local academic expertise in combining EMG and EEG. For example, it is possible that the 8-electrode montage, whilst appropriate for bedside EEG in a hospital setting, was not adequate

for the refined experimental needs of my laboratory study. In future experiments I would aim to use a 32 electrode montage to reduce the signal to noise ratio (Usakli, 2010). Additionally, I would increase the finger movement trials to 160; it has been suggested that a minimum of 80 trials are required for a reliable average measurement so increasing the number of trials would allow for the data loss associated with this methodology (Shibasaki & Hallet, 2006).

General Discussion

This set of experiments sought to provide evidence that GVS can induce neuroplastic change and thereon justify and constrain its application to the symptoms of mTBI in UK military veterans. In Experiment 1, 10minutes of ~ 0.35mA AC GVS was shown to have no significant effects on MEP amplitudes. However, there were methodological problems that raised the possibility of a Type II error. The median split methodology that was used in Experiments 1 and 2 to separate High from Low TMS intensities can sometimes cause a loss of individual variability and statistical power thus increasing the possibility of a Type II error (Iacobucci et al., 2014). Typically, this might mean that the observed outcomes are overly conservative, as is arguably the case in Experiment 1. However, it has been argued by Iacobucci et al., (2014) that as the null hypothesis is never accepted and whilst median splits are suboptimal from the perspective of power, there is no material risk to science posed by median splits unless they produce a Type I error with the use of dichotomization which was not the case in the current study. An additional limitation was the short time window of post-stimulation recordings in Experiment 1 which may not have been long enough to capture potential effects of late phase LTP/LTD induction that can take place up to 4 hours and days later (Abraham, 2003; Linden, 1998). This limitation was therefore addressed in Experiment 2 by changing the experimental protocol and increasing the post stimulation measurement time window from 60minutes up to 24hours post stimulation. These changes revealed significant late phase LTD

type effects in participants who had cortical hyperexcitability at baseline and received 25minutes of ~1mA DC GVS.

Further albeit indirect evidence of vestibular stimulation providing a reduction in cortical activity can be seen in research by Kantner et al., (1982). Who showed that vestibular stimulation induced a significant reduction of proximal activity post-stimulation in seizure prone children. Also, hyper-excitability in the motor cortex is strongly correlated with attentional problems and mood disturbances in neurologically healthy participants (Bolden, et al., 2017). Indeed, dysfunctional homeostatic plasticity has been linked to a number of neuropsychiatric disorders such as PTSD, anxiety, attention-deficit/hyperactivity disorder (ADHD), epilepsy, Tourette's syndrome and schizophrenia (Centonze et al., 2005; Machado et al., 2011; Badawy et al., 2012; Hasan et al., 2013; Bolden et al., 2017). In light of these current findings GVS may hold potential therapeutic value in remediating a number of neuropsychiatric conditions in military veterans that are related to cortical hyperexcitability such as anxiety. The next chapter will test this hypothesis.

Chapter 5

The Effects of Galvanic Vestibular Stimulation on Anxiety Symptoms: A Case Study of 5 UK Military Veterans

Introduction

The aim of this Chapter is to determine whether the reduced motor excitability seen in the last Chapter translates into reduced positive symptoms in UK military veterans with mTBI and PTSD. To this end, I chose to target the effects of GVS on anxiety for the following reasons. Firstly, pathological anxiety disorders such as PTSD can induce emotional responses that are chronically dysfunctional. Fear responses can become maladaptive resulting in autonomic, cognitive and somatic reactions that can cause exaggerated emotional responses, defensive, freezing or avoidant behaviours (Rosen & Schulkin, 1998). Pathological anxiety can also induce a sense of uncontrollability that is characterized by hypervigilance (Eysenck, 2013). This psychological distress causes fear circuits to become hyperexcitable and more readily activated. In line with this, patients with PTSD demonstrate widespread impairment in GABA function and right lateralized dysfunction with increased cortical excitability (Rossi et al., 2009). Furthermore, patients suffering from PTSD and mTBI have shown lower MEP inhibition and significantly higher MEP amplitudes than controls, which is also indicative of cortical hyperexcitability (Centonze et al., 2005). These physiological factors coupled with the high prevalence of anxiety lends anxiety as a useful indirect marker of excitability change.

Vestibular disorders and anxiety are functionally related via both somatopsychic and psychosomatic mechanisms (Jacob and Furman, 2001). Symptoms of dizziness and imbalance are synonymous with comorbid anxiety and evidence suggests that the vestibular system exerts a

significant influence on the ascending pathways that are integral to anxiety symptoms (Balaban & Porter, 1998; Balaban & Thayer, 2001). Somatopsychic symptoms involve the integrated activity of three neural networks; the vestibulo-parabrachial nucleus (PBN) network, coeruleo-vestibular network and raphe nuclear-vestibular network (Balaban, 2002). There are dense ascending projections from the vestibular nuclei to the PBN which have reciprocal connections with the amygdaloid nucleus, infralimbic cortex and hypothalamus regions involved in conditioned fear and anxiety responses, which may mediate panic and anxiety disorders (Charney & Deutsch, 1996; Ressler & Nemeroff, 2000). These excitatory networks are activated in states of fear or vigilance and alter vestibular evoked ocular and motor responses (Balaban, 2002). In fact, abnormal nystagmus has been observed in 50% of US soldiers with blast mTBI along with symptoms of dizziness (Scherer et al., 2011).

Psychosomatic mechanisms such as fear and anxiety are also known to affect balance control (Kalueff et al., 2008) along with autonomic malfunctioning which may be a probable cause of vertigo (Furman, Jacob & Redfern, 1998). Support for this idea can be seen in veterans with PTSD, where greater severity of PTSD is associated with worse symptoms of dizziness (Harber et al., 2016). mTBI is also associated with greater incidence of anxiety disorders and is known to share neurobiological links (Moore et al., 2006; Meyer et al., 2012). A single impact to the skull in rats that mimics mTBI, has been shown to produce discrete alterations in neuronal numbers within the limbic system and specific emotional deficits that links mTBI to a number of anxiety disorders (Meyer et al., 2012).

It is important to understand how emotional deficits can manifest and affect cognition so that appropriate pre and post GVS measures can be harnessed to detect potential change. Anger,

impulsivity and aggressive behaviours are common and associated with anatomical structures such as the brain stem, hypothalamus, limbic system, orbitofrontal cortex and neocortex (Boke et al., 1992; Blair, 2001). It is suggested that impulsive and aggressive behaviours emerge due to impairment in inhibitory control when processing threat response. This can arise by failure of the limbic system (hippocampus, amygdala) to comply with regulatory functions and failure of inhibitory functions within the frontal cortex (Bolu et al., 2015). Fear responses can become dysregulated and hyperresponsive leading to attentional bias in the detection of potential threat and an inability to disengage from perceived trauma reminders (Hayes, VanElzakker & Shin, 2012). As a consequence of this, the availability of cognitive resource to engage in non-threat goals and task demands is decreased (Hayes, VanElzakker & Shin, 2012; Jovanovic & Norrholm, 2011), and executive function declines.

The emotional Stroop task (EST) can assess attentional biases and allied executive dysfunction in PTSD and mTBI (Buckley, Blanchard & Neill, 2000; Cisler et al., 2011; Constans et al., 2004; Stroop, 1935; Varna, Roodman & Beckham, 1995). In military veterans deficits in attention and executive control have been linked to both neutral (Vasterling & Verfaellie, 2009; Vasterling et al., 2009; Qureshi et al., 2011); and emotional Stroop stimuli related to combat trauma (Ashley et al., 2013; McNally et al., 1990; 1993; Mogg et al., 1989). Ashley et al., (2013) demonstrated that US veterans with PTSD were disproportionately slower responding to combat related words in an EST compared to controls. Those individuals with greater depression and PTSD generally produeced larger interference effects. This specificity in detecting attentional biases to combat related words in the EST, may provide a useful pre- and post-intervention measure for the current study. Arguably, hyperexcitability and anxiety may not only manifest in slower reaction times but delays in colour naming combat words.

Hyperarousal symptoms and aggressive behaviours have been hypothesised by Bolu et al., (2015) to be linked to motor cortex hyperexcitability that is frequently seen in individuals with PTSD. However, vestibular influences are also known to effect motor cortex excitability, this is hardly surprising given the vestibular systems role in muscle sympathetic nerve activity and limbic regulation (Balaban, 2002). Evidence of this can be seen in patients suffering from Mal de debarquement syndrome a condition which occurs when habituation to passive ground movement becomes resistant to preadaptation of stable conditions, resulting in a phantom perception of self-motion. Like PTSD, this vestibular disorder has also been associated with hyperexcitability of the motor cortex compared to healthy controls (Clark & Quick, 2011). Further evidence of the vestibular system directly influencing motor responses can also be seen from using GVS which has been shown to improve performance in motor execution tasks and elicit shorter reaction times (Yamamoto et al., 2005). Combined these factors and the results from Chapter 4 highlight the need to introduce a secondary task that can indirectly measure motor cortex excitability. A simple reaction time task (SRT) would provide a good pre and post GVS measure that unlike the EST, is free of inducing anxiety symptoms. Given the extensive networks between the vestibular, limbic systems, reciprocal ocular/motor responses and the inhibitory effects of GVS seen in Chapter 4, it is likely that vestibular stimulation may influence emotion, motor responses and cause hypoexcitability eliciting the opposite effects.

The Current Study

Given the findings in Chapter 4 that GVS can reduce cortical hyperexcitability at 24hours post stimulation, this study will assess if a common symptom such as anxiety associated with hyperexcitability can be reduced by GVS. If this is shown to be the case then a tentative link will have been made between a psychological effect of GVS and its clinical impact. Hyperexcitability

was measured in several ways. The State-Trait Anxiety Inventory for adults was employed to measure change in current anxiety levels. This measure was deemed an appropriate metric due to the time constraints of testing over a three-day period. Measuring current anxiety was more practical than measuring PTSD symptomology, which would require a much longer time period. The SRT was also utilised as a behavioural correlate of motor cortical hyperexcitability. The EST was used to measure anxiety related attentional bias and inhibition. Changes in current anxiety, SRT and the EST were measured at five time points over three consecutive days in an ABAB design which allowed each case study to serve as their own control.

Methods

Participants

Eligible participants from the previous epidemiological study in Chapter 3 were offered the chance to participate in the current study if they fully met the inclusion criteria (prior consent had been granted by all participants in the previous epidemiological study to be contacted and offered the opportunity to participate in the current study if eligible). The inclusion criteria comprised a lifetime history of one or more mTBI, a PTSD score of >38 (PCL-5), and an anxiety score of >12 (K10) indicating severe symptom severity. Participants also needed to show no evidence of colour-blindness when tested by the Ishihara's Tests for Colour-blindness so that they could perform the emotional Stroop task (Ishihara, 1985). Six UK military veterans were selected from the previous sample and invited to participate. Data from participant 002 were excluded from the study due to an electrode failure during active GVS which meant that a full dose of stimulation was not received. All participants provided written informed consent prior to participation and were fully debriefed when data collection was complete. A favourable ethical opinion was granted prior to study commencement from the University of Kent School of Psychology research ethics

committee.

Participant Psychiatric and Medical History

Participant 001

Participant 001 was a 56-year-old Caucasian male who served as medical support officer (Rank: Squadron Leader) in the Royal Airforce for 26years. He had a history of being abused during adolescence and had been exposed to multiple traumatic events over six tours of combat duty during his military career. Patient 001 had been diagnosed as suffering from PTSD, depression, had a history of alcohol abuse and suicidal ideation. Over the course of his lifetime, he frequently exhibited aggressive behaviour and reported involvement in several physical altercations that along with boxing and rugby resulted in him sustaining repeated mTBIs. He reported suffering from an impaired sense of smell, memory and attention problems. His PTSD symptoms had a delayed onset from adolescence only manifesting 2years before leaving the armed services, triggered by another traumatic event. He was physically abusive towards his first wife with whom he had two children. The marriage dissolved and he has since remarried. His home life and relationship with his current wife is unremarkable. He described his premorbid personality as outgoing "*life and soul of the party*". However, he now avoids participating in social events as he struggles to manage his anger, he finds this along with symptoms of anxiety and depression to be particularly debilitating as it also affects him at work. He currently works in a senior management role within the National Health Service. One year prior to participating in this study he received six weeks of psychological therapy as an in-patient at Combat Stress. He was medicated on 50mg of Sertraline per day.

Participant 003

A 53-year-old Caucasian male who served in the British Army as a Coldstream guardsman (Rank:

Corporal) for 24years. During his military career he had three deployments to a war zone and was exposed to multiple combat related traumatic events. He was diagnosed with PTSD and depression before leaving the army. He also has a history of alcohol abuse, self-harm and has previously attempted suicide. Participant 003 reported a history of repeated mTBIs due to blast exposure and blunt force injuries due to banging his head during his military career. He described these blunt force injuries as an occupational hazard, due to being 6ft 8inches tall. During 2012 participant 003 received treatment for Mantle cell lymphoma, which is in remission. He also suffers with chronic pain due to a spinal disc herniation. His marriage failed after seven years due to his PTSD symptoms. He has lived with his current partner for the past 10years and describes his behaviour at home as frequently volatile. Participant 003's mother suffers from Alzheimer's and is cared for in a retirement home, which causes him considerable distress. Since leaving the army six years ago he has worked as a security guard. He described his premorbid personality as "*fun*" but also reported to "*always being emotionally closed*". Controlling emotions of anger has been particularly difficult for him since the onset of his PTSD. This along with severe anxiety and hypervigilance cause him considerable distress. He received six weeks of psychological therapy as an inpatient at Combat Stress 12 months ago. As a result, he now practices mindfulness meditation, yoga and Buddhism as he finds this helps him to cope. His prescribed medication included, 20mg of fluoxetine daily and when needed Sildenafil, Omeprazole, Tramadol, Naproxen, Matrifen and Diazepam.

Participant 004

A 45-year-old Caucasian male who served in the British Army as an infantryman (Rank: Lance corporal) for nine years. Participant 004 suffered the bereavement of a sibling during childhood which had a profound effect on him. Behavioural problems were evident prior to him joining the

army, as he attained a criminal record for actual bodily harm and burglary. He had one deployment to a war zone where he was subjected to psychological trauma and has been diagnosed with PTSD, depression, and attention deficit hyperactivity disorder (ADHD). He had a history of alcohol/substance abuse and suffers with chronic pain due to a spinal disc herniation. A history of repeated mTBIs mechanisms included blast, road traffic accidents, ruby and fighting. He has been married to his wife for 23years and explained that he is now a full-time carer to her as she is unwell. His four children are all adults and no longer live with him and their relationship is unremarkable. Patient 004 is very troubled by agoraphobia and particularly anxious when in a crowd, as he becomes disorientated. Generally, he will not leave his home unless it is essential and as a consequence he has been unemployed for the past 15years. He described his premorbid personality as "*not very pleasant, antagonistic and difficult"* and said that *"I am easier to get along with now and try to avoid trouble"*. Participant 004 received six weeks psychological therapy as an inpatient at Combat Stress 6 months prior to participation in this study. His daily medication includes 200mg Serterline, 15mg Ozlanzapine, 54mg Concerta and when needed 2mg of Diazepam.

Participant 005

A 32-year-old Caucasian male who served as an infantryman in the British Army (Rank: Private) for 6years. Participant 005 was subjected to abuse during childhood and was deployed to a war zone on three occasions where he was exposed to extreme psychological trauma. After returning from a deployment in Afghanistan, participant 005 was absent without leave for 3months which resulted in him being incarcerated for 90days and discharged from the army. He was diagnosed with PTSD before leaving the army and has a history of repeated mTBI. Mechanisms of injury include blast, participating in extreme sports and fighting. Sensory problems include extreme dizziness, imbalance, tinnitus and impaired hearing. He previously suffered from substance and

alcohol abuse and has caused significant self-harm, attempting suicide twice. Difficulties with attention and concentration are particularly debilitating for him, along with issues controlling his anger. He was married for 3years and has two children from this marriage which has dissolved due to domestic abuse towards his wife. He has occasional contact with his children. Since leaving the army he has been arrested several times for violent conduct but has no convictions. At the time of testing he had been suspended from his role as a prison warden, whilst an investigation was carried out over him using excessive force when restraining a prisoner. He currently lives with his girlfriend who is pregnant and mentioned that he is dissatisfied with their relationship. Participant 005 received six weeks psychological therapy as an inpatient at combat stress 8 months prior to participation and is medicated on 100mg of Sertraline per day.

Participant 006

A 45-year-old Caucasian male who served three years as an infantryman (Rank: Private) in the British Army. Participant 006 suffered the loss of his father at 13years of age and brother in early adulthood. He said that he was bullied at school and excluded. This led to his involvement in gang culture, where he became leader of a football hooliganism gang. He attained a criminal record for serious assault and was arrested for attempted murder but not convicted prior to joining the armed services. Other psychological trauma involved one deployment to a war zone where he also sustained a blunt force mTBI. He has been diagnosed with ADHD, PTSD, depression and has a history of substance/alcohol abuse. Participant 006 also suffers from fatty liver disease but has been abstinent for the past 3years. He has extreme agoraphobia and tries not to leave his house, he has planned his suicide on a number of occasions. Estranged from most of his family, participant 006 no longer has contact with his mother or other siblings. He has a son from a previous relationship although he has never met him. Currently, he lives with his girlfriend of 10years. His

home life was unremarkable. He described his premorbid personality as "*loving and caring, closer to his family, well liked and helpful*". Three months prior to participating in this study participant 006 received 6weeks of psychological therapy at Combat Stress. He was unable to provide evidence of his medication, but indicated that he is prescribed drugs for PTSD.

Design

Testing for each of the six case studies took place over three consecutive days and comprised five repeated experimental blocks. Measures were presented in a pre and post stimulation design, with a follow-up session at 24hours post stimulation to ensure that the effects of delayed change in excitability seen in Chapter 4 were captured. All participants received both active and sham GVS. I employed an A,B,A,B design to counter balance active and sham stimulation on either day 1 or day 2 of testing (see *figure 5.1*). Two words sets A and B were used for the Emotional Stroop test and counterbalanced between active and sham and across participants (see *figure 5.1*).

Figure 5.1 Protocol A,B,A,B Experimental Design

Day 1				Day 2			Day 3
Participant	**Task**	**Treatment**	**Task**	**Task**	**Treatment**	**Task**	**Task**
002	**SRT EST (A) STAI**	**GVS (A) Active**	**SRT EST(B) STAI**	**SRT EST (A) STAI**	**GVS (B) Sham**	**SRT EST(B) STAI**	**SRT EST (A) STAI**
001	**SRT EST (B) STAI**	**GVS (B) Sham**	**SRT EST(A) STAI**	**SRT EST (B) STAI**	**GVS (A) Active**	**SRT EST(A) STAI**	**SRT EST (B) STAI**
005	**SRT EST (B) STAI**	**GVS (A) Active**	**SRT EST(A) STAI**	**SRT EST (B) STAI**	**GVS (B) Sham**	**SRT EST(A) STAI**	**SRT EST (B) STAI**
003	**SRT EST (A) STAI**	**GVS (B) Sham**	**SRT EST(B) STAI**	**SRT EST (A) STAI**	**GVS (A) Active**	**SRT EST(B) STAI**	**SRT EST (A) STAI**
004	**SRT EST (A) STAI**	**GVS (A) Active**	**SRT EST(B) STAI**	**SRT EST (A) STAI**	**GVS (B) Sham**	**SRT EST(B) STAI**	**SRT EST (A) STAI**
006	**SRT EST (B) STAI**	**GVS (B) Sham**	**SRT EST(A) STAI**	**SRT EST (B) STAI**	**GVS (A) Active**	**SRT EST(A) STAI**	**SRT EST (B) STAI**

Note. SRT = simple reaction time task, EST = emotional Stroop task, STAI = State-Trait Anxiety Inventory for adults which comprised of two-word sets = (A) and (B). GVS= galvanic vestibular stimulation in either active (A) or sham (B) conditions.

Materials

Self-report Current Anxiety Symptoms

Section Y-1 of the State-Trait Anxiety Inventory for adults (STAI) was administered to measure current anxiety symptoms. Section Y-1 was designed to measure mood in the moment of ‘State’. Participants indicate the severity of current anxiety symptoms on a four-point Likert scale, ranging from 1 ‘not at all’ to 4 ‘very much so’. Calculating participant total anxiety scores involves the use of a template that inverts scores of 1’not at all’ and 4 ‘very much so’ to 4 and 1 in 10 out of the

total 20 responses. Higher total STAI scores are indicative of greater severity in current anxiety symptoms. This measure has excellent internal consistency (average *as* > .89) and excellent test re-test reliability (average *r* =.88) (Barnes, Harp & Jung, 2002).

Simple Reaction Time Task

Based on a simple reaction time (SRT) task designed by Deary et al., (2010), one white square with a black cross was positioned in the centre of a computer screen against a blue background. Each time a cross appeared on the screen, participants needed to press the space bar on a computer keyboard as quickly as possible. Each cross remained on the screen until the key was pressed. The inter-stimulus interval (time between each response and when the next cross appeared) was randomly set to between 1 and 3 seconds. Stimulus triggers were programmed using a psychopy script and RT responses were automatically recorded on .csv spreadsheets. A practice session was provided with eight trials and the main experiment script was programmed to deliver 40 trials. Participants viewed an instruction screen prior to trials starting.

Colour Blindness

To ensure that participants were able to complete the EST, the Ishihara Test for Colour-blindness was administered. This test involves a series of test plates designed to detect colour deficiency of congenital origin (Ishihara, 1985). If the reading of 17 or more plates are read normally, colour vision is regarded as normal.

Emotional Stroop Task

The emotional Stroop task required participants to name the font colour of emotional and neutral words whilst ignoring the meaning of those words. In the classic Stroop task, incongruent words

and colours (i.e. yellow colour font, word green) interfere with the task responses and slow colour naming (Golden & Freshwater, 1978). In the current experiment the name of the colour was replaced with neutral and emotionally negative, positive and combat words that appeared in one of four font colours (red, green, yellow or blue). Previous evidence from Ashley et al., (2013) suggests that the emotional Stroop can be used to examine cognitive alterations in PTSD, as veterans with PTSD were shown to be proportionally slower at responding to combat words compared to controls. Two word sets A and B, in 48pt Times font using only capital letters were prepared. Each set contained 320 different words that consisted of four target word types; 1) positive, 2) negative, 3) neutral and 4) combat words and 5) matched neutral words. All colours were presented the same number of times for each word type but in random order. Throughout trials comprised 80 red, blue, green and yellow words that were presented on a black background.

The matched neutral words provided a controlled comparison against paired combat words. These matched neutral words equated the following lexical features with paired combat words: length, frequency, ortographic and phonological neighbourhood size. All positive, negative neutral and matched neutral words were taken from the Affective Norms for English Words (ANEW) data base which provided emotional normative ratings of pleasure, arousal and dominance. Combat words described common aspects of traumatic war experiences such as: exposure to IED blasts, suicide bombers, seeing human remains, engagement in killing, violent deaths and injuries. A list of modified combat words was compiled with the help of four UK veterans who were deployed to the Falklands, Iraq, Afghanistan and Northern Ireland during conflict and who did not participate in this study. This is because the list of combat words used in the Ashley et al., (2013) study was only relevant to US troops and not to the UK armed forces. These replacement words contained the same lexical features as the words they replaced and were comprised of four types of combat

words which included 1). Combat events (*i.e. insurgent*), 2). Places (*i.e. Helmand*), 3). Military abbreviations (*i.e. AK47*) and 4). General war trauma words (*i.e. morphine*). All combat and matched neutral word pairs were presented in randomised order in the four different colours.

Participants were shown an instruction screen informing them to clearly speak into a microphone when naming the colour of the word that appeared. After completing a practice trial of 15neutral words on day one of testing, participants started the main experiment. Each word in the EST was presented for 500ms with an inter-stimulus interval of 1500ms making a total trial time of 2000ms. Each experimental block used either word set A or B containing 320 words. Experimental trial scripts were written using Psychopy and voice reaction times were recorded on .csv files. Participants were informed that we were recoding their responses by video camera to enable us to check their accuracy in naming the correct colour of word stimuli. Participants were able to take a one-minute break after 100 and 200 trials.

Galvanic Vestibular Stimulation

A Neuroconn DC stimulator was utilised to deliver the same waveform used in Chapter 4. This waveform comprised 25minutes of Gaussian noise bipolar direct current. Stimulus intensity varied randomly from 0.5-1.5mA with a mean intensity of 1mA at a frequency of 1000Hz and was delivered to the mastoid processes via 5.1cm x 10.2cm rubber self-adhesive electrodes. This bipolar current was delivered with the anode placed on the left mastoid and the cathode on the right. Skin over the mastoids was prepared prior to electrode placement using surgical wipes and Nuprep gel, to ensure low impedance. Sham stimulation involved the same preparation however, the stimulation device remained out of sight and turned off. Due to GVS electrode failure during active stimulation on participant 002, his data was withdrawn from the study, leaving (N=5)

remaining participants. There were no reports of prickling or dizziness sensations after active GVS in the remaining participants, indicating that participants remained blinded to the active and sham stimulation conditions.

Procedure

Testing took place over three consecutive days. On Day 1, participant gave informed consent and a full medical and psychiatric history. The main experimental protocol can be seen in Figure 5.1. At baseline participants first completed the SRT followed by the EST and then the STAI. This process was repeated in either active or sham conditions immediately after GVS and at 24hours post-stimulation on day three.

Statistical Approach

Descriptive statistics were employed to examine the effects of GVS on STAI scores over time. Inferential statistics were not employed for further analysis of the STAI, due to the small sample size and the fixed nature of STAI scores which do not provide a variance measure.

The SRT responses were analysed via one-way ANOVA with Time as the independent variable comprising of three levels (Baseline, Post-stimulation, 24hours post-stimulation). Separate ANOVAs were used for the Active and Sham conditions as the use of 24hour post-stimulation on Day 2 also was used as a baseline for the next session, which prevented a symmetrical design.

Before conducting colour-naming latency analysis for the EST, standard data trimming procedures were performed. This involved the removal of incorrect trials (see Table 5.1.). Only correct responses were included in the statistical analysis. It was predicted that participant

responses would be slower to emotionally salient combat words compared to neutral, negative and positive words. However, this Stroop effect was not predicted in the analysis of matched neutral words that form a comparison. To examine if GVS reduced reaction times to combat or matched neutral words in the EST, four within-subjects 3x4 repeated measures ANOVAs were performed, and consisted of 3 (Time: Baseline, Post-stimulation, 24hrs Post-stimulation) x 4 (Target words: Combat, negative, neutral, positive) or 4 (Matched Neutral words: Combat, Negative, Neutral, Positive) factors. Two of these ANOVAS were employed in the Active stimulation condition to examine changes in RT to either Target or Matched Neutral words over Time. The same two ANOVAs were also conducted in the Sham condition. Significant main effects were explored via t-tests with Bonferroni corrections. All statistical analysis was conducted on SPSS version 24.

Results

Table 5.1. EST Incorrect Response Percentages

Participant	Session	Condition	Word Set	Incorrect %	Total Mean %
001	1	Baseline 1	B	13	10.6
	2	Post Sham	A	7.5	
	3	Baseline 2	B	7.5	
	4	Post GVS	A	15	
	5	24hrs Post GVS	B	10	
003	1	Baseline 1	A	2.5	6.4
	2	Post Sham	B	6.2	
	3	Baseline 2	A	8.2	
	4	Post GVS	B	10	
	5	24hrs Post GVS	A	5	
004	1	Baseline 1	A	13.7	14.2
	2	Post GVS	B	11.2	
	3	Baseline 2	A	13.7	
	4	Post sham	B	16.2	
	5	24hrs Post sham	A	16.2	
005	1	Baseline 1	B	1.25	2.2
	2	Post GVS	A	1.25	
	3	Baseline 2	B	0	
	4	Post sham	A	5	
	5	24hrs Post sham	B	3.7	
006	1	Baseline 1	B	36.2	27.9
	2	Post Sham	A	25.0	
	3	Baseline 2	B	26.2	
	4	Post GVS	A	28.7	
	5	24hrs Post GVS	B	23.7	

Participant 001

STAI

At baseline participant 001's STAI score was 33, and increased slightly to 35 post Sham GVS. At 24hours post Sham GVS his STAI dropped to 29 which indicated a reduction in current anxiety. On day 2 his anxiety levels rose from 29 at baseline to 35 post Active GVS and elevated further to 43 at 24hours post-stimulation on day three. Graphical representation of STAI scores for all participants in both active and Sham conditions can be seen in Figures 5.2 and 5.3.

Figure 5.2 STAI Scores in Active GVS Protocol

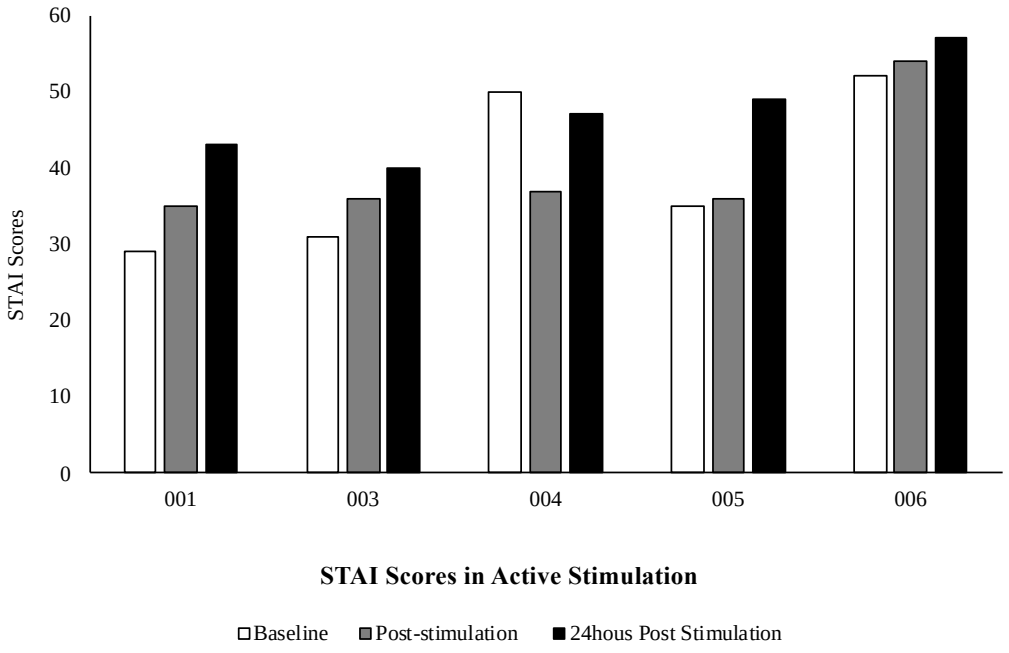
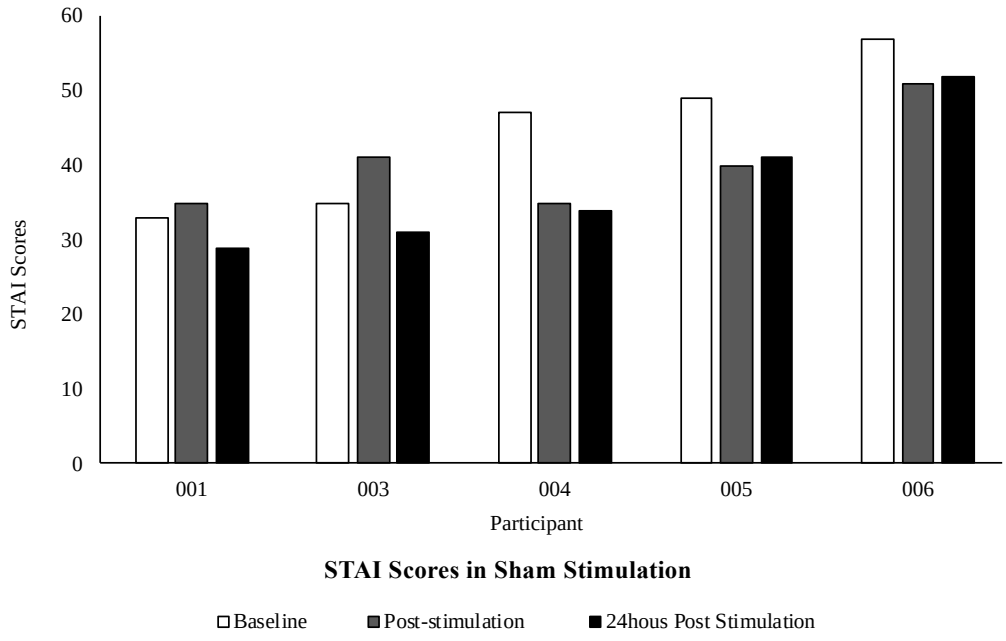


Figure 5.3 STAI Scores in Sham GVS Protocol



SRT

The two one-way ANOVAs revealed no significant effects in either Active $F(2, 78) = .332$, $p = .718$, $n2 = .081$or Sham $F(2, 78) = .362$, $p = .697$, $n2 = .009$ conditions.

EST ANOVAs for Target words

Analysis of the EST in the Active stimulation condition first examined RTs for Target words. This involved a within subjects repeated measures 3 (Time: Baseline, Post-stimulation, 24hrs Post-stimulation) x 4 (Target words: Combat, Negative, Neutral, Positive) ANOVA. This revealed a significant main effect of Time $F(2,58)=9.438$, $p =<.001$, $n2 = .246$. Consistent with my prediction, paired t-tests revealed significantly shorter RT $p =<.001$ between baseline (M=.700sec, SE =.030) and 24hrs post-stimulation (M=.522sec, SE =.022). This effect was not evident between baseline and post stimulation or post-stimulation and 24hrs post-stimulation. There was also a significant main effect of Target words $F(3,87)=2.938$, $p =.038$, $n2 = .092$. Contrary to my prediction that RTs to Combat words would be slower given participants high anxiety; pairwise comparisons indicated that RT were significantly shorter $p =.025$ for negative words (M =.518sec, SE=.033) compared to positive words (M= .642sec, SE=.024). There were no significant interactions between Time and Target Words $F(6, 174) = 1.204$, $p = .306$, $n2 = .040$. The same analysis conducted in the Sham stimulation condition failed to reach significance $F(2, 58) = 2.933$, $p = .061$, $n2 = .092$.

EST ANOVAs for Matched Neutral words

The next ANOVA examined RTs to Matched Neutral words over Time in the Active stimulation condition. Again there was a marginally significant effect of Time $F(2,31)=3.265$, $p =.059$, $n2 = .095$ in the Active condition. Pairwise comparisons showed a significant reduction in RTs $p =.001$

between Baseline (*M*=.653, *SE*=.025) and 24hrs Post-stimulation (*M*=.548, *SE*=.024). No significant differences in RTs between baseline and post-stimulation were evident. There were also no significant main effects of Matched Neutral words $F(3, 93) = 1.982$, $p = .132$, $n^2 = .060$ or interactions with Matched Neutral words and Time $F(6, 186) = 2.640$, $p = .497$, $n^2 = .078$. The same ANOVA was repeated for the Sham stimulation condition and again revealed no significant effects $F(2, 62) = 2.500$, $p = .090$, $n^2 = .075$.

Participant 003

STAI

Participant 003 presented with a Baseline STAI score of 35 which increased to 41 Post Sham GVS. On day two at 24hours post Sham, his STAI score reduced to 31. From this baseline score an increase STAI score of 36 was evident post Active GVS and unfortunately elevated further to 40 at 24-hours post Active stimulation (See *Figures* 5.2 & 5.3).

SRT

A one-way ANOVA of the SRT in the Active GVS condition revealed a significant effect $F(2, 78) = 5.078$, $p < .05$, . $n^2 = .115$ Pairwise comparisons revealed significantly slower RTs $p = .043$ between Baseline (*M*=.247sec, *SE*=.010) and Post-stimulation (*M*=.280sec, *SE*=.009). This analysis was repeated for the Sham stimulation condition and also uncovered a significant effect $F(2,78)=9.752$, $p =<.001$, $n^2 = .200$. Paired t-tests showed significantly shorter $p = .006$ RT between Baseline ($M = .297$, $SE = .013$) and Post-stimulation ($M = .250$, $SE = .006$). RTs were also significantly shorter $p = .001$ between Baseline ($M = .297$, $SE = .013$) and 24hrs Post-stimulation ($M = .247$, $SE = .010$).

EST ANOVAs for Target words

The repeated measures ANOVA for Target words in the EST revealed a significant main effect of Time $F(2,42)=16.484$, p =.<001, n_2= .440 in the Active GVS condition. Paired t-tests revealed significantly longer RTs p =<.001 between Baseline (*M*=.526sec, *SE*=.027) and Post-stimulation (*M*=.922sec, *SE*=.067) which was in contrast to the prediction of shorter RTs. Significantly longer RTs p =.<001 were also evident in comparisons between Baseline (*M*=.526sec, *SE*=.027) and 24hrs Post-stimulation (*M*=.886sec, *SE*=.054). There were no significant differences in Time between Post-stimulation and 24hrs Post-stimulation, and no main effects of Target words $F(3, 63) = 1.817$, p = .153, n_2= .080 or interactions between Time and Target words $F(6, 126) = .689$, p = .659, n_2=032.

In the Sham stimulation condition a significant main effect of Time $F(2,32)=7.2622$, p =.002, n_2= .323 was evident. Paired t-tests revealed no significant differences in RTs between Baseline and Post-stimulation. However, RTs became significantly shorter p =.049 between Baseline (*M*= .761sec, *SE*=.078) and 24hrs Post-stimulation (*M*= .519sec, *SE*=.033). RTs were also significantly shorter p =.001 between Post-stimulation (*M*= .827sec, *SE*=.061) and 24hrs Post stimulation (*M*= .519sec, *SE*=.033). Target words also showed a significant main effect $F(3,48)=6.595$, p =.001, n_2= .292. Paired t-tests showed shorter RTs p =.005 for Combat (*M*=.578sec, *SE*=.045) compared to Negative words (*M*=.867sec, *SE*=.064). RTs were also significantly shorter p =.031 on positive words (*M*=.618sec, *SD*=.397) compared to negative (*M*=.867sec, *SD*=.400). There was also significant interaction between Time and Target words F (6,96)=5.228, p =<.001, n_2= .246.

EST ANOVAs for Matched Neutral words

In the Active stimulation condition a significant main effect of Time $F(2,46)=30.061$, p =.<001, n_2= .567 was evident. t-tests showed a significantly longer RTs p =.<001 between Baseline (*M*=.516sec, *SE*=.028) and Post-stimulation (*M*=.937sec, *SE*=.049). Significantly longer RTs p =.<001 were also evident between Baseline a (*M*=.516sec, *SE*=.028) and 24hrs Post-stimulation (*M*=.887sec, *SE*=.072). There were no significant differences between Post-stimulation and 24hrs Post-stimulation. Matched Neutral words $F(3, 69) = 1.424$, p = .243, n_2= .058 and the interaction between Time and Matched Neutral words $F(6, 138) = 1.001$, p = .427, n_2= .042 failed to reach significance.

In the Sham stimulation condition, RTs to Matched Neutral words showed a significant main effect of Time $F(2,32)=9.837$, p =<.001, n_2= .381. Paired t-tests revealed no significant difference in RT between Baseline and Post-stimulation. However, RTS were significantly shorter p =.029 between Baseline (*M*=.800sec, *SE*=.080) and 24hrs Post-stimulation (*M*=.500sec, *SE*=.035) and between Post-stimulation p =.001 (*M*=.897sec, *SE*=.064) and 24hrs Post-stimulation (*M*=.500sec, *SE*=.036). There were no significant main effects of Matched Neutral words $F(3, 28) = .498$, p = .68, n_2= .030 or interactions with Time and Matched Neutral words $F(6, 96) = .390$, p = .884, n_2= .024.

Participant 004

STAI

Participant 004's baseline STAI score was 50. Post Active GVS his anxiety score reduced to 37, and at 24hours post Active GVS on day 2 his STAI score was slightly reduced from baseline to

47. From this score a further reduction in STAI scores was observed post Sham to 35 and at 24hours post Sham scores were further reduced to 34. (see Figures 5.1 & 5.2).

SRT

The one-way ANOVAs for the SRT failed to reach significance in the Active GVS condition $F(2, 78) = .472$, $p = .625$, $n_2 = 012$. In Sham there was a significant effect $F(2, 78) = 3.452$, $p = .037$, $n_2 = 081$. Paired T-tests failed to reach significant values between any Time points. However, there was an apparent trend towards shorter RTs post Sham (*M*=.249 *SD*=.036) and at 24hours post Sham (*M*=.246 *S* =.060) compared to baseline (*M*=.297 SD=.082).

EST ANOVAs for Target words

The EST ANOVA in the Active GVS condition showed no significant main effect of Time $F(1.722, 63.779) = 2.347$, $p = .110$, $n_2 = 061$. However, in the Sham condition a significant main effect of Time $F(2,70)=4.270$, $p =.018$, $n_2 = .109$ was evident. Paired t-tests showed significantly longer RTs $p =.041$ from Baseline (*M*=.609sec, *SE*=.028) to Post-stimulation (*M*=.698sec, *SE*=.025). There were no significant differences between Baseline and 24hrs Post-stimulation $p= 1.00$. Yet, significantly shorter RTs $p =.022$ were evident between Post-stimulation (*M*=.689sec, *SE*=.025) and 24hrs Post-stimulation (*M*=.610sec, *SE*=.028). There were no significant main effects of Target words $F(3, 105) = 1.467$, $p = .228$, $n_2 = 040$ and the interaction between Target words and Time $F(6, 210) = .565$, $p = .758$, $n_2 = 016$ failed to reach significance.

EST ANOVAs for Matched Neutral words

The ANOVAs for RTs to Matched Neutral words in Active showed no main effect of Time $F(2, 72) = .934$, $p = .398$, $n_2 = .025$. Main effects of Matched Neutral words $F(3, 108) = .942$, $p = .423$,

n_2= .025 and interactions between Time and Matched Neutral words $F(5.33, 192.003) = 1.019$, $p = .410$, n_2= .028 also failed to reach significance. In the Sham condition there were also no significant $F(62, 72) = 1.127$ $p = .330$, n_2= .030 effects of Matched Neutral words $F(3, 108) = .528$, $p = .664$, n_2= .014 or interactions between Matched Neutral words and Time evident $F(6, 216) = .760$, $p = .602$, n_2= .021.

Participant 005

STAI

Participant 005 had a baseline STAI score of 35, post Active GVS his score increased to 36 and 24hours post Active stimulation his STAI score elevated further to 49. From this score on day 2 his STAI score reduced post Sham to 40. At 24hours post Sham a STAI score of 41 was evident (see Figures 5.1 & 5.2).

SRT

One-way ANOVAS for the SRT failed to reach significance in both Active $F(2, 78) = .332$, $p = .718$, n_2=.008 and Sham $F(2, 78) = 2.638$, $p = .078$, n_2= .063 GVS conditions.

EST ANOVAs for Target words

In the Active stimulation condition a significant main effect of Time $F(2,52)=6.616$, $p =.003$, n_2= .203 was evident. Paired t-tests showed no significant differences in RT between Baseline and Post-stimulation. However, RTs between Baseline (M=.873sec, SE=.045) and 24hrs Post-stimulation (M=.600sec, SE=.060) were significantly shorter $p =.008$. Significantly shorter RTs $p =.008$ were also evident between Post-stimulation (M=.871sec, SE=.061) and 24hrs Post-stimulation (M=.600sec, SE=.060). There were no significant main effects of Target words $F(3,$

78) = .534, p = .661, n_2= .020 or interactions between Target words and Time F(6, 144) = .558, p = .763, n_2= .040.

In the Sham GVS condition there was also a significant main effect of Time F(2,60)=9.239, p = <.001, n_2= .235. Paired t-tests showed a significantly longer in RTs p = .024 between baseline (*M*=.593sec, *SE*=.053) and post-stimulation (*M*=.784sec, *SE*=.039). RTs were also significantly longer p = .006 between Baseline (*M*=.593sec, *SE*=.053) and 24hrs Post-stimulation (*M*=.935sec, *SE*=.073). There were no significant differences between Post-stimulation and 24hrs post Stimulation. Target words F(3, 90) = 1.042, p = .378, n_2= .034 and interactions between Target words and Time F(6, 180) = .311, p = .931, n_2= .010 also failed to reach significance.

EST ANOVAs for Matched Neutral words

In the Active stimulation condition a significant main effect of Time F(2,48)=12.443, p =.001, n_2= .341 was evident. Paired t-tests showed no significant differences between Baseline and Post-stimulation. However, a significantly shorter RTs p =.001 between Baseline (*M*=.927sec, *SE*=.054) and 24hrs Post-stimulation (*M*=.604sec, *SE*=.061); also between Post-stimulation (*M*=.881sec, *SE*=.044) and 24hrs Post-stimulation (*M*=.604sec, *SE*=.061). There was no significant main effect of Matched Neutral words F(3, 72) = 1.059, p = .372, n_2= .042 or interactions between Matched Neutral words and Time F(6, 144) = .558, p = .763, n_2= .023.

In the Sham GVS condition RTs to Matched Neutral words showed a significant main effect of Time F(2,50)=8.988, p =.001, n_2= .264. Paired t-tests revealed significantly longer RTs p =.010 between Baseline (*M*=.602sec, *SE*=.059) and 24hours Post-stimulation (*M*=.973sec, *SE*=.079), also between Post-stimulation (*M*=.751sec, *SE*=.050) and 24hrs Post-stimulation (*M*=.973sec,

SE=.079). There were no significant main effects of Matched Neutral words $F(3, 75) = 1.013$, $p = .392$, $n_2 = .039$ and no significant interactions between Matched Neutral words and Time $F(4.430, 110.761) = .945$, $p = .447$, $n_2 = .036$.

Participant 006

STAI

Participant 006 showed a Baseline STAI score of 57. Post Sham GVS his STAI scores decreased to 51. On day two of testing 24hours post Sham his STAI score was reduced from baseline to 52. Post Active GVS on day two, his STAI score increased to 54 and 24 hours post Active GVS a further increase to 57 was observed (see Figures 5.1 & 5.2).

SRT

ANOVAs for the SRT in both Active and Sham stimulation showed no significant effects in either Active $F(1.503, 58.625) = 1.296$, $p = .275$, $n_2 = .032$ or Sham $F(2, 78) = .552$, $p = .578$, $n_2 = .014$ GVS conditions.

EST ANOVAs for Target words

In the Active stimulation condition a significant main effect of Time $F(2,62)=13.799$, $p = <.001$, $n_2 = .308$ was evident. Paired t-tests indicated no significant differences in RTs between Baseline and Post-stimulation. However, significantly longer RTs were evident $p = <.001$ between Baseline (*M*=.497sec, *SE*=.033) and 24hrs Post-stimulation (*M*=.743sec, *SE*=.043). There were also significantly longer RTs $p = .006$ between Post-stimulation (*M*=.583sec, *SE*=.030) and 24hrs Post-stimulation (*M*=.743sec, *SE*=.043). Target words showed no significant main effect $F(3, 93) = .468$, $p = .705$, $n_2 = .015$ and there was no significant interaction between Target words and Time

F(4.064, 125.988) = .330, *p* = .860, n_2= .015. In the Sham stimulation condition ANOVAs for the Target words RTs failed to reach significance *F*(1.674, 48.542) = 3.064, p = .064, n_2= .096.

EST ANOVAs for Matched Neutral words

In the Active GVS condition a significant main effect of Time *F*(2,48)=11.544, *p* = <.001, n_2= .325 was evident. Paired t-tests indicated no significant differences in RTs between Baseline and Post-stimulation *p* =.111. However, significantly longer RTs *p* =.001 were apparent between Baseline (*M*=.474sec, *SE*=.042) and 24hrs Post-stimulation (*M*=.767sec, *SE*=.059). RTs were also significantly longer *p* =.025 between Post-stimulation (*M*=.576sec, *SE*=.034) and 24hrs Post-stimulation (*M*=.767sec, *SE*=.059). There was no significant main effect for Matched Neutral words *F*(3, 72) = 2.349, *p* = .080, n_2= .089 or significant interactions between Matched Neutral words and Time *F*(6, 144) = .503, p = .805, n_2= .021 evident.

The ANOVA for Sham GVS *F*(1.477, 42.847) = 3.835, *p* = .043, n_2= .117 showed a significant main effect of Time. Paired t-tests revealed no significant differences in Time between Baseline and Post-stimulation *p* = .100 or Baseline and 24hours Post-stimulation *p* = .127. However, significantly *p* = .009 shorter RTs between Post-stimulation (*M* =.605 SE =.057) and 24 hours Post-stimulation (*M* = .485, SE=.049). There were no significant main effects of Matched Neutral words *F*(3, 87) = .490, p = .690, n_2= .017 or interactions with Matched Neutral words and Time *F*(4.428, 128.420) = 1.447, *p* = .218, n_2= .048.

Discussion

In Chapter 4 GVS was shown to reduce cortical hyperexcitability of the motor cortex at 24hours post-stimulation. In the current study I therefore predicted that firstly, GVS would have an inhibitory effect on the symptoms of anxiety and lower STAI scores. Secondly, I predicted that GVS would shorten reaction times to the EST by reducing attentional bias to emotionally relevant words; and thirdly reduce reaction times in the SRT at 24hours post GVS. These predictions were not met. Four out of the five veterans showed an increase in current anxiety symptoms 24hours post active stimulation. Additionally, the SRT indicated that GVS was not effective in reducing RTs at 24 hours post active stimulation. There was some evidence that GVS shortened RTs in the EST, but only in participants 001 and 005. By contrast, in participants 003 and 006 GVS lengthened RTs in the EST at 24hours post-stimulation compared to sham condition.

One explanation for the increase in anxiety seen in the STAI scores is that although GVS induced an inhibitory effect on the motor cortex at 24hours post stimulation, an excitatory effect may have occurred in the frontal lobes. This idea is based on an fMRI study by Kilinger et al., (2012), that shows hemodynamic evidence of caloric vestibular stimulation (CVS) in neurologically healthy individuals deactivating BOLD signals to the pre and post central gyrus, and yet activating BOLD responses to the frontal, pre-hippocampal and temporal gyrus; temporoparietal cortex and hippocampus. This upregulation from CVS was evident in areas associated with response inhibition, executive function and mood disturbance (Hoffmann, 2013; Kilinger et al., 2012). This type of upregulation or cortical hyperexcitability is known to exert a great influence on mood state and is associated with greater mood disturbance as well as GABA network dysfunction (Bolden et al., 2019). On a cautionary note, the fMRI evidence from Kilinger et al., (2012) was attained immediately after CVS and not at 24hours post-stimulation. It is therefore not known if same

patterns of activation would have occurred from GVS at 24hours post-stimulation. Nonetheless, this may provide a tentative explanation for why anxiety increased in all of the participants.

The effects of GVS in the EST were mixed, only two participants showed a reduction in RTs to negative versus positive words. Additionally, the predicted Stroop effects were not evident as combat words showed no significant differences in RTs compared to any other word group before or after GVS. This was surprising, as anecdotally all participants described the combat words used as "*unnerving"* and contributory to sleep disturbance. However, a review of 12 studies using the modified Stroop effect from Kimble, Fruech & Marks, (2009) revealed that using trauma related words had only resulted in delayed reaction times in 8% of participants with PTSD. They conclude that whilst these ratios are much lower than those of other peer reviewed literature, only 44% of controlled studies have shown a modified Stroop effect and propose a re-evaluation of the test is warranted in the case of PTSD. A further limitation of the EST in this study was the lack of a trauma control group to allow separation. Compared to controls there may well have been a significant difference in reaction times specifically to combat words.

In the SRT shorter reaction times were observed in one participant at 24hours post sham and in contrast slower responses were observed at 24hours post active GVS. There was no evidence of GVS affecting the SRT in any other participants. This investigation into the effects of GVS on motor cortex excitability is novel, and it is therefore unknown what level of motor cortex inhibition is needed to drive clinical change. It is plausible that more sessions of stimulation may be required to induce clinical effect. Evidence to support this idea has come to light via personal communication from Wilkinson (2019) whereby several sessions of vestibular stimulation have been shown to affect mood. Here thirty-three patients with Parkinson's disease received 25minutes

of twice daily CVS over eight weeks. All showed improvements in the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and the Non-motor Symptom Scale, which measures mood, sleep, fatigue, and cognition (Chauduri et al., 2007). All improvements exceeded minimal clinically important differences, and the most noticeable improvements from baseline were evident at one-month follow-up. The increase of current anxiety symptoms as a result of GVS seen in the current study and evidence from Wilkinson (2019), highlights an intrinsic relationship between the vestibular system and affect on mood. Vestibular dysfunction is well known is closely associated with both anxiety disorders and depression (Smith et al., 2018) but this relationship is reciprocal as its also known that anxiety can drive vestibular disturbance (Yardley, 1995). The defuse cortical connections from the vestibular nuclei to the HPA axis may well provide an appropriate pathway that can be modulated to affect autonomic function and mood (Dodson, 2004, Pettigrew & Miller, 1998; Preuss; Hasler &Mast, 2014). The mood changes seen in the present study were specifically related to GVS. As the increase in anxiety symptoms was only present at 24hour post-GVS compared to lower STAI scores 24hours post-sham, which illustrates a modulated influence via the vestibular pathways.

There were a number of limitations in the current study. The short window for data collection limited the use of available psychiatric assessments forcing the focus only on current anxiety. This also prevented the use of several sessions of GVS; which in light of Wilkinson (2019) where psychiatric symptoms were reduced after daily stimulation for two months highlight a need to extend the testing protocol. This would allow for a more comprehensive test battery that can detect change in symptomology when individuals have returned to their everyday life and home environment. All participants reported that they were fatigued and suffered from sleep disturbance during participation of the study. The nature of their PTSD symptoms had a large impact on their

participation, which caused significant stress to all five veterans. This stress was attributed to four factors: 1) travel, 2) crowds of people on the university campus, 3) using hotel accommodation and 4) combat related words from the EST. Combat related words were reported by all participants to have caused some distress, for some a consequence this was the induction of flashbacks and nightmares. One participant also needed to use public transport to reach the university and suffered two severe panic attacks. All of these factors combined may well have had adverse effects on the study results.

In conclusion, this study showed that GVS induced an increase in current anxiety symptoms at 24hours post stimulation. At the very least, this evidence reaffirms the intrinsic relationship between the vestibular and limbic systems, even if the therapeutic value is not yet clear. Future research should aim to reduce environmental stress for participants and introduce several sessions of GVS to promote stronger physiological change and accommodate a broader psychiatric and wellbeing test battery that is sensitive to change over a longer period of time.

Chapter 6

General Discussion

"All actions have a physical origin" (Baize, 2011. *p*55)

Currently, the impact of mTBI on long-term mental wellbeing in UK military veterans is poorly understood. Previous estimates of mTBI in UK military personnel on deployment are between 3.2% and 13.5% (Hawley et al., 2014; Jones et al., 2011; Rona et al., 2012), compared to 15% and 23% in the US (Hoge et al., 2008; Terrio et al., 2009). Symptoms of dizziness have frequently been reported however, the effect of vestibular disorder on the neuropsychiatric sequalae of mTBI have been overlooked (Harber et al., 2016; Terrio et al., 2009). This thesis has examined the impact of vestibular injury on the neuropsychiatric symptoms of mTBI, and also examined the utility of the vestibular system as a therapeutic pathway for treatment of mTBI.

Summary of the Findings

In Chapter 3, 162 UK military veterans receiving treatment for PTSD at Combat Stress completed a broad range of validated self-report questionnaires that probed lifetime history of mTBI, neuropsychiatric symptoms and general disability. The results revealed that the prevalence of mTBI in these UK military veterans was much higher than previous estimates suggest, with 72% reporting one or more mTBI in their lifetime. Repeated mTBI affected 49% of these UK veterans who indicated periods in their life when they had sustained repeated concussions. Exposure to blast also constituted a significant potential health risk, such that 81% of veterans who participated in the study had been exposed to blast. 50% of these exposures resulted in mTBI and 53% of this subgroup reported three or more blast mTBIs in their lifetime.

Vestibular disturbance was seen frequently in UK veterans with a history of mTBI. Chi-square analyses indicated that vestibular disturbance affected 69% of the sample that had sustained one or more mTBI. Here vestibular disturbance was equally prevalent following blunt (59%) and blast (47%) injuries, but was even more frequent in blunt and blast injuries combined (83%). The neurobehavioural impact of vestibular dysfunction was clearly evident in the mediation analysis conducted on this samples data. This revealed that vestibular disturbance was singularly predictive of the chronic neurobehavioral symptoms of mTBI and disability independent of its influence on psychiatric symptoms. The interplay between vestibular disturbance and psychiatric symptoms also showed that the vestibular system exerts a strong influence on PTSD, depression and anxiety. In fact, the symptoms of dizziness combined with those of mTBI, PTSD, depression and anxiety comprised a particularly harmful combination within this sample of UK veterans who were more debilitated than 90% of the general international population. Together these scores highlight the need to introduce mandatory vestibular screening for veterans and to innovate more effective treatment interventions for mTBI.

In Chapters 4 and 5 I sought to identify a means by which vestibular links to cognition and emotion could be therapeutically harnessed. GVS had been previously shown to induce lasting amelioration of hemi-spatial neglect (Wilkinson, 2014), this combined with the findings of neuroimaging studies which show wide spread activation patterns may indicate that GVS is inducing neuroplastic change (Stephan et al., 2005; 2009). To this end, in Chapter 4 I sought evidence that GVS can induce an LTP or LTD type effect (as measured by recording MEP up to 24hours post-stimulation). If a marker of LTP or LTD could be found, this would then inform an attempt to remediate either the positive or negative symptoms of mTBI in Chapter 5. The evidence presented in Chapter 4 suggested that individuals who demonstrate cortical hyperexcitability at baseline, show an LTD-

type effect at 24hours post-stimulation after one session of ~1mA DC GVS. As a consequence, this waveform was then utilised in Chapter 5 to determine via a series of case studies if GVS might provide therapeutic remediation of anxiety. I chose to target symptoms of current anxiety as a main outcome measure, firstly, because it is a commonly seen symptom in veterans with mTBI and is associated with cortical hyperexcitability, but also because it was possible to measure changes in mood in a short time frame (Centonze et al., 2005). The results revealed that GVS did influence mood. However, this influence did not reduce current symptoms of anxiety, but instead exacerbated them. This experiment confirmed the intrinsic relationship between the vestibular and limbic systems. But it also showed that while GVS might have inhibitory effects on the motor cortex it may well have an excitatory effect in other brain regions (Kilinger et al., 2012). Further study is required to provide a clearer mechanistic account.

The Theoretical and Clinical Implications of Vestibular Influences in mTBI and PTSD

Psychological combat trauma and exposure to blast are known to pose a substantial risk of sustaining a mTBI and developing PTSD (Kamnaksh et al., 2011). The symptoms of mTBI, PTSD and vestibular dysfunction share many distinct clinical features (Rosenfeld et al., 2013; Smith et al., 2018) and the substantial overlap in symptomology has made it difficult to distinguish between the conditions. Previous research on UK military personnel has suggested that the symptoms of PCS are not specific which may have resulted in vestibular and neurological deficits being attributed to psychiatric disturbance (Fear et al., 2014). This misattribution is particularly worrying because the repercussions of blast overpressure trauma are significant and can lead to large scale cerebrovascular pathology in adults (Chen et al., 2013). Blasts also frequently result in secondary blunt head injuries and tympanic membrane perforation in approximately 50% of adults (Chandler & Edmond, 1997). Damage to the inner ear resulting from blast exposure is commonly seen (Fausti

et al., 2009) and this raised the possibility that vestibular pathology may be partly driving the symptoms of mTBI and exacerbating the symptoms of PTSD. Evidence for this possibility can be seen in the mediation analysis of this thesis which shows a directional direct association between vestibular disturbance and neurobehavioural outcomes in mTBI and indirectly on PTSD. Further albeit unwelcome evidence seen in Chapter 5 where GVS was shown to exacerbate mood also demonstrates how the vestibular system exerts a significant influence on the ascending pathways that are integral to psychiatric disturbance (Balaban & Porter, 1998; Balaban & Thayer, 2001).

The means by which frequently seen psychiatric disturbance occurs relates to a reciprocal relationship between somatopsychic and psychosomatic mechanisms that involve both the vestibular system and HPA axis (Jacob and Furman, 2001). Symptoms of dizziness can cause autonomic hyperarousal and severe disequilibrium which evoke a sense of fear, losing control and panic (Balaban & Porter, 1998; Balaban & Thayer, 2001). The role of stress in human vestibular disorders is complex and lacks definitive evidence. Stress responses evoked by vestibular symptoms can promote synaptic and neuronal plasticity in the vestibular system. However, evidence for this is mainly reliant on animal models where both electrical and caloric stimulation of the vestibular pathways has resulted in a response in the PVN of the hypothalamus (Azzena et al., 1993; Liu et al., 1997; Horii et al., 2001; Markia et al., 2008). Stress responses mediated by the HPA axis involves the release of corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) hormones from the PVN and the release of adrenocorticotropic hormone (ACTH) from the pituitary gland which then causes the release of glucocorticoids from the adrenal cortex (Herman et al., 2003). This response may well regulate the function of ion transporters and ionic homeostasis of the inner ear (Hamid et al., 2009) and demonstrates a bidirectional relationship between the vestibular system and the HPA axis. This idea is further supported by

evidence from Haber et al., (2016) where veterans with worse dizziness handicap and VSSL scores showed greater severity of PTSD symptoms. Furthermore, the symptoms of dizziness have been suggested by Staab et al., (2003) to precipitate anxiety and phobic avoidance resulting in a vicious cycle that causes chronic disability. An idea that is also supported by the significant levels of long-term disability and the direct influence of the vestibular system on disability irrespective of psychiatric symptoms seen in the mediation analysis of Chapter 3. The distinct overlap between mTBI, PTSD and vestibular pathology has previously muddied the waters when trying to differentiate between this set of non-specific symptoms (Fear et al., 2014). What is clear, is that there is an intrinsic bio-directional link between the vestibular system and HPA axis (Mazurek et al., 2010; Paterson et al., 2004; Seemungal et al., 2001; Straka et al., 2005).

The significant long-term levels of disability, high prevalence rates of mTBI and the pervasive influence of the vestibular system seen in the UK military veterans of this thesis, highlights that mTBI and vestibular dysfunction should be taken more seriously in the UK and that veterans' symptoms should not just be attributed to PTSD. Not only was the prevalence of mTBI in line with estimates of US veterans at 72% (McGlinchey et al., 2016). But approximately half of the veterans in Chapter 3 reported periods in their life where they had sustained repeated mTBI. This highlights a need to evaluate mTBI in a lifetime context, as the repeated nature of blunt and blast mTBI has been posited to increase the subsequent incidence of chronic cognitive decline and neurodegenerative conditions through the course of aging (Faden & Loane, 2015). Cognitive decline can also be seen in the symptoms of vestibular dysfunction that can cause difficulties with concentration and memory (Smith et al., 2018), which can significantly impact on functional status, quality of life and the ability of individuals to return to work (Chamelian et al., 2004; Hillier, Sharpe & Metzer, 1997). Recently, evidence has emerged from a large-scale study of 2318 UK

military personnel who were deployed to the conflicts in Iraq and Afghanistan; and shows at a seven-year follow-up individuals who sustained a mTBI were more likely to suffer from dizziness and loss of concentration, than personnel who sustained other injuries or no injury at baseline (Rona et al., 2019). This potentially demonstrates the pervasive nature of vestibular dysfunction which can frequently result in devastating consequences in terms disability. Interestingly, of the original 4601 eligible participants at baseline, individuals who had suffered a mTBI or had alcohol misuse problems, were considered as less likely to complete the follow-up study survey which potentially may indicate that they have ongoing problems that have also not received treatment.

Social and Clinical Barriers to Vestibular Assessment and Treatment

Currently, the UK armed forces do not screen for mTBI, PTSD or vestibular symptoms on deployment. However, monitoring head injury in an operational combat arena is problematic. Sometimes the acute symptoms of concussion are brushed off or overshadowed by the combat situation. Symptoms can also be concealed by emotional distress (Hodge et al., 2008). The ability to display psychological resilience when faced with extreme adversity is highly valued in military communities. On deployment higher levels of PTSD and/or greater combat exposure has been associated with UK soldiers endorsing higher rates of stigma, which can cause barriers to help seeking behaviour (Osorio et al., 2012). UK service personnel have been shown to view suffering from physical illness as more legitimate than having mental health problems (Greenberg et al., 2003), even reporting stress has been viewed as potentially having adverse effects on promotional prospects, and a fear of peers holding negative attitudes (Langston et al., 2010). Research from Combat Stress suggests that it takes veterans an average of 14years after leaving the armed services before they seek help for PTSD (Murphy & Busutti, 2014). These factors coupled with front line medicine needing to prioritise treatment for life-threatening injuries can frequently result in mTBI

going unreported. It has been estimated by Farmer et al., (2014) that of the 220,550 British troops who were deployed to Iraq and Afghanistan between 2001-14 as many as 75,000 may have been left sick or psychologically harmed as a result of the conflict and many will never seek help. More recently, 17% of veterans who served in a combat role during the Iraq and Afghanistan conflicts have endorsed symptoms of PTSD, a significant rise from the figures of 2004 where military PTSD was at 4% which highlights a growing concern for our veterans (Greenberg et al., 2008; Stevelink et a., 2018).

During mass casualty events the priority of treatment must be to save lives. However, Scott et al., (2006) suggest that polytrauma patients with blast related injuries in mass casualty events have sensory impairments such as hearing loss, tinnitus, vision changes and vestibular problems that get frequently overlooked. Estimates suggest that dual sensory impairment has been sustained in 35% of US soldiers with blast TBI (Lew et al., 2001). Furthermore, computerised dynamic post-urography testing of 322 US veterans by Walker et al., (2018), suggests that veterans with a lifetime history of three or more mTBI show worse symptoms of imbalance than those who suffered 1-2 mTBI.

The results of this thesis suggest that veterans presenting with disequilibrium at a GP level should be screened for vestibular dysfunction. Fife and Fitzgerald (2005) suggest that in the case of conditions such as BPPV (which has a long association with blast exposure), it can take an average of 93 weeks for a first specialist referral appointment to receive a diagnosis and then subsequent treatment within the NHS. More recently Smith et al., (2018) suggested that this problem has worsened as referral to a neuro-otologist with East Kent NHS can now take up to two years. This is particularly worrying as it means that veterans with vestibular disorder could be going

undiagnosed. But Fife and Fitzgerald (2005) suggest that 85% of the patients that presented with classical BPPV symptoms, could have been diagnosed by their GP if adequate awareness was in place. All too frequently a diagnosis relating to vestibular dysfunction is missed. Research from Polensek et al., (2008) supports this idea as only 11% of health care providers were shown to evaluate patients with the appropriate diagnostic tests. Polensek et al., (2008) suggests that when patients report symptoms of dizziness/light-headedness or complain of nonspecific "spells", family practitioners and emergency physicians look to cardiovascular testing. While this is an appropriate approach for disequilibrium, it misses a diagnosis such as BPPV. Similarly, referral to a neurologist can result in CT or MRI scans which are expensive and have no diagnostic value in patients with isolated BPPV (Belanger et al., 2007; Dash et al., 2010; Polensek et al., 2009). Frustratingly, symptoms of dizziness are frequently present in chronic mTBI and can be diagnosed relatively easily with the Dix-Hallpike manoeuvre at a primary care level if physicians have received the appropriate training (Polensek et al., 2008; 2009).

The Next Steps for Treatment of mTBI, PTSD and Vestibular disorder

The next steps towards helping veterans with mTBI and PTSD should be to introduce vestibular and mTBI screening at a GP level. The results of this thesis suggest that GPs should consider a vestibular diagnosis when patients with dizziness, depression, anxiety, memory loss and headache present. These symptoms may have arisen as a result of mTBI and this should be taken into account by attaining a lifetime history of mTBI. Currently, measures such as the OSTIM, dizziness handicap inventory and the vertigo symptom scale provide a reliable metric to assess a lifetime history of mTBI and to detect potential vestibular pathology (Corrigan & Bogner, 2007; Jacobson & Newman, 1990; Yardley et al., 1992). However, these measures are time consuming to administer and whilst reliable may not be practical for GPs who only have a few minutes to spend

with each patient. To this end, it is suggested that a new screening measure should be developed that can briefly screen for mTBI history, blast exposure, dizziness, psychiatric symptoms, headaches, sleep disturbance and memory problems that can be administered in just a few minutes. This would also help to facilitate a new standardised care pathway where referral to a neuro-otologist can be made and the appropriate treatments could be administered. Given the interconnectability of the vestibular system shown in this thesis, one can assume that if you treat the symptoms of imbalance, improvements will be seen across a broad range of symptoms that accompany mTBI and PTSD. As mentioned in Chapter 2 the use of vestibular rehabilitation (VR) therapy, in 75 US veterans with mTBI and PTSD resulted in improvements of Clinician Administered DSMIV PTSD Scale (CAPS) scores (Carrick et al., 2015). VR therapy has also showed improvements in balance, PCS symptoms, quality of life, anxiety and depression in a series of four case studies of US veterans with mTBI and not PTSD (Kleffelgaard et al., 2016). Future research should further investigate the efficacy of VR therapy in mTBI as it is already available with the NHS for the treatment of imbalance, but may also prove beneficial in treating mTBI sequalae.

The Mechanistic Basis of GVS

In Chapter 4 of this thesis, I examined the mechanistic basis of GVS by measuring its effect on motor cortex excitability. Identifying a mechanism of effect enabled me to target either positive or negative symptomology in Chapter 5. Two different doses of GVS were employed. The first involved 10minutes of .35mA AC. This dose had previously been shown in neurologically healthy individuals to influence audio-motor synchronisation and thereon enhance beat perception (Scmidt-Kassow, Wilkinson, Denby & Ferguson, 2016). In the present study this low amplitude of current, showed no significant difference in MEP amplitude between the active and sham

stimulation conditions at up to 30min post-stimulation. It is possible that such a narrow time window for post-stimulation MEP measurements prevented me from detecting change. The second dose consisted of 25 minutes 1mA DC GVS which had previously been shown to be clinically efficacious in ameliorating hemi-spatial neglect (Wilkinson et al., 2014). The initial statistical analysis showed no significant changes in MEP amplitudes between the active and sham control group. However, subsequent exploratory analysis revealed that individuals in the active stimulation condition with high levels of cortical excitability at baseline showed a significant reduction in cortical excitability at 24hours post stimulation compared to controls.

This late phase inhibitory effect is indicative of LTD which is typically mediated via the release of GABA (Vallance & Ridding, 2014), a finding that lends itself to normalizing dysfunctional homeostatic plasticity in PTSD (Centonze et al., 2005; Machado et al., 2011). The means by which this inhibitory effect occurred might be explained by the vestibulosympathetic reflex this type of homeostatic response is autonomic and regionally selective (Balaban, 1999). Here, vestibular stimulation activates the midbrain and pons; and Halberstadt and Balaban (2006) report that the same neurons involved in serotonin release in the dorsal raphe nucleus (DRN) send projections to the brain stem and vestibular nucleus. The projections from the DRN are widespread and many transmitters are secreted here including cortico- releasing factor (CRF) and GABA (Gervasoni et al., 2000; Michelsen et al., 2008; Samoudi et al., 2012). The DRN plays a major role in the regulation of neuroplasticity and is known to be involved in learning, memory and affect. Definitive evidence is still lacking however, it is plausible that GVS may have elicited these inhibitory responses in light of the reduced amplitudes of MEP. The late phase alterations seen in Chapter 4 share physiological similarities to LTD obtained from animal slice preparation experiments. However, excitability monitoring via MEP amplitudes does not uncover all aspects

of LTD as it only accounts for the motor cortex, it is possible that GVS may also induce LTP in alternative brain regions (Kilinger et al., 2012).

As evidenced throughout this thesis, the vestibular system exerts a significant influence on the ascending pathways that are integral to anxiety (Balaban, 2002; Balaban & Porter, 1998; Balaban & Thayer, 2001). These excitatory networks are intrinsically linked to the HPA axis and yet the inhibitory effects of GVS seen in the motor cortex at 24hours post stimulation did not cause a reduction in anxiety symptoms as predicted. Instead, GVS increased STAI scores. Although counter to my prediction, this does suggest that GVS interacted with the HPA axis. As stated in the discussion of Chapter 5, one reason for this might be that there was an inhibitory effect to the motor cortex and excitatory effects to frontal, hippocampal and temporal regions (Kilinger et al., 2012), which are associated with executive function and mood disturbance (Hoffmann, 2013; Kilinger et al., 2012). Against this explanation, these effects were evident immediately after stimulation and I was unable to find evidence of hemodynamic change 24hours later. The exacerbation of anxiety observed may well have influenced the slowing of responses to the SRT task in one participant, but with no detectable effects in the other case studies it is difficult at this stage to link the type and level of inhibition with a clear clinical correlate.

Further investigation in to the therapeutic effects of GVS is nevertheless still warranted. As in contrast to the findings of this thesis, recent research has shown a single session of 1mA GVS lasting 38 minutes can reduce current anxiety symptoms immediately after stimulation, in 22 neurologically healthy adults (Pasquier et al., 2019). Whilst the amplitude used in this study was the same as that used on the veterans in Chapter 5, the duration of stimulation was longer which highlights the need for further dose manipulations to better understand the utility of GVS as a

therapeutic tool. Further support for this idea can be drawn from evidence of GVS reducing the symptoms of imbalance using low amplitude optimal intensities of DC GVS. Improvements in postural stability have been noted in healthy subjects and in patients with bilateral peripheral vestibular dysfunction using low amplitude mean optimal intensities of 281 μA DC GVS (Iwaski et al., 2014). Here 76% of 21 healthy subjects and 91% of the 11 patients showed significant improvements in postural stability in three two-legged stance tasks, that were performed with eyes closed. Support for this was also evident in 13 patients with bilateral peripheral vestibular dysfunction up to six hours post stimulation using a mean optimal intensity of 455 μA DC GVS for 30minutes in two sessions of stimulation day one and 14 days later (Fujimoto et al., 2018). GVS has also been shown to improve body balance in elderly adults (Fujimoto et al., 2016), with a mean optimal intensity of 178 μA DC GVS in two sessions lasting thirty minutes and 3hours.

Clearly, GVS can induce a range of effects that are dependent on dose manipulation. For instance, Wilkinson et al., (2017) used 25minutes of CVS twice daily over eight weeks using pre-programmed devices resulting in an immediate and steady decline in episodic migraine frequency, compared to (placebo) controls. It should be noted that this was the same dose that correspondence from Wilkinson (2019) reported had reduced symptoms of anxiety and depression in patients with Parkinson's disease at one-month follow-up. Providing vestibular stimulation over longer periods of time may well be beneficial not only because it provides a larger time window to examine the effects of GVS but potentially it would facilitate detecting change in mTBI and PTSD symptomology. It is suggested that future research should aim to provide pre-programmed GVS devices, allowing treatment to take place in the patient's home over a longer period of time. This would accommodate a research design that would examine various dose manipulations and enable the use of a broader cognitive test battery, monitoring of PTSD, mTBI, headaches, depression and

anxiety symptoms over time. A test battery conducted over three months with a one-month follow-up, would provide a more sensitive and practical method of treatment for individuals with mTBI and PTSD.

Taking the approach to treatment that GVS offers, could potentially tackle the underlying mechanisms of injury and may well be advantageous for many reasons. Firstly, GVS is a simple and cost-effective procedure. Unlike VR therapy which requires lengthy treatment sessions three times a day for two weeks (Carrick et al., 2015), GVS could be delivered in pre-programmed portable devices can be delivered to patients in their homes. Secondly, it is well known that the stigma associated with neuropsychiatric disorders in the Armed Forces can deter individuals from seeking much needed help (Greenberg, Langston & Jones, 2008). Therefore, treating brain injuries and PTSD in this modality may lessen perceived stigma and enhance potential treatment outcomes that will be of benefit for both the patients and their families.

Limitations

The insights attained from this thesis are subject to several limitations, many of which have been highlighted in the previous empirical chapters. One overriding concern is in relation to the distinct overlap of mTBI, PTSD and vestibular symptomology. The data acquired for this thesis contrasts with previous research on serving UK military personnel which suggests the symptoms of PCS are not specific and instead PCS is attributed to psychiatric disturbance (Fear et al., 2009). Associations here were shown between blast, depleted uranium exposure, aiding the wounded and PCS symptomology. It should also be noted that the research from Fear et al., (2009) did not use validated self-report questionnaires and the regression analysis employed did not provide causal pathways to mediate for psychiatric disturbance influencing PCS, unlike the research of this thesis.

This overlap in symptomology is nonetheless undeniable and clearly the sample of veterans in this thesis were suffering from significant psychiatric problems.

The reliance on self-report questionnaires was also a considerable limitation of this thesis. Indeed, the results of the MCI confirm this, as approximately half of the sample demonstrated symptom exaggeration. However, it should be noted that vestibular dysfunction causes severe disequilibrium and is associated with high rates of depersonalization/derealization, difficulty focussing attention, memory problems and blurred thoughts (Smith & Darlington, 2013). Accordingly, it is therefore possible that veteran's perception of actual memory impairment is at odds with measures that examine malingering. Nonetheless, the use of self-report questionnaires did limit the findings as they cannot determine a diagnosis, are subject to responder bias and only provide an initial limited evaluation. Arguably responses may have been narrow and it is possible that veterans only indorsed the most obvious or noticeable symptoms. Equally, self-report measures are known to be inherently biased by the participants mental state at the time of participation (Kampmann, Emmelkamp and Morina, 2018). As this sample of veterans were undergoing therapy it is plausible to assume that many individuals were in a particularly negative mindset which may have biased their responses. Using clinician-rated scales in a structured psychiatric interview may have gleaned more insight into symptomology when veterans are in their typical home or work environments; and not faced with revisiting emotionally traumatic experiences in therapy. Conducting psychiatric interviews might have offered a more objective perspective and would have also provided an opportunity for me to attain training and greater expertise in neuropsychiatric assessment.

The results seen in Chapters 4 and 5 indicate that artificial stimulation of the vestibular system induced inhibitory effects on cortical hyperexcitability and an increase in anxiety symptoms at

24hours post-stimulation. A significant limitation of this data is that TMS evoked MEPs measured via peripheral muscles, arguably provide a very narrow view of cortical responses and fail to account for excitatory processes occurring elsewhere. One way this problem could be tackled is to employ the use of the electroencephalograph (EEG). This would enable an accurate measurement of brain wide cortical reactivity via oscillatory processes (Saari et al., 2017) and shed more light onto the mechanistic effects of GVS, currently there is a distinct lack of convergent evidence for this. There is also a need for replication of this research to better understand the mechanisms of GVS and define the efficacy of dose manipulations. This research should be pre-registered with journals to eliminate bias reporting and the likelihood of type 1 errors so that we can be confident that the results exist (Chambers, 2014). Another, limitation of the research in Chapter 4 was that it was conducted by a single researcher with newly acquired self-taught technical skills. This may explain why I was unable to utilise the Bereitschaftspoetntial effectively as a marker of neuroplastic change, having access to training and receiving support from an experienced physiological engineer would have been extremely advantageous to me. Lastly, the small sample size and short periods of testing limited the utility of GVS, as I was only able to uncover transient symptoms and effects. Furthermore, it prevented comparative group analysis with only five case studies.

Conclusion

This thesis has demonstrated an intrinsic relationship between the symptoms of mTBI, PTSD and vestibular dysfunction in UK military veterans. The role of the vestibular system in mTBI had previously been overlooked. However, the research conducted in this thesis has shown that the vestibular system is relevant to the healthcare of those with mTBI, especially veterans. Coupled with the effects on cortical excitability and albeit unexpected effects on anxiety, the data point to

the idea that the vestibular system is somehow foundational in nature exerting profound domain general effects across many brain networks. This foundational nature is seemingly evident in the developing foetus, for which the vestibular system is the first to mature, the child for who gentle rocking is soothing and relaxing and the adult for who vestibular disorder is functionally devastating. The concept of vestibular cognition is still emerging but it is becoming increasingly clear that the ‘silent sense’ is perhaps the most pervasive of all.

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Appendix

EST Combat and Matched Neutral words

Combat Words	Matched Neutral Words	Combat Words	Matched Neutral Words
ABDUCT	OBSESS	WAR	NET
BLINDFOLD	BLUEPRINT	EXPLODE	CONSUME
MEDIC	TENOR	BOMB	WEEK
AMPUTATE	RENOVATE	CONCUSSION	COMPLEXION
ARSENAL	MATADOR	RPG	DVD
GUN	ODD	TRIAGE	PICKET
EXECUTE	EXAMINE	MILITANT	PARTISAN
BODY	CITY	WMD	NBA
CHECKPOINT	PAINTBRUSH	HOSTAGE	SENIORS
HV	UV	RECCE	NOISY
APACHE	ATHENA	CONVOY	PASTRY
EVACUATE	UNIFYING	MILITIA	ANTENNA
VCP	PDA	TOURNIQUET	DISHWASHER
GUNFIRE	BISCUIT	APC	AKA
EIDER	DRYER	JANKERS	SUBJECT
COMBAT	BOTTLE	GUNNER	JURORS
INFIDEL	PURITAN	TOUR	RIDE
DECAPITATE	REDECORATE	BELTER	RATTLE
IED	DNA	EXPLOSIVE	UNDEFINED
TORPEDO	SOCIETY	TORTURE	THUNDER
GUNMEN	SITTER	AK-47	BLVD
KILL	MOVE	PATROL	SKIING
KIDNAP	PERUSE	CASUALTY	TAPESTRY
KALASHNIKOV	APPALACHIANS	WARFARE	BOOKLET
SUICIDE	FACULTY	WINCH	TRUNK
SM-70	RSVP	TERROR	PERMIT
MORTAR	COMETS	FIREFIGHT	FIELDWORK
PRISONER	OBSERVER	WOUNDED	ROUNDED
TRIGGER	HOUSING	MARTYR	DINING
VEST	VINE	HK417	SCUBA
AMBUSH	GOSSIP	BAYONET	VOLCANO
CROSSFIRE	STAIRCASE	MORPHINE	NEWSROOM
SHELL	QUOTE	CAPTOR	CADDIE
INCOMING	HOSPITAL	GUNSHOT	ADHERE
CAPTIVE	REPTILE	DETAINEE	DETECTIVE