The effects of galvanic vestibular stimulation on motor cortical related potentials in Parkinson's disease

Jade Leigh Fawkes

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School of Psychology

University of Kent

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Contents

COVID-19 Statement

The completion of data collection for this thesis was prevented because of the global pandemic of COVID-19. The original plan for was to recruit 20 participants with Parkinson's disease (PD) and 20 healthy, age-matched control participants. However, given that both PD and elderly participants were particularly vulnerable to COVID-19 infection, we were only able to collected data from 17 PD participants.

Abstract

A recent study showed that vestibular stimulation can produce long-lasting alleviation of motor and non-motor symptoms in Parkinson's disease (PD) sample. The mechanisms of action behind the alleviation of PD symptoms through vestibular stimulation are currently unknown. An electrophysiological marker known to be abnormal in PD is a particular movement-related cortical potential (MRCP) known as the Bereitschaftpotential (BP). The aim of this thesis was to observe the effects of galvanic vestibular stimulation (GVS) on reaction time and MRCPs in PD using electroencephalograph (EEG) to better understand its underlying physiological mechanisms. All Seventeen participants with a diagnosis of Parkinson's disease completed a voluntary finger and foot tapping task and seven participants also completed a simple reaction time task whilst receiving both active and sham GVS. Analysis revealed that active GVS did not influence any of the mean amplitudes of the MRCPs nor participants reaction time. Exploratory correlation analysis revealed certain clinical characteristics modulated participants responsivity to GVS, however post-hoc manipulation of these correlations did not find them significant. It is unclear whether these null effects were observed due to a lack of sample size and neurologically healthy control group for baseline comparison. It is speculated whether a different GVS technique is needed in order to understand the previous literatures findings, and this is considered through GVS type and frequency.

Keywords: Vestibular stimulation, Parkinsons disease, Movement-related cortical potentials, Simple reaction time task

Literature Review

Overview

Parkinson's disease (PD) is a progressive neurological disorder, caused by the degeneration of dopamine producing neurons. Primarily, this degeneration occurs within a group of interconnected subcortical nuclei known as the basal ganglia. PD is most characterized with motor symptoms including tremor, rigidity and bradykinesia; however, sufferers may also experience non-motor symptoms including mood disorders, sleep disturbances, memory loss, cognitive impairment, depression and anxiety (Chopade et al., 2022; Armstrong & Okun, 2020). As can be assumed, these symptoms cause serious detriment to those who suffer from PD. In response to this, a variety of treatment options have been introduced to lessen the severity of symptoms, most notably, dopamine replacement therapy and brain stimulation (both invasive and non-invasive). Each treatment has been shown to induce positive effects (Bergman, Wichmann & DeLong, 1990; Benazzouz, Gross, Feger, Boraud & Bioulac, 1993; Macleod & Counsell, 2019); nevertheless, certain undesirable side-effects have also presented themselves, for example causing other health conditions such as dystonia (Jankovic, 2005). Henceforth, a novel treatment must be explored. The current treatment in question, vestibular stimulation (VS), has shown promising results in decreasing parkinsonian symptoms (Yamanoto et al., 2005; Wilkinson et al., 2016). Nonetheless, the electrophysiological mechanisms behind the effects of VS are unknown (Kim et al., 2013); this must be investigated to better understand the origin of the therapeutic effects previous research has shown, which in turn will inform development of efficacious treatment and management. To address this, the current study aims to identify physiological markers of change caused by galvanic vestibular stimulation (GVS) using concurrent EEG. This thesis begins with a literature review outlining the current

treatment options for PD, the vestibular system, vestibular stimulation, and its potential influence on the pathological mechanisms of PD.

Drug therapy

PD is currently regarded as incurable, however, there are current drug treatments available to help manage motor symptoms, especially during the early stages of the disease. The current pharmacological treatment for PD aims to raise levels of natural dopamine levels, by acting as a surrogate for the lost dopamine, in the synaptic cleft (Lloyd, Davidson, & Hornykiewicz, 1975). The medicine most commonly prescribed is levodopa, which is used in conjunction with dopamine agonists, decarboxylase inhibitors and inhibitors of dopamine. Levodopa was introduced in the 1960's and was viewed as revolutionary in not only treating PD but also in helping to diagnose it (Hughes, Daniel, Kilford & Lees, 1992; Cotzias, Van Woert & Schiffer, 1967). Levodopa has proven to improve most motor symptoms, measured by the Unified Parkinson's Disease Rating Scale (UPDRS), overall (Macleod & Counsell, 2019). Nevertheless, many undesirable side-effects of levodopa have been perceived in most of those it is prescribed to, especially after chronic use. Long-term use of levodopa has been linked to significant motor fluctuation, most commonly, interchangeable states of akinesia and dyskinesias (Goetz, Poewe, Rascol, & Sampaio, 2005), formally known as ON/OFF periods. This has been referred to as the "yo-yo effect" to highlight the rapid oscillations that can occur between ON and OFF phases (Marsden & Parkes, 1977). Other dopamine replacement drugs may be combined with levodopa when dyskinesias begin to emerge, such as Dopamine agonists (Rinne, 1991), amantadine and catechol *O*-methyltransferase (COMT) inhibitors (Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang, 2000). As with levodopa, however, after several years of usage the dyskinesias will re-emerge (Rinne, 1991, Goetz,

Poewe, Rascol, & Sampaio, 2005). As well as long-term side effects, immediate negative effects of levodopa usage commonly emerge; one of which, is an increase in impulse control behaviours (Donzuso, Agosta, Canu, & Filippi, 2020). Moreover, levodopa has been shown to cause another movement disorder known as dystonia (Jankovic, 2005). Dystonia causes: disruption to posture, persistent painful muscle contractions, and repetitive twisting movements (Tarsy & Simon, 2006). Levodopa also fails to control or treat non-motor symptoms, such as depression and sleep disturbances, and has been linked to their worsening (Quin et al., 2009). Lastly, alongside the majority of medication, levodopa can cause many common minor side effects such as dizziness, nausea and loss of appetite. A PD sufferer taking levodopa who experiences many of the side effects may be unable to justify if the benefits of the drug outweigh the negatives, thus, other outlooks for treatments must be explored.

Deep Brain Stimulation

Another prominent treatment used for the management of parkinsonism symptoms is deep brain stimulation (DBS). DBS is a form of treatment that involves electrodes being inserted into the brain via open-head surgery and is typically only used if there is a reduction in efficacy of levodopa. Most commonly, DBS electrodes are inserted into the subthalamatic nucleus (STN) and the globus pallidus internus (GPi) as this has been shown to cause a significant decrease in parkinsonism motor symptoms by regulating abnormal cortical excitability (Bergman, Wichmann & DeLong, 1990, Benazzouz, Gross, Feger, Boraud & Bioulac, 1993). Furthermore, when compared to dopamine agonistic medication, such as levodopa, DBS alone has been shown to be more effective (Deusch et al., 2006), most notably at reducing levodopa-induced dyskinesias (Krack et al., 2003). The mechanisms of

dyskinesia reduction in STN and GPi DBS are fundamentally different. GPi stimulation improved dyskinesia through direct stimulation effects on dopaminergic pathways to inhibit abnormal electrical activity of GPi (Anderson et al., 2005), while STN stimulation reduced dyskinesia by lowering greater dopaminergic medication Odekerken et al., 2013). This beneficial effect, however, may in part be due to the cessation or reduction of medication, such as levodopa, after long-term use (Obeso et al., 2001). Despite this improvement of overall motor symptoms, DBS has not been shown to cause any improvement in fine motor movements, such as handwriting or hand gripping, and may contribute to their decline (Saint-Cyr, 2000). Moreover, DBS has shown no benefits towards the cognitive or psychiatric fluctuations of PD and has been shown to worsen some of these symptoms. Saint-Cyr et al. (2000) monitored PD sufferers for 12 months after undergoing DBS surgery and found a significant decrease in executive functioning, particularly in those over the age of 69, and a slow decline in mental health. This decline in mental health has been shown to be a common theme underlying DBS with some participants even becoming suicidal (Berney et al., 2002). It has been hypothesised that the decline in cognitive abilities following DBS is a result of both chronic inadequate and excessive dopaminergic stimulation of the frontal lobes combined with the postoperative reductions in dopaminergic medication (Saint-Cyr et al., 2000). Finally, alike most surgeries, DBS has health risks unrelated to PD such as intercranial haemorrhages and infections (Obeso et al., 2001), which in turn could result in death (Weaver, 2009).

The vestibular system as a therapeutic pathway in PD

The current section will first outline the anatomy and function of the vestibular systems before then considering its potential relevance to PD management. The vestibular

system is a sensory system located within the inner ear that has been primarily associated with autonomic functions such as regulating balance and spatial orientation (Day & Fitzpatrick, 2005). The system consists of five sense organs: three semi-circular ducts and two otolith organs (saccule and utricle), all of which are filled with endolymph fluid. The semi-circular ducts detect head rotation, the saccule detects movement on the sagittal plane and the otolith detects horizontal movement (Day & Fitzpatrick, 2005). Each contains sensory epithelium which supports hair cells that function as mechanoreceptors to generate afferent signals which are innervated by the vestibular nerve. The vestibular nerve combines with the cochlear nerve to become the vestibulocochlear nerve which enters the brainstem at the level of the pontomedullary junction. From here the signals are predominantly transmitted to the vestibular nuclei which integrates input from vision, hearing, proprioception, and touch. Signals may also be transmitted to the cerebellum which monitors vestibular performance and can adjust central processing if necessary. Output signals are mainly sent to the spinal cord to allow quick reflexive postural reactions to regain balance (Day & Fitzpatrick, 2005). These output signals are controlled by vestibular-ocular reflex (VOR) neurons which are associated with oculomotor control of eye movements (Smith, 1997). In addition, it has been evidenced through tracing studies of rats, cats and monkeys, as well as radiological research in humans that there are multiple divergent projections from the vestibular nuclei within the thalamus (Shiroyama et al., 1999; Kotchabhakdi et al., 1980; Meng et al., 2007; Kirsch et al., 2015). Many of the nuclei targeted by the thalamus are not specific to the vestibular system, such as the ventrolateral and intralaminar nuclei, and receive input from multiple different peripheral sensory and cortical regions (Wijesinghe, Protti & Camp, 2015). As such, it has been suggested that these vestibulothalamatic circuits could form discrete pathways within the thalamus that integrate both vestibular and other modality-specific signals (Lopez & Blanke, 2011). In response, a recent surge of research has

implied that the vestibular system may indeed also play a role in higher-order functions such as emotions, cognition, and volitional movement which, as to be discussed, further increase the relevance of the vestibula projections to managing PD.

Vestibular system and cognition

Over recent years, research has been able to better characterise the cortical anatomy and networks of the vestibular and the responsivity to peripheral vestibular inputs. Understanding this network is vital for the development of vestibular stimulation for therapeutic interventions which could potentially produce widespread effects on neurocognitive function in health and disease. Researchers have identified a tentacular ascending vestibular network that goes beyond the classical brainstem circuits for sensorimotor postural and oculomotor reflexes with which the vestibular system is traditionally identified with. This widespread cortical and subcortical network has been described by electrophysiological studies on non-human primates who identified the core area as the Parieto-Insular-Cortex (PIVC) which lies in the posterior parietal operculum extending into the posterior insular lobe (Shinder & Taube, 2010; Lopez & Blanke, 2011). In addition, experimentally activating the vestibular system through thermal or electrical stimulation in humans has produced haemodynamic responses in both many cortical and subcortical areas including, but not limited to, the secondary somatosensory cortex, the inferior parietal cortex, the premotor cortex, and the superior temporal cortex (Frank & Greenlee, 2018). From this basic neuroanatomical knowledge, predictions can be made regarding the effect of artificial vestibular stimulation on behaviour and cognition; through the vestibular cortical network, vestibular inputs could have pervasive, modulatory influence on multiple neurocognitive functions.

A growing body of literature has emerged in recent years showing vestibular influences on a variety of cognitive processes, including executive function, memory, attention and perceptual/visuospatial ability. Visuospatial ability encompasses several functions including spatial memory, navigation and mental rotation which have all been linked to vestibular dysfunction. The virtual Morris Water Maze Task (vWMT) where participants must locate a concealed platform in a virtual pool using visual cues (Astur, Ortiz & Sutherland, 1998), has been used to examine the effects of various vestibular dysfunctions on spatial memory. Ten participants with bilateral vestibular dysfunction (BVD) were compared to age-, sex-, and educational-matched controls on their performance of the vWMT (Bottini, Gandola, Sedda & Ferrè, 2013; Brandt et al., 2004). Interestingly, the BVD participants demonstrated no difference in intelligence or non-spatial memory however, had significant impaired performance on several aspects of the test despite the vWMT not involving any vestibular inputs (the head is stationary throughout). BVD participants were also found to have significant decrease in hippocampal size (16.9%) which is one area demonstrated to be part of the broad cortical network associated to the vestibular system also including the insula, superior temporal gyrus and inferior parietal lobe (Dieterich & Brandt, 2008). In addition to receiving vestibular input, these brain regions are part of a complex neural network for visuospatial processing and memory (Astur, Taylor, Mamelak, Philpott & Sutherland, 2002; Kravitz, Saleem, Baker & Mishkin, 2011). The Corsi block test, a validated test of spatial memory which participants are asked to repeat increasingly longer sequences of taps on blocks until they can no longer replicate the pattern (Roy, van Zandvoort, Postma, Kappelle & Haan, 2000), has also been used to investigate vestibular dysfunction. Guidetti, Monzani, Trebbi and Rovatti (2008) compared fifty unilateral vestibular neuritis patients to age- and sex-matched controls on their performance of the Corsi block test. Unsurprisingly,

the patients scored significantly worse than the controls and were also found to have higher co-morbid depression and anxiety.

Clear links have been established when there has been a loss of vestibular function, most notably the relationship between affective disorders and vestibular disturbances (Grabherr et al., 2015). High prevalence rates of traumatic stress, anxiety and panic disorders, depression, phobias and obsessive disorders have been reported in epidemiological studies of individuals presenting with vertigo syndrome, peripheral vestibular loss (BVL) and postural-perceptual dizziness (PPPD) (Best, Eckhardt-Henn, Tschan & Dieterich, 2009; Staab, 2016). Similarly, individuals who suffer with psychiatric disorders, such as depression, schizophrenia, anxiety and phobias frequently also present with symptoms associated with vestibular disturbances such as vertigo and balance problems (Jacob, Moller, Turner & Wall, 1985; Best, Bense & Dieterich, 2007). Furthermore, activation of the stress response has been induced through extreme vestibular conditions, such as hypo-gravity or hyper-gravity environments (Horowitz, Blanchard & Morin, 2004). These studies suggest a link between the vestibular system and emotional processing through the limbic network (Rajagopalan et al., 2017). The stress response highlighted previously was specifically associated with the activation of the hypothalamo-pituitary-adrenocortical (HPA) axis which was observed to be underpinned by a pathway to the hypothalamic paraventricular nuclear (PVN) from the medial vestibular nucleus (Horowitz, Blanchard & Morin, 2004; Markia, Kovacs & Palkovits, 2008). Furthermore, the limbic system has also be proposed to be modulated by vestibular influences via indirect pathways between the amygdala and the vestibular system (Metts, Kaufman & Perachio, 2006). Metts, Kaufman and Perachio (2006) injected neural tracer viruses into the vestibular neurons of Mongolian gerbils which spread rapidly to the amygdala. This body of research signifying that the vestibular system may play a role in higher-order functions, such as emotions and cognition, highlight the coverage of the

vestibular cortical network. This leads to questions whether artificial vestibular inputs, such as vestibular stimulation could have pervasive, modulatory influence on multiple neurocognitive functions and harnessed to treat neurodegenerative disorders such as Parkinson's disease.

Vestibular Stimulation

Currently, there are two different ways to artificially stimulate head movement – caloric vestibular stimulation and galvanic vestibular stimulation. Caloric Vestibular stimulation (CVS) stimulates the vestibular nuclei in the brainstem through the application of thermal currents to the external ear canal (Been, Ngo, Miller & Fitzgerald, 2007). This mode of thermal current induction alters the firing rate of the vestibular nerve by causing density changes in the endolymphatic fluid in the semi-circular canals, thereby eliciting vestibular-ocular reflexes (VORs) and horizontal nystagmus (Been et al., 2007). Traditional CVS irrigators used short-duration applications of hot and cold water/air using a syringe with a piece of soft silastic tubing attached (Been et al., 2007); however, this commonly resulted in unpleasant side effects, such as nausea, and was not amendable for home use (Black et al., 2016). To tackle these issues, recently a solid-state CVS device has been developed. The device consists of a wearable headset with ear-probes which warm and cool and has since been proven to be considerably more efficient for therapeutic treatment (Black et al., 2016).

There is a growing number of links that have been made between the vestibular system and higher-order brain functioning, which has inspired a new surge of investigations in the use of vestibular stimulation as a new adjunctive or alternative therapy for certain neurological injuries and disorders. CVS has been demonstrated to be beneficial at alleviating both physical and neurological symptoms in post-stroke patients (Ruben, 1985;

Ramachandran et al., 2007). For example, Ruben (1985) showed that bias towards the ipsilesional visual field associated with hemi-spatial neglect in post-stroke patients could be transiently alleviated using CVS. This was shown through 17 participants significant improvement in tests of visual neglect as well as increased spontaneous exploration of the contralesional area. This was further supported by the alleviation of both extrapersonal neglect and personal neglect which lasted for 15 minutes following CVS in four in-depth case studies of post-stroke patients (Cappa, Sterzi, Vallar, & Bisiach, 1987). These findings are hypothesised to be a result of CVS activating the contralesional "dominant" hemisphere, including the parietal and insular cortices, which has been supported by several functional imaging studies into CVS (Suzuki et al., 2001; Naito, 2003). Previous fMRI findings have also been used to explain how CVS has shown to provide an immediate and sustained reduction in self-reported pain relating to thalamic pain following stroke, also known as Dejerine-Droussy Syndrome (Ramachandran et al., 2007a, 2007b). More recently, Wilkinson et al. (2017) found that migraineurs who received a three-month treatment using the solid-state CVS showed significant reductions in number of headaches, migraine medication intake and self-reported pain scores compared to patients receiving placebo stimulation. This finding is significant as many neurological studies have hypothesised that migraine is a neurological disorder involving brainstem dysfunction which is one of the neural areas activated by CVS (Aurora, Barrodale, Tipton, & Khodavirdi, 2007; Dieterich & Brandt, 2008; Chong, Plasencia, Frakes, & Schwedt, 2017).

Another form of vestibular stimulation currently under investigation for its therapeutic benefits through non-invasive neuromodulation is Galvanic Vestibular Stimulation (GVS). GVS involves the application of low amplitude (< ~2 mA) transcutaneous current to the mastoid bones just behind the ears. Bilateral bipolar GVS, the most common form of GVS, delivers the signal to the mastoid process via an anodal electrode behind one ear and a

cathodal electrode behind the other (Fitzpatrick & Day, 2004). Other configurations are bilateral monopolar GVS with electrodes of the same polarity at both ears and a distant reference electrode, and unilateral monopolar GVS which only uses one stimulating electrode behind one ear. GVS emulates natural head motions by activating the vestibular nerve via polarisation effects of the eighth cranial nerve projecting from both the semi-circular canals and the otolith organs (Fitzpatrick & Day, 2004; Utz, Dimova, Oppenlander & Kerkhoff, 2010). Primarily in clinical research, either alternating current GVS (AC GVS) or noisy GVS (nGVS) are used. nGVS consists of a subthreshold ban-limit noisy current that adds stochastic resonance to the peripheral vestibular system (Dlugaiczyk et al., 2019). Alternatively, AC GVS delivers a sinusoidally modulated current to attempt to represent the eye movement patterns during head rotation and mimic the employed sinusoidal head rotations (Gensberger et al., 2016).

GVS has been shown to alleviate neurological symptoms following stroke or brain injury. Rorsman, Måns Magnusson, and Ba (1999) observed a reduction of visual neglect in a line cancellation task during subsensory GVS. Moreover, the modulation of the counter clockwise tilt of the subjective visual vertical during left-cathodal GVS in patients with right-hemispheric lesions, particularly in those patients with left sided neglect has been observed (Saj, Honore, & Rousseaux, 2006). Furthermore, single case studies in brain-damaged patients showed an amelioration of visuo-constructive deficits in the Rey-Osterrieth complex figure test during GVS (Wilkinson, Zubko, DeGutis, Milberg, & Potter, 2010) and a permanent reduction of tactile extinction by 40% after 2 stimulation sessions (Kerkhoff et al., 2011). Moreover, a recent randomised control trial demonstrated that an active treatment of GVS was associated with significant reductions in the attentional deficits of patients diagnosed with hemi-spatial neglect following right hemisphere strokes (Wilkinson et al., 2014). Additionally, during the application of GVS, a single-case study of a patient with

prosopagnosia as a result of right hemisphere damage showed significant improvements in face matching tasks (Wilkinson, Ko, Kilduff, Mcglinchey, & Milberg, 2005). These recent studies hope to identify ways of alleviating the disfunction caused by damage to higher-order brain regions through manipulating their link to the vestibular system (Black and Rogers, 2020). Of most relevance, the above studies show that a range of neurological symptoms respond to vestibular stimulation which suggests that multi-faceted conditions such as PD may be especially good therapy targets. The current thesis has chosen to use GVS over CVS due to its inherent ability to deliver sub-sensory stimulation, allowing for the blinding of participants. This is a crucial methodological point for the current research as it enables the ability for conclusions to be drawn without the threat of findings being influenced or the result of placebo effect.

Vestibular stimulation and Parkinson's

Recent research has highlighted VS as a new potential avenue to treat PD. Wilkinson et al.'s (2019) randomised, double-blind and placebo-controlled study showed that active treatment with a solid-state CVS device was associated with clinically significant improvements in both motor and non-motor symptoms of PD. Baseline measures of symptoms were acquired before stimulation and then participants were randomised to either active (n = 16) or placebo (n = 17) treatment group. Both treatments were administered twice daily at home by participants themselves or with the help of a partner/carer for eight weeks. The active treatment group received CVS as a time-varying, warm, saw-tooth thermal (37 °C – 42 °C) stimulus to one ear and a cold saw-tooth thermal (37 °C – 17 °C) to the other ear, lasting for approximately 19 minutes. The placebo treatment involved the same procedure as the active treatment, but no power was delivered to the device. The baseline measures were

then compared to follow-up assessments at the end of treatment, 5- and 24-weeks post treatment. CVS was associated with clinically relevant reductions across all motor symptoms, whereas no reduction was seen in the control group. The main reduction of motor symptoms was primarily observed in the MDS-UPDRS Part (II) - motor aspects of experience of daily living - and Part (III) – motor examination- which measure both subjective and objective experiences of motor symptoms. Non-motor features as measured by the MDS-UPDRS Part I (Non-Motor Aspects of Experiences of Daily Living) were also significantly reduced for the active treatment group compared to placebo. The most notable result of Wilkinson et al. (2019) was that symptoms were still clinically reduced, surpassing the previously established minimal clinically important difference (MCID), 5-weeks after the treatment ceased (Horváth et al., 2017). At 6 months follow-up, most of the gains had started to recede back to baseline status (Wilkinson et al., 2019). These results were unlikely to have resulted from a placebo effect as active participants were unable to correctly guess whether they had received active or placebo treatment. Moreover, the durability of the effects supported the likelihood that the results were driven by true underlying mechanisms of action such as neural entrainment (Black et al., 2016). Thus, these findings suggest that a twice daily treatment with the CVS device can produce lasting and clinically relevant improvements in PD symptoms comparatively to DBS devices which when turned off result in the re-emergence of motor symptoms almost immediately (Black & Rogers, 2020). The robustness of these effects is perhaps the strongest justification for a thorough investigation into the physiological mechanisms of action of vestibular stimulation.

Positive effects of GVS, as opposed to CVS, have also been observed in Parkinsonism. Yamamoto et al. (2005) applied noisy continuous GVS to 6 PD participants for 24 hours whilst assessing motor/cognitive tasks. During cognitive tasks, a significant decrease in participants reaction time was observed, suggesting an improvement in motor

execution. Moreover, improvements in autonomic responsiveness, specifically parasympathetic, evidenced by participants increased heart rate frequency fluctuations. Lastly, participants also experienced a significant quickening of bradykinetic rest-to-active movements measured by trunk activity. As well as presenting influential results, Yamanoto et al. (2005) study's participants were PD sufferers who were unresponsive to levodopa treatment. This proposes that GVS goes beyond what drugs can provide for those with PD, without producing any major adverse effects seen in established PD treatments. Further studies using GVS to alleviate specific targeted symptoms of PD have since been conducted. Lee et al. (2015) applied both sham and active noisy GVS to 12 PD participants in a pseudorandom order whilst completing a sinusoidal visuomotor joystick tracking task and found a significant improvement in visuomotor processing during active stimulation. Moreover, several studies have focused on GVS alleviating postural instability (PI) in PD participants through increased balance maintenance following perturbation using the pull test of the MDS-UPDRS and/or dynamic balance mats and reductions in sway using centre-of-pressure measures (Kataoka et al., 2016; Pal, Rosengren & Colebatch, 2009; Samoudi, Jivegård, Mulavara & Bergquist, 2015; Tran et al., 2018; Okada et al., 2015; Khoshnam et al., 2018; Pal et al., 2010).

None of the studies to date fully explain the mechanisms of action related to motor improvements seen in the Wilkinson et al. (2019) trial. As such, the current thesis will explore motor-related cortical potentials (MRCPs) in association with the different phases associated with motor preparation and execution.

The BP

The cortical activity recorded around the time course of movement are referred to as movement-related cortical potentials (MRCP's). The main MRCP focused on in the current research is the Bereitschaftspotential (BP), which is activated during voluntary movements (Jahanshahi & Hallett, 2003). Kornhuber and Decker (1964) recorded concurrent EEG and EMG activity during repetitive self-paced movements, without external triggers, and found a slow rising negativity one to two seconds prior to movement onset. It has since been discovered that the BP occurs in two separate phases, the early BP and the late BP, which are associated with different preparatory functions (Shibasaki & Hallett, 2006). The early BP occurs 1-2 seconds prior to movement onset and is reported to be maximum over the midline (Cz). The early BP is associated with SMA activity (Boschert, Hink & Deecke, 1983; Boschert & Deecke, 1986) and is reflective of the preconscious readiness for the oncoming movement as it precedes participants reported decision to perform the voluntary movement (Libet, Gleason, Wright & Pearl, 1983). The late BP occurs around 400 milliseconds before movement onset and is frequently observed as maximal sites lateralised to the hemisphere contralateral to the limb movement (C3 and C4) (Shibasaki, Shima & Kuroiwa, 1978). Moreover, the late BP is believed to represent activity in the motor cortex, specifically the selection of appropriate muscles through the interaction between the SMA and M1 (Shibasaki, Shima & Kuroiwa, 1978; Neshige, Lüders & Shibasaki, 1988). Proceeding the early and late BP is the MP which reflects the recruitment signals being sent to the peripheral nerves prior to the observable movement. This co-occurs with movement at approximately 100-200milliseconds and is the highest peak of the rising negativity (Deeke, Eisinger & Kornhuber, 1980; Shibasaki & Hallett, 2006).

Abnormality of the BP in PD can be anticipated, especially in the early BP, as difficulties engaging in voluntary movement it is a known symptom of PD. Traditional investigations into the effect of PD on the BP elicited results that indicated the BP was

abnormally small in PD groups (Deecke, Englitz, Kornhuber & Schmitt, 1977; Shibasaki, Shima & Kuroiwa, 1978). However, the methodology of these studies was subsequently scrutinised due to questions arising on whether the smaller BP observed in PD participants was due to the significant age differences between control subjects compared to PD groups (Barrett, Neshige & Shibasaki, 1985; Deeker, 1985). The BP has been noted to decrease with age, causing it to be significantly smaller in comparison to younger individuals (Deeker, 1985). Despite this, after controlling for age, Dick et al. (1989) did indeed find a significant decrease in the mean amplitude of the early BP elicited by voluntary self-paced finger extensions in PD compared to healthy, age-matched individuals. Furthermore, Jahanshahi et al., (1995) observed the PET measurements of both neurologically aged-matched controls and PD participants whilst each completed both externally triggered and self-initiated finger extensions. Scans from the externally triggered finger extensions did not differ between controls and PD participants on any of the measure for cortical negativity before movement. Comparatively, during the self-initiated movements, the mean amplitude of the early BP was significantly reduced in the PD group compared to controls. PD patients have difficulties with self-initiated movements such as walking, however their performance has been shown to improve when external stimuli are presented, such as a line to follow on the floor (Martin, 1967); henceforth, explaining why the BP has been observed not to differ between PD and controls during externally triggered movements.

SRT

As stated earlier, in conjunction with motor symptoms, PD patients also suffer non-motor symptoms including, but not limited to, cognitive impairment, which generally affects executive abilities (e.g., decision-making), memory, visuospatial processing, psychomotor

speed and attention (Chopade et al., 2022; Armstrong & Okun, 2020). The development of such symptoms has been linked to the presence of Lewy bodies in the frontal and cingulate gyrus caused by the natural disease progression of PD (Barone et al., 2011; Halliday et al., 2015). Research commonly assesses cognitive impairment of PD participants by focussing on bradyphrenia – the slowness of information processing (SIP) - through reaction time tasks (RT) as it encompasses many of the former non-motor sub-symptoms (Shipley at., 2002). By implementing a variety of RT tasks, research has highlighted that PD patients' response to stimuli is slower than that of healthy age-matched individuals (Goodrich, Henderson, & Kennard, 1989; Pullman, Watts, Juncos, Chase, & Sanes, 1988; Jahanshahi, Brown, & Marsden, 1992). Critics argued that slowness in response is due to PD impaired motor functions, specifically bradykinesia (Stelmach, Worringham, & Strand, 1986). In response, research addressed such a question by investigating PD patients' responses to simple reaction time (SRT) tasks by differentiating between RT and movement time, to obtain data that would be more specifically representative of PD's cognitive impairment symptoms. Jahanshahi, Brown & Marsden (1993) required participants to press and hold a "home" key until an imperative stimulus was presented at which point participants must release the "home" key and press an allocated "response" key. The RT was calculated by assessing the time between the imperative stimulus and the release of the "home" key. Even when controlling for bradykinesia, PD participants scored significantly higher RT's than healthy age-matched controls (Jananshahi, Brown & Marsden, 1993). To date there is sparse research that has been conducted to determine the effects of VS on RT in PD samples. The previously mentioned Yamamoto et al. (2005) study, which applied continuous GVS to L-DOPA-unresponsive PD participants, also observed a significant decrease in RT on a continuous performance task any increase in omission or commission error rates. Lee, Smith, Lee and McKeown (2021) demonstrated that GVS significantly improved RT in SRT tasks in both PD

and neurologically healthy controls. The current thesis hopes to investigate these findings further to give insight into the effects of GVS on cognitive symptoms of PD.

Neurological theories of Vestibular Stimulation

Currently the most popular hypothesis accepted to understand the putative mechanisms underlying the positive effects of vestibular stimulation is that the motor symptoms of PD are caused by aberrant oscillations which can be altered or corrected by vestibular stimulation thus improving motor function (Black & Rogers, 2020; Smith, 2018). Previous research hints that a random noise signal, such as nGVS, can amplify the responsiveness of a non-linear biological system, such as the central nervous system (CNS), to weak, sub-threshold signals (McDonnell & Ward, 2011). However, this hypothesis fails to explain the ongoing alleviation of symptoms in PD participants 5 weeks post-treatment described in the Wilkinson et al. (2019) paper. Instead, Rogers and Black (2020) propose that the most likely explanation is that multiple neuronal pathways were improved through the use of CVS, through a type of neuroplastic modification called neural entrainment.

Neural entrainment refers to the assumption that frequencies of underlying cortical oscillations will align with the frequency of the externally applied oscillations from a sinusoidal current (Schutter, 2016). Neural entrainment has been demonstrated frequently through the use of transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) in healthy participants as well as PD populations (Helfrich et al., 2014; Krause et al., 2014). tDCS has showed some promising results at improving motor deficits within PD in accordance with the UPDRS and at increasing motor evoked potentials (MEP) (Fregni et al., 2006). Moreover, PD participants have been shown to experience significant bradykinetic improvements for up to 3 months after receiving repetitive tDCS

(Benninger et al., 2010). Despite these results, the benefits seen using tDCS may be temperamental and short-lived (Lavano, Guzzi & Chirchiglia, 2018). Notwithstanding the positive results of Benninger, et al. (2010) study regarding bradykinesia, any improvement in participants gait was short-term and no significant improvements were found within participant's UPDRS or mental health scores. Moreover, one of the most recognised studies for treating PD with tDCS is Brittain, Probert-Smith, Aziz and Brown (2013) study when they showed that applying tDCS to M1 reduced the tremor of their participants by 50%. Conversely, when one or both electrodes were removed from the participants scalp, the reduction in the tremor ceased completely. As a result of this, it can be assumed that the positive effects of tDCS are transient and stop as soon as stimulation ends. This could be attributed to the fact that tACS and tDCS both use highly localised methods of induction; thus, despite the activity of the regions directly underneath the electrodes being altered, this may not line up with the naturally occurring oscillatory patterns intrinsic to those regions. This is unlike vestibular stimulation which specifically activates the vestibular end organs, whose widespread ascending pathways reach many areas of the brain in an endogenous, natural manner (Black & Rogers, 2020; Lopez & Blanke, 2011).

The specific method of neural entrainment associated with vestibular stimulation has been described as "sensory neuromodulation" which refers to the modulation of cortical oscillations via the artificial, bottom-up activation of sensory receptors (Black & Rogers 2020). Sensory neuromodulation proposes that the innate sensory networks process the artificial external signal in the same way as a naturally occurring sensory stimulus. It is therefore hypothesised that dysfunctional neural networks could be closely rehabilitated back to their developmental state through neuroplastic modification using sensory neurorehabilitation. Research to support this hypothesis is in its infancy, however some clinical evidence has presented itself that are consistent with the theory. Black et al. (2016)

used the same time-varying CVS method employed by Wilkinson et al. (2019) on episodic migraine subjects. Observations of the effects of CVS on cerebrovascular dynamics, measured using transcranial Dopple sonography (TCD) of intracranial blood vessels, was consistent with neural entrainment of the Pons, a structure which has previously been identified to receive direct projections from the vestibular nuclei (Balaban, Jacob & Furman, 2011). This study employed the same time-varying CVS method used in the Wilkinson et al. (2019) study giving reason to the theory that alterations in neurovascular dynamics may explain the prolonged effects of CVS on PD.

The current thesis

The present study used EEG to observe seventeen PD participants BP over two sessions whilst they received either active GVS or sham stimulation for 20 minutes each during a voluntary finger or foot tapping task and a simple reaction time task. Finger and foot movements were measured concurrently with EEG using Electromyography (EMG). Finger and foot taps were chosen as the voluntary movements as they relate to specific tasks within the MDS-UPDRS, particularly Part II and Part III, making the study clinically relevant. The study aimed to identify mechanisms of effect behind GVS to explain the previous motor improvements observed within the focused literature. It is hypothesised that there will be a significant difference in mean amplitude of the MCRPs (early and late BP and MP) between active GVS and sham stimulation. The thesis predicts a significant increase in the negativity of the mean amplitude of all components and a significant decrease in participant's RT during active GVS compared to sham stimulation. Such effect would be indicative of active GVS causing an electrophysiological marker of change to provide an explanation for previous findings stating GVS results in long-lasting decrease in symptoms. Furthermore, the thesis

predicts a significant decrease in participant's RT during active GVS compared to sham stimulation insinuating GVS could be an all-round novel treatment for PD as RT provides insight into the non-motor symptoms of PD.

Methods

Participants

Within this body of work, data from ten participants pre-COVID lockdown and seven participants post-COVID lockdown have been combined to form a cohort of seventeen PD (6 females, M_{age} = 65, age range = 54-79) volunteer participants who were recruited from either local Parkinson UK branches or news advertisements. To be eligible, participants could not have any skin abrasions or lesions behind the ears, no implanted electronic devices, had good ear health, and no metallic objects in the head. Participants must also have had no history of or current neurological conditions, other than Parkinson's disease, and were required to provide a letter confirming their diagnosis of idiopathic Parkinson's from their neurologist, be on stable medication throughout the study and not be a recipient of dopamine or apomorphine infusion therapy. Examples of medication taken by participants include Sinemet, rasagiline, co-careldopa, madopar and ropinirole. Participants showed a high variability in all demographic and clinical assessments (see Table 1).

Table 1

Table showing demographic and clinical characteristics of all participants.

Participant number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total (mean (SD))
Demographics																		
Age	65	65	68	57	76	60	55	66	67	54	65	68	56	66	66	79	72	65 (6.99)
Gender*	2	2	2	1	1	1	2	2	1	1	2	1	1	1	1	1	1	1
Years since PD diagnosis	4	4	4	8	2	6	5	11	1	7	8	1	7	18	5	2	8	5.9 (4.18)
Baseline assessment scores																		
MDS-UPDRS																		
Part I	12	11	19	20	15	4	2	11	10	13	14	3	17	11	8	14	5	10.2
Part II	18	16	16	19	5	16	4	10	10	16	11	3	18	22	15	14	10	13.3
Part III	49	36	37	45	29	27	25	30	16	47	14	21	23	42	34	13	43	27.1
Part IV	5	1	10	8	8	10	4	12	0	1	6	0	6	11	7	0	6	5.1
Hoehn Yahr	2	2	3	2	2	2	1	2	1	2	1	2	3	5	3	3	3	2.9
MoCA (MIS)	27 (14)	28 (15)	19 (10)	27 (13)	28 (13)	28 (14)	29 (15)	25 (13)	26 (13)	24 (11)	29 (15)	26 (12)	27 (13)	25 (10)	30 (15)	26 (13)	24 (10)	26.9 (12.6)
MiniBEST	21	20	23	23	26	22	27	25	27	24	18	22	22	19	20	15	18	20.3
HADS anxiety	7	6	12	10	2	0	1	3	8	5	15	3	7	7	2	3	2	5.1

HADS depression	6	5	11	11	3	0	2	3	2	5	9	1	2	2	5	6	5	5.6

*Gender – 1 = male, 2 = female

Materials

The Movement Disorder-Sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS). The scale consisted of four parts within in which all items are rated on a 5-point scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 = severe). Part I assessed non-motor aspects of daily living and was split into two parts; IA focused on symptoms such as cognitive impairment, hallucinations, apathy, anxiety, and depression, and IB focused on symptoms such as fatigue, constipation, and urinary problems. An interview style format was used to administer part IA by the experimenter whereas Part IB was self-administered by the participant with or without the assistance of a carer. Part II assessed motor aspects of daily living, such as speech, saliva/drooling, dressing, and handwriting, and alike part IB, was also a self-administered questionnaire. Part III was a motor examination in which participants performed a series of tasks used to assess movement, rigidity, postural stability, gait, and tremor (see Appendix A for example items 3.4 and 3.7 from Part III). Experimenters rated performance on these tasks based on observations during that session only. Identical to part IA, part IV was conducted in an interview format by the experimenter, and assessed motor complications, dyskinesias and motor fluctuations associated with the OFF-state; for example, the functional impact and complexity of fluctuations, and time spent in the OFF state.

The Montreal Cognitive Assessment (MoCA). The MoCA is an interactive interview questionnaire wherein participants are asked to complete different tasks, guided by instructions given by the experimenter, to measure mild cognitive dysfunction (See appendix B). A total score was generated by summing sub scores from the different domains and adding one point for individuals who have had 12 years or fewer years of formal education. Each domain assessed a different aspect of cognition such as visuospatial/executive control, memory and attention. A final score of 26 or above was considered normal, a score of 21-25

indicated mild cognitive impairment (MCI) and below 21 indicated severe cognitive impairment.

The Mini-Balance Evaluation Systems Test (Mini-BESTest). The Mini-BESTest is a shortened (14-item) version of the BESTest and contains four out of the original six sections: anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait using a 2-level ordinal scale (2 = normal, 1 = moderate, 0 = severe). The test is used to assess five different balance domains: vestibular and non-vestibular balance, functional mobility, gait and vestibular function see (see Appendix C for example items).

The Hospitalised Anxiety and Depression scale (HADS). The HADS is a 14-item measure designed to assess anxiety and depression symptoms (see Appendix D). Each question is scored between zero (no impairment) and three (severe impairment), with a maximum score of 21 for anxiety and depression. Scores of greater than or equal to 11 on either scale indicate a definitive case.

Galvanic vestibular stimulation (GVS).

Stimulation was delivered to the mastoid processes behind the ears via a pair of rubber, self-adhesive, disposable electrodes (5.1cm x 10.2cm; ComfortEase, Empi Inc.) which were connected to a *Neuroconn DC Stimulator* (GmbH, Ilmenau, Germany) through anode and cathode wires to the right and left, respectively. The *Neuroconn DC Stimulator Device* dispensed a small alternating current (AC) at a stimulation frequency of 0.01Hz and the amplitude was between 0.25-0.35mA. These parameters were set to facilitate the blinding of participants between active and sham conditions as lower intensities have been demonstrated to be sub-sensory (de Jesus Guirro et al., 2015). To ensure the stimulation was sub-sensory and participants were blinded to active vs sham conditions, a perception of stimulation questionnaire (see appendix B) was given at the end of each session. To ensure

that stimulation did not affect EEG recording of the scalp potentials, a 0.01Hz frequency was used as it produced a distinct different pattern to those underlying the BP which is thought to be between 1-4Hz (Duncan et al., 2022). The duration for which stimulation was administered varied between participants (15-20 minutes per task block) depending on how long each participant took to complete the simple reaction time task and the pace in which they moved their limbs to complete the motor tasks.

Electroencephalogram (EEG) and electromyography (EMG) acquisition.

Both electro-cortical and muscle activity was recorded simultaneously using an eegoTMsports 32 (ANT Neuro, Enschede, Netherlands) amplifier connected to a DELL tablet for online monitoring. EEG data was recorded from a 32-channel electrode cap (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC1, FC2, FC5, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, POz, O1, Oz, O2), configured according to the International 10-20 system (Klem, 1999). An online bandwidth filter of 0.01-70 Hz was applied, and the data were recorded at a sampling rate of 500 Hz, with CPz as the online reference electrode and Fz as ground. Disposable EMG electrodes where connected to the amplifier via a bipolar channel adaptor. During recording, both a notch filter of 50Hz and a bandwidth filter of 20-249Hz were applied. These filters were applied only during recording purely for clearer visualization of the data, raw data with no filters were used during the offline processing. Impedance was kept below 10 kΩ throughout EEG recording.

Procedure

To mitigate the potential threat of fatigue, the study was conducted over three sessions on three separate days. This also ensured that participants remained in the “ON” state throughout testing. All sessions took place in a quiet, temperature-controlled laboratory. The

study took place over two phases due to COVID-19. During the first cohort participants did not complete the SRT task, this was created and added in the time of the break between phases meaning only the second cohort (7 participants) completed the SRT.

The first session was always the clinical assessments which consisted of the administration of the neuropsychological test battery outlined above which was administered in the same order for everyone. Participants were first presented with a formal introduction to the study, given the opportunity to ask any preliminary questions and then provided written informed consent. Participants were administered a demographic questionnaire which requested their age, occupational, marital, and educational status. All participants were asked to provide a list of any non-parkinsonian medication and PD participants provided the dosage information for their anti-parkinsonian medication. The MoCA, mini-BEST and HADS was completed by all participants, whereas the MDS-UPDRS was only completed by PD participants. The MoCA was administered first followed by Part IA of the MDS-UPDRS. Parts IB and II were completed by the participant on their own or with their spouse/carer. Part III of the MDS-UPDRS was then assessed along with part IV which was administered by the experimenter. Participants then completed the HADS and mini-BEST.

The next two sessions were the experimental sessions which always occurred at least 48-hours. Prior to the experimental sessions, all participants were instructed to avoid the consumption of caffeine or alcoholic beverages in the 24-hours before the sessions. Furthermore, participants were asked to refrain from using conditioner and any hair products on the day of the experimental sessions that may increase EEG impedances, such as hair spray or gel. The order of the sham and active experimental sessions and whether they completed the foot or finger movements first was counterbalanced across participants (see Table 2). Both sessions were identical except for the movement task performed by participants in each; one session was for finger tapping and the other for foot tapping. During

experimental sessions, the affected side was utilized for the motor tasks as determined by the scores on the motor examination of the MDS-UPDRS and the participant's self-report of their subjectively worse side.

For the experimental sessions, the skin over the mastoids was first prepared using sterilising alcohol wipes and Nuprep® (Weaver and Company, Colorado, USA) skin prep gel after which the GVS electrodes were attached. An EEG cap was fitted to the participant's head and electroconductive gel was applied to maintain impedance below 10 kΩ throughout data collection. To collect HRV (not presented in this thesis) ECG electrodes were placed under both the left and right clavicle, within the rib cage frame, and a third electrode was positioned on the lower edge of the right 12^{th} rib. The skin over the extensor digitorum communis (ED) muscle of the chosen forearm or the tibialis anterior (TA) muscle of the chosen leg was then prepped in the same manner as the skin over the mastoids. EMG electrodes were then placed over the ED or TA muscles in a bipolar montage with the ground electrode over the wrist or ankle, respectively, to the European SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) recommendations. Both EEG and EMG were recorded within the same software and therefore used the same sampling rate, allowing for the time-locking of movement-related EEG activity in association with the EMG phase – movement onset.

Table 2

Table showing an example of the randomized and counterbalanced experimental sessions.

	Session 1	Session 2
Participant 1	Rest sham GVS	
	150 finger movements sham GVS	150 foot movements sham GVS

	Rest active GVS	
	150 finger movement active GVS	150 foot movements active GVS
Participant 2	Rest sham GVS	
	150 foot movements sham GVS	150 finger movements sham GVS
	Rest active GVS	
	150 foot movements active GVS	150 finger movements active GVS
Participant 3	Rest active GVS	
	150 finger movements active GVS	150 foot movements active GVS
	Rest sham GVS	
	150 finger movements sham GVS	150 foot movements sham GVS
Participant 4	Rest active GVS	
	150 foot movements active GVS	150 finger movements active GVS
	Rest sham GVS	
	150 foot movements sham GVS	150 finger movements sham GVS

To minimise artefacts within the EEG data, participants were shown their live EEG activity on a DELL tablet screen and the experimenter highlighted how tension in the jaw and neck muscles affect the data. Moreover, a fixation cross was presented on a computer screen in front of participants to minimise blinking or saccadic eye movement-related artefacts. Each experimental session consisted of two identical sections, as illustrated in Figure 1, in which participants either received active or sham GVS stimulation. During rest breaks, participants were encouraged to focus on the fixation cross and remain as still and relaxed as possible. The rest blocks were included to mitigate the risk of central and peripheral fatigue.

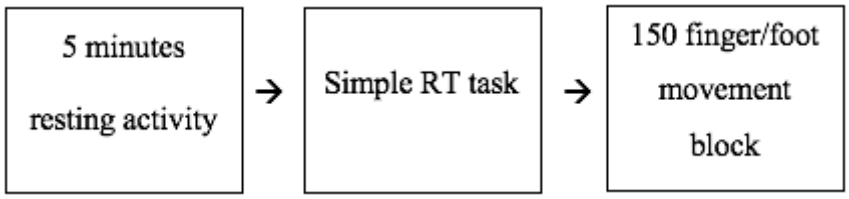

Figure 1. Single section of each session

As demonstrated by Figure 2, the simple reaction time task paradigm was designed as follows: a white fixation cross appeared in the middle of a black screen for a random amount of time, no shorter than 1,000 ms and no longer than 3,000 ms, to prevent predictability followed by an imperative stimulus (red square) which remained on screen until participants pressed the response key. The red square appeared in either the top left, top right, bottom left or bottom right corner of the screen 50 times and in random order. Participants were instructed to press the SPACEBAR button on the keyboard as quickly and accurately as possible every time the imperative stimulus appeared on screen. The imperative stimulus would not leave the screen until the SPACEBAR was pressed, allowing for the next trial to commence beginning with the white fixation cross. Participants completed 3 practice trials in which the experimenter provided cues if needed: *"try to wait until the red box appears", "try to touch a little quicker", "keep your hand near the spacebar".* The simple reaction task (SRT) took 2-3 minutes to finish and a total of 50 trials were completed per section of each experimental sessions.

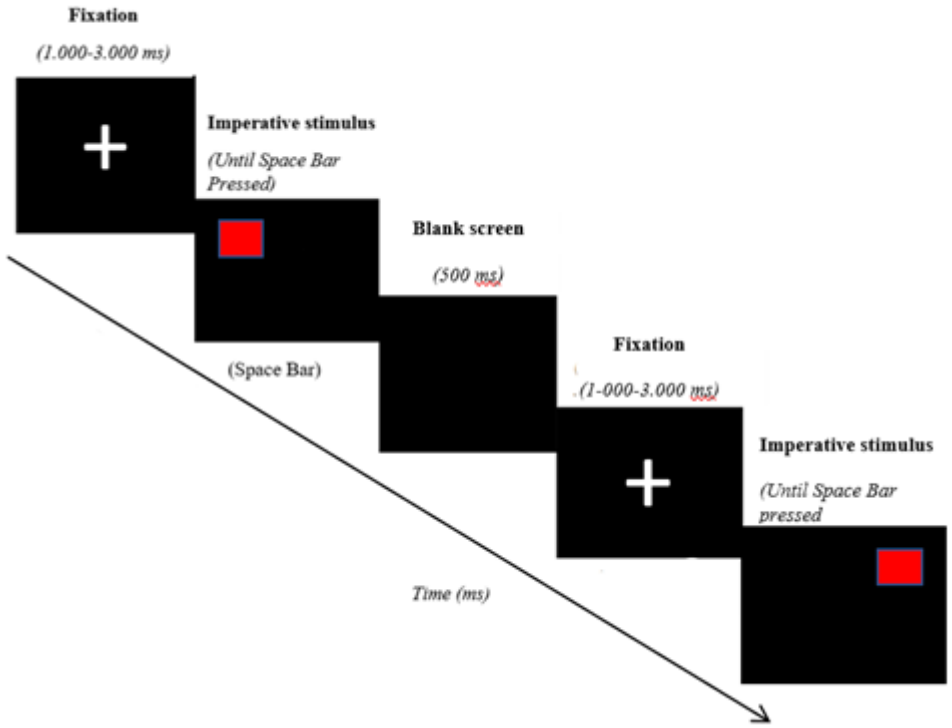

Figure 2. Simple reaction time paradigm

For the finger/foot tapping task, participants were verbally instructed to either perform voluntary extensions of the index finger or dorsiflexion's of their foot, at their own pace without relying on external cues. They were provided with 2 minutes of practice in which the experimenter provided feedback on the timing, magnitude, and velocity of movements via observing the EMG trace on the tablet screen. If movements were occurring too close together in time (under two second intervals), participants were instructed to slow down. Additionally, only movements that commenced from complete muscle relaxation were considered acceptable. This was done to allow for the offline assignment of markers that time-locked EEG epochs to EMG onset. Trigger time stamps were also manually inserted during data collection by the experimenter to help identify the EMG trace of relevance in the offline processing. To minimise muscle-related artefacts, participants were instructed to avoid any muscle activation other than the finger/foot tapping, for example jaw-clenching,

fidgeting, head and shoulder movements. Moreover, to avoid ocular artefacts, participants were instructed to maintain their gaze on a fixation cross and this was monitored by experimenters throughout the task. A total of 150 movements were executed per section with 30 second breaks in between every 50 movements to avoid fatigue.

Following the completion of the final block of movements in the second section of the experimental sessions, participants were given a perception of stimulation questionnaire to complete (see Appendix E). This questionnaire allowed any GVS-related physical sensations participants may have felt to be reported. After the commencement of the second experimental session, participants were given a full verbal and written debrief of the experiment and were thanked for their participation. Each experimental sessions lasted between two and two and a half hours.

Data offline processing

All offline data processing was conducted using Brain Vision Analyser 2 (Brain Products, GmbH, Gliching, Germany) software. A bandwidth digital filter of 0.1-40Hz was applied as previous research indicated this would have minimal overlap with the oscillatory frequencies of the BP and MP (0.01-2Hz) (Armstrong et al., 2018; Schmidt et al., 2016). Previous MRCPs studies have employed linked earlobes (electrodes M1 and M2) or mastoids as reference electrodes (Mota & Lins, 2017; Patil, Sood, Goyal, & Kochhar, 2017), however, these were not used in the current study due to their proximity to the stimulation site for GVS. Data was re-referenced to an offline average reference due to the proximity of the physical online reference – CPz – to the maximal site for the MRCPs at Cz. Channels T7 and T8 were removed from analysis because their locations (lower temporal position) above the stimulation sites meant that they were exposed to a high level of GVS-related activity.

For each participant, independent component analysis (ICA) using the Infomax (Gradient) restricted algorithm returned 30 maximally independent components. Components that reflected eye movements (blinks and saccades), muscle activity, and GVS-related noise previously defined (Duncan et al., 2022) were excluded from further analysis.

Each participants' data was segmented into epochs time-locked to EMG onset. Epoch length was -1500ms prior and 500ms following EMG onset. EMG onset was determined by the manual placement of markers prior to the earliest rise in the trace amplitude beyond steady state identified by visual inspection. Visual discrimination of EMG traces has been extensively used and its accuracy has been shown to equal that of statistical methods (Hodges & Bui, 1996). Any EMG trace that failed to show an abrupt and clear deviation from the steady state EMG was not included in the segmented epochs. For the Finger data set 1.9% (n = 43) of trials in the GVS condition and 2.4% (n = 66) in the sham condition were excluded. For the Foot data set 0.7% (n = 17) of trials in the GVS condition and 0.8% (n = 18) in the sham condition were excluded. Grand averages were calculated separately for the Finger and Foot data. The Finger data used 97.6% (n = 2,244) sham and 98.1% (n = 2,175) active trials to calculate grand averages. The Foot data used 99.2% (n = 2,314) sham and 99.7% (n = 2,331) active trials to calculate grand averages.

MRCP waveforms were identified using a collapsed localizer average for the active and sham GVS conditions. Electrode sites over the bilateral and central motor cortex (C3, Cz, C4) were selected based on maximal sites identified in previous literature (Shibasaki, Barrett, Halliday & Halliday, 1980). The BP component was divided into the subcomponents of the early and late BP, as previously established in the literature (Shibasaki & Hallett, 2006; Colebatch, 2007). The epoch length defined for the early BP was -1500 to -500 milliseconds prior to EMG onset. The epoch length for the late BP was defined as -500 – 0, with 0 being EMG onset. The epoch for the MP was determined using the waveforms derived from the grand

averaged data which showed the largest negative voltage deflections between 100 – 250 milliseconds after EMG onset. All statistical analyses were conducted on the mean amplitudes obtained from these epochs.

All statistical analyses were conducted using the software package Statistical Product and Service Solutions (SPSS). Mean amplitudes of the early and late BPs and MP were computed with separate analyses being conducted for each of the ERP components (early BP, late BP and MP) using 2 (stimulation: active and sham GVS) x 3 (electrode site: C3, Cz, C4) within-subjects ANOVA individually for both the foot and finger data sets, with a p value of $< .05$ being considered statistically significant. Post-hoc comparisons conducted on the electro-cortical data were Bonferroni corrected with a p value of $< .01$ considered statistically significant for when six comparisons were conducted. SRT analysis used a 2(Condition: GVS vs Sham) x 2(Limb: Finger vs Foot) repeated measures ANOVA. All mean differences at Cz for each ERP components for both the finger and foot data were correlated with each clinical assessment using linear correlation. Any significant correlations relevant to the current thesis were then interrogated using Quade's rank analysis of co-variance.

Results

Missing data

One participant was excluded from the Finger ERP analysis due to incomprehensible EMG traces as a result of a severe tremor and drifts due to sweat. One participant was excluded from the Foot ERP analysis as half of their trials were deleted due to technical error within the tablet's software.

Main analyses

ERP Analyses

ERP data were analysed via a 2(Condition: GVS vs Sham) x 3(Electrode site: CZ vs C3 vs C4) repeated measures ANOVA. Significant main effects (comprised of more than 2 levels) and interactions were interrogated using Bonferroni corrected pairwise comparisons. There were no instances in which sphericity was violated.

Finger ERP result

Early BP. The ANOVA for the early BP of the finger yielded no statistically significant main effect of Condition ($F(1,15) = 0.059$, $p = 0.812$) or Electrode Site ($F(1,15) = 0.947$, $p = 0.399$). There was also no significant interaction between Condition and Electrode Site ($F(1,15) = 0.998$, $p = 0.384$).

Late BP. The ANOVA for the late BP of the finger yielded no statistically significant main effect of Condition ($F(1,15) = 0.040$, $p = 0.843$) or Electrode Site ($F(1,15) = 3.117$, $p = 0.059$). There was also no significant interaction between Condition and Electrode Site ($F(1,15) = 0.135$, $p = 0.874$).

MP. The ANOVA for the MP of the finger yielded a significant main effect of Electrode Site ($F(1,15) = 18.532$, $p < 0.001$), but not Condition ($F(1,15) = 0.568$, $p = 0.463$). There was also no significant interaction between Condition and Electrode Site ($F(1,15) = 1.276$, $p = 0.294$). Paired sample t-tests across the three electrode sites revealed that the mean amplitude was significantly larger at Cz (Sham: M = -2.7542, SD = 2.3940, GVS: M = -3.5337, SD = 2.0730) than C3 (Sham: M = -0.9667, SD = 1.6745, GVS: M = -0.8079, SD = 2.1797) ($t(15) = 4.741$, $p < 0.001$) and C4 (Sham: M = -0.5697, SD = 1.4078, GVS: M = -0.6235, SD = 1.5056) ($t(15) = 5.477$, $p < 0.001$) in both conditions.

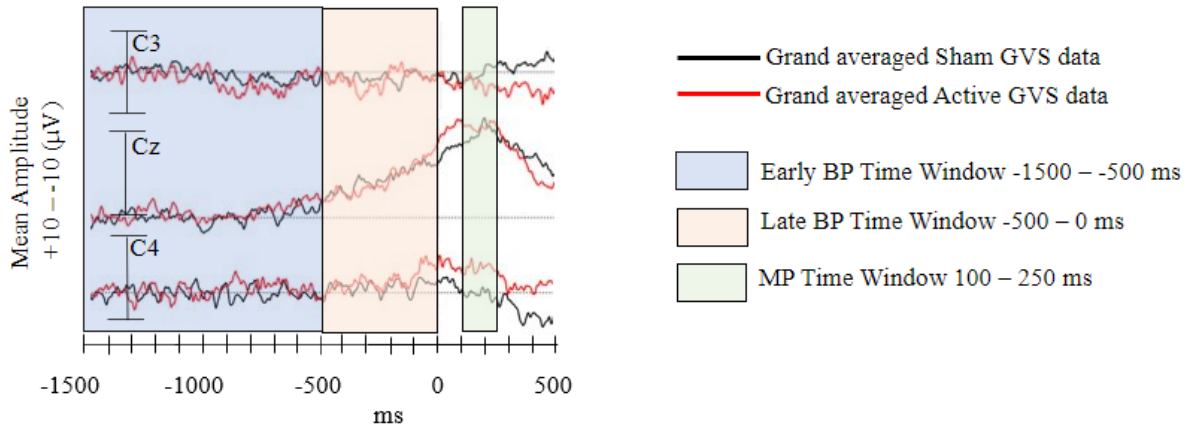

Figure 3. MRCP waveforms obtained from finger movements.

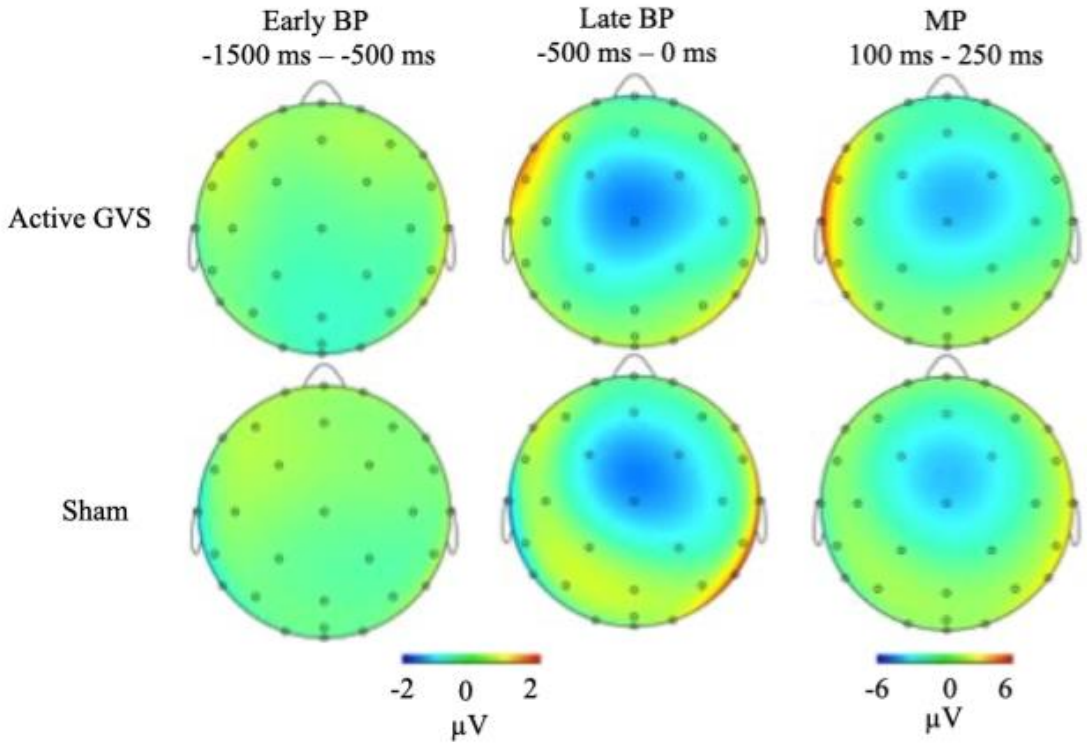

Figure 4. Topographical distribution of MRCPs obtained from finger movements.

Foot ERP results

Early BP. The ANOVA for the early BP of the foot yielded no statistically significant main effect of Condition (F (1,15) = 0.406, p = 0.534) or Electrode Site (F (1,15) = 0.475, p

= 0.626). There was also no significant interaction between Condition and Electrode Site (F (1,15) = 1.142, p = 0.333).

Late BP. The ANOVA for the late BP of the foot yielded a significant main effect of Electrode Site (F (1,15) = 10.912, p < 0.001), but not Condition (F (1,15) = 0.418, p = 0.528). There was also no significant interaction between Condition and Electrode Site (F (1,15) = 0.843, p = 0.440). Paired sample t-tests across the three electrode sites revealed that the mean amplitude was significantly larger at Cz (Sham: M = -1.5860, SD = 1.7582, GVS: M = -1.2721, SD = 2.2950) than C3 (Sham: M = -0.8528, SD = 1.2403, GVS: M = 0.8890, SD = 0.9269) (t(15) = 4.232, p < 0.001) and C4 (Sham: M = 0.2976, SD = 0.9976, GVS: M = 0.1077, SD = 1.1050) (t(15) = 3.954, p < 0.001) in both conditions.

MP. The ANOVA for the MP of the foot yielded a significant main effect of Electrode Site (F (1,15) = 30.443, p < 0.001), but not Condition (F (1,15) = 0.224, p = 0.643). There was also no significant interaction between Condition and Electrode Site (F (1,15) = 1.925, p = 0.164). Paired sample t-tests across the three electrode sites revealed that the mean amplitude was significantly larger at Cz (Sham: M = -4.0803, SD = 2.8497, GVS: M = -3.6516, SD = 3.2657) than C3 (Sham: M = -0.4274, SD = 2.1744, GVS: M = -0.2780, SD = 1.6126) (t(15) = 6.002, p < 0.001) and C4 (Sham: M = 0.6566, SD = 1.7020, GVS: M = 0.3268, SD = 1.8235) (t(15) = 6.082, p < 0.001) in both conditions.

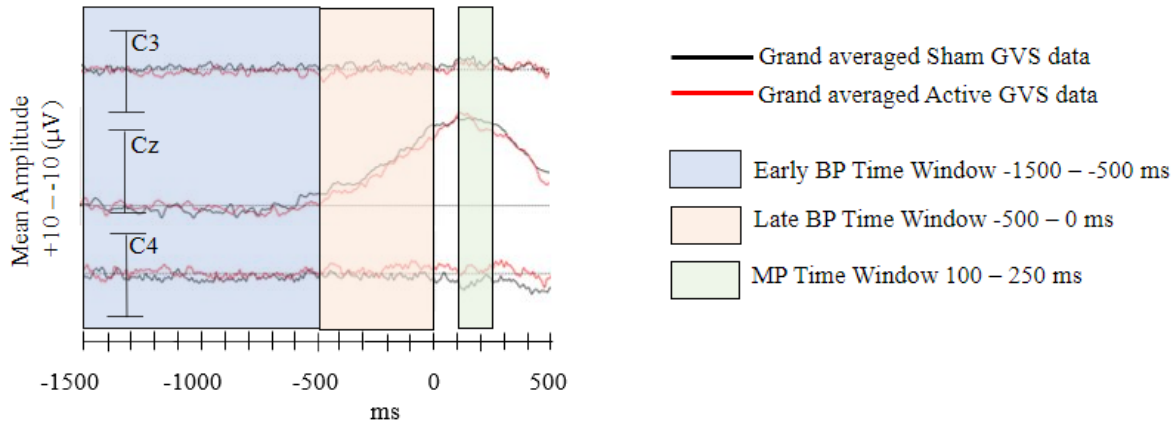

Figure 5. MRCP waveforms obtained from foot movements.

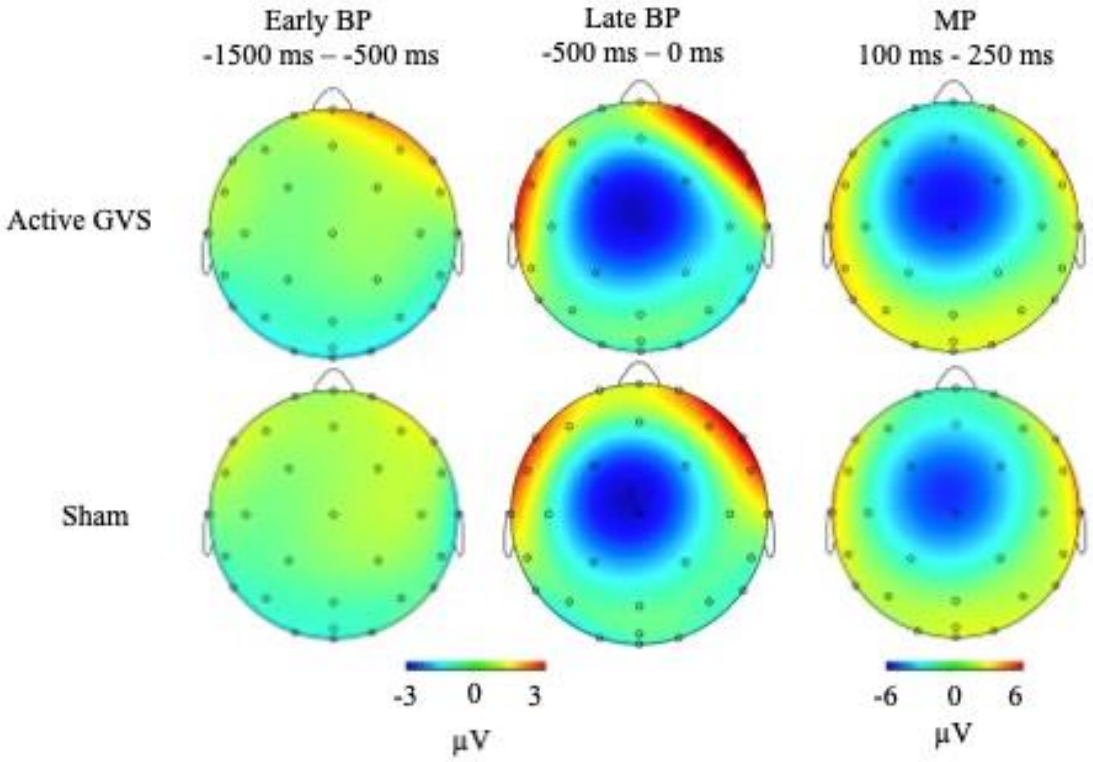

Figure 6. Topographical distribution of MRCP's obtained from foot movements.

SRT analysis. The SRT data were interrogated using a 2(Condition: GVS vs Sham) x 2(Limb: Finger vs Foot) repeated measures ANOVA

The ANOVA yielded no statistically significant main effect of Condition (F (1,6) = 0.057, p = 0.819) or Limb (F (1,6) = 0.183, p = 0.684). There was also no significant interaction between Condition and Limb (F (1,6) = 0.122, p = 0.739).

Exploratory Analysis

Exploratory analyses were conducted to help determine if certain clinical or demographic characteristics of the sample may help explain the absence of effect in the above ERP analyses. For both the Finger and Foot data, each of the independent components (early BP, late BP and MP), mean difference scores were calculated between the GVS and sham amplitudes and then correlated with the following participant characteristics: Years since diagnosis (to model disease chronicity), Hoehn & Yahr score (to model disease specificity), MDS-UPDRS Part III scores (to model motor impairment), MoCA score (to model cognitive impairment) and MiniBest score (to model balance).

Correlations

Overall. Linear correlations between the mean difference of Cz for each independent component (early BP, late BP and MP) of the Finger and Foot data and the participants' clinical and demographic characteristics listed above were completed. From these correlations only two correlations reached statistical significance, both in the foot data. The first significant correlation demonstrated that the fewer the years that had elapsed since diagnosis, the larger the negative difference mean amplitude of the Late BP between GVS and Sham amplitudes (see Table 3 and figure 7). The second significant correlation showed that those who scored higher on the MiniBest showed a larger negative mean difference of the MP between GVS and Sham (see Table 4 and figure 8). In addition, as expected many correlations between clinical characteristics reached significance - such as the lower a

participant scored in the miniBest, the higher their Hoehn & Yahr score - however the current thesis will not focus on these.

Table 3

Correlations between the Mean Difference of the Late BP Foot and Clinical Characteristics

Measure	Years Since Diagnosis	MDS-UPDRS Prt III	Hoehn & Yahr	MiniBest	MoCa
Years Since Diagnosis	-	-	-	-	-
MDS-UPDRS Prt III	0.390	-	-	-	-
Hoehn & Yahr	0.551*	0.351	-	-	-
MiniBest	-0.135	0.043	-0.503*	-	-
MoCa	-0.084	-0.298	-0.357	-0.081	-
Mean Difference	**0.606***	0.044	0.225	0.152	0.253

*Correlation is significant at the 0.05 level (2-tailed)

Table 4

Correlations between the Mean Difference of the MP Foot and Clinical Characteristics

Measure	Years Since Diagnosis	MDS-UPDRS Prt III	Hoehn & Yahr	MiniBest	MoCa
Years Since Diagnosis	-	-	-	-	-
MDS-UPDRS Prt III	0.390	-	-	-	-
Hoehn & Yahr	0.551*	0.351	-	-	-
MiniBest	-0.135	0.043	-0.503*	-	-
MoCa	-0.084	-0.298	-0.357	-0.081	-

Mean Difference	0.303	0.007	0.16	**0.514***	-0.133

*Correlation is significant at the 0.05 level (2-tailed)

Foot Late BP and Years since diagnosis.

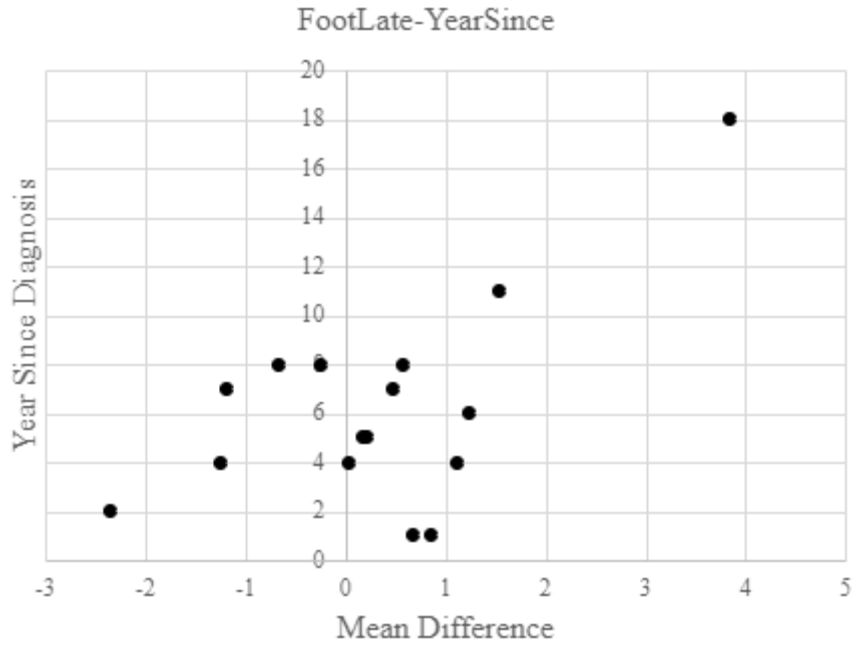

Figure 7. Scatter graph representing the mean difference in Cz of participants Foot Late BP correlated with Years since diagnosis.

Foot MP and MiniBest scores.

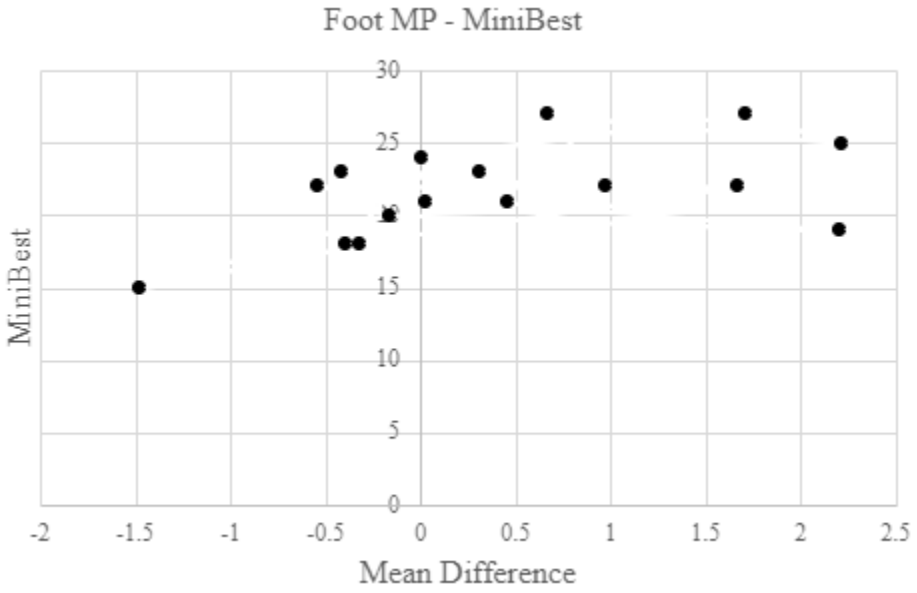

Figure 8. Scatter graph representing the mean difference in Cz of participants Foot Late MP correlated with MiniBest scores.

To further investigate if the significant correlates of Time since diagnosis and MiniBest score might have affected the ANOVA outcomes reported in the main ERP analyses, a Quade's test was conducted which is the non-parametric equivalent of the ANCOVA. It was not possible to use the ANCOVA because, for both the Time since diagnosis and MiniBest comparisons, Levene's test for the equality of variances was violated indicating that the sample variances were too uneven to proceed.

The Quade's rank analysis of co variance detected no significant differences between the GVS and Sham conditions when controlling for Years since diagnosis in participant's Late BP Foot data, $F(1, 11) = 0.908$, $p = 0.343$. Similarly, no significant differences were detected between conditions when controlling for MiniBest scores in participant's MP Foot data $F(1, 11) = 0.347$, $p = 0.557$.

Discussion

Overview

The present aim was to identify the effects of GVS on MRCPs obtained from a PD sample. This was done to identify an electrophysiological marker of change to help explain previous observations that vestibular stimulation can alleviate both clinical motor and cognitive symptoms of PD. It was hypothesised that during active GVS stimulation the mean amplitude of participants' BP would increase negatively compared to sham stimulation. This increase in negativity associated with active stimulation would be an indicative marker of change as the BP has previously been observed as diminished in PD populations. Contrary to the hypothesis, the main analysis of all components of the BP and MP found no differences between active GVS and sham stimulation. Exploratory correlations controlling for particular clinical characteristics did however reveal an increase in negativity of the late BP and MP in participants' Foot data. A secondary aim of this study, conducted on a subset of participants, was to investigate the effects of GVS on participants' ability to make a speeded response to the appearance of an external stimulus. No evidence was found in support of a modulatory effect. The pattern of effects that support these conclusions are described below.

The results for the main effect of Condition for Finger data found no significant effects of GVS on BP across all electrodes (C3, C4 and Cz). Likewise, the main analysis of Condition for participants Foot data found no significant effects of GVS on the BP across all electrodes. Significant main effects of Electrode Site were however identified for the MP in participant's Finger data as well as both the Late BP and MP in participants' Foot data. Consistent with previous literature, a larger mean amplitude at Cz compared to C3 and C4 irrespective of condition was observed. Analysis of participants reaction times in the SRT also failed to show a reliable difference between GVS and sham.

More informative outcomes were observed in the exploratory correlational analyses. These showed that the fewer the years that had elapsed since diagnosis, the larger the negative difference in mean amplitude of the Late BP during active GVS compared to sham. Further exploratory correlational analysis also demonstrated that those who scored higher on the MiniBest showed a larger negative mean difference of the MP during active GVS compared to sham. That is, those who struggled more with balance related symptoms showed a greater response to GVS. These significant correlations were further interrogated using Quade's analysis which showed that when modelled as co-variates they did not influence the outcomes of the main ANOVAs reported above

Theoretical implications

The current section will focus on the outcomes of the exploratory correlation analysis described above and consider why no significant interaction effects were found in the main analyses.

All correlation effects relating to the MRCPs were observed within the foot and not the finger data set. This thesis proposes that this may in part be due to the somatotopic representation of the different limbs. Foot movement has been observed to be in the superior part of the central sulcus, close to the midline, comparative to hand/finger movement which is predominantly associated to be more inferior and laterally located along the central sulcus (Eickhoff et al., 2007; Ruben et al., 2001). As such, lateralisation of MRCPs associated with finger movements compared to centralisation of foot movements can be anticipated. This has been observed in the late BP whereby Cz is reported as the maximal site, however, it has frequently been reported as maximal at the sites contralateral to the movement when investigating finger-movements (C3 and C4) (Shibasaki & Hallett, 2006). Of note, is that 12

of the 17 participants within this study used the right limb, as such, the lack of a significant finger effect may be in relation to insufficient power to detect a GVS-related change. The current thesis findings support this as a main effect of electrode was observed in the late BP within the foot data but not the finger data; in which the late BP was observed to be maximal at Cz compared to C3 and C4. During the correlation analysis, only the mean difference observed at Cz was used.

The link between vestibular dysfunction and balance problems is a well-rehearsed area of research, most commonly conducted through the observation of individuals with vestibular disease or loss (Halmagyi & Cremer, 2000; Baloh & Halmagyi 1996; Strupp et al. 2017). People with vestibular malfunction can experience a range of symptoms from dizziness, orientation problems and postural disequilibrium to the distressing visual symptoms of vertigo and nystagmus during activities that require head movement (Halmagyi & Cremer, 2000; Baloh & Halmagyi 1996). All of these symptoms caused by vestibular disturbances suggest that vestibular disorders markedly disrupt balance control. Most recently, bilateral vestibulopathy (BVP), a severe bilateral reduction or loss of vestibular function, has been defined by the Bárány Society and demonstrated to lead to severe balance deficits (Strupp et al. 2017). Disorders such as BVP highlight the significant impact deficits of the vestibular system has on balance. Vestibular dysfunction in PD is associated with deficits in VORs and vestibulospinal reflexes associated with gait and posture (White, Saint-cyr, & Sharpe, 1983). For example, Huh et al. (2016) applied the "sensory organization test" to study vestibular contributions to postural control in 47 PD patients and 26 age-matched controls. The sensory organization test comprises 6 conditions in which postural stability is challenged by changing visual and somatosensory input, thereby altering the dependence on vestibular input: (1) eyes open, floor fixed, visual surround fixed; (2) eyes closed, floor fixed, visual surround fixed; (3) eyes open, floor fixed, visual surround sway-referenced; (4) eyes

open, floor sway-referenced, visual surround fixed; (5) eyes closed, floor sway-referenced, visual surround fixed; (6) eyes open, floor sway-referenced, visual surround sway-referenced. They found that the PD patients exhibited significantly poorer postural sensory processing, especially when there was a greater reliance on vestibular information. In the present context, it is interesting that that those who presented with greater balance problems showed a greater MRCP response to GVS. The finding reaffirms the importance of vestibular afferent input in motor preparation and control. Moreover, it may also be the case that GVS benefited responses partly due to the rhythmic, predictable waveform administered, it helped restore signals from an otherwise under-active or dysfunctional vestibular system. In those individuals with more intact vestibular systems, such compensatory, 'upregulatory' stimulation may have been less important.

A further GVS-related effect uncovered by the exploratory correlation analysis was a larger GVS- related mean amplitude in the late BP in those with fewer years that had elapsed since their diagnosis of PD. This greater receptivity to vestibular stimulation was not observed in the earlier clinical trial conducted by Wilkinson and colleagues (2019) and has not been reported elsewhere. One possible reason why GVS exerted a stronger effect here is because, notwithstanding specific deficits within the vestibular pathways, the overall brain health of participants was better. In turn, this may have better supported signal transduction and the potential for sensory neuromodulation. It is well known that as PD progresses, neural pathways weaken and begin to degrade which can result in the progression of symptom and loss of synaptic plasticity due to dopaminergic loss (Zhuang et al., 2013). For example, motor skill learning in PD is highly variable results across patients (i.e., Abbruzzese et al., 2009), and worsens in participants who have had a diagnosis of PD for longer. Furthermore, as PD progresses, complex disturbances in functional connectivity on cortico-subcortical and cortico-cortical levels seem to worsen (Bočková & Rektor, 2019). Studies have reported

specific movement-related coupling from the prefrontal cortex (PFC) to the SMA in the gamma band in healthy controls; comparatively, PD patients in the off state did not express any frequency-specific coupling between these areas (Hertz et al., 2013). This deterioration of functional connectivity as PD progresses may affect the capacity for GVS to modulate some aspects of motor processing.

Although the exploratory analyses cast some light on how GVS might modulate motor responses in PD, it is worth noting that the neural entrainment effect that this study hoped to induce via use of a sinusoidal waveform did not materialise in the main analyses. By contrast, Lee et al. (2019) observed effects of sinusoidal GVS on resting state cortical functional connectivity in a PD sample. They observed that the application of AC GVS normalised the altered cortical coupling in M1, SMA and the premotor area (PMA) of theta, alpha and gamma frequency bands, and concluded that it is possible for VS to have a 'resting' effect on brain oscillations, disrupting pathological rhythms (Smith, 2018). On one hand, it could be argued that the exploratory effects of the Late BP and MP found in the current thesis perhaps provide some limited evidence of entrainment. However, the main analyses did not show a moderating effect. One reason for this may be the type of GVS frequency used. The current study used a small alternating current (AC) at a stimulation frequency of 0.01Hz. A recent study assessed the reaction time of 18 PD participants who underwent nine different random noise (RN) and ms (multisine) stimulation conditions - RN (4–200 Hz), ms-θ (4–8 Hz), ms-α (8–13 Hz), ms-β (13–30 Hz), ms-γ (30–50 Hz), ms-h1 (50–100 Hz), ms-h2 (100–150 Hz), and ms-h3 (150–200 Hz) - to assess if GVS motor affects were a function of stimulation frequency (Lee et al., 2021). Interestingly, both the ms-γ and the ms-β conditions produced a significant reduction time in RT compared to the RN condition, suggesting GVS is most beneficial in PD at frequencies between 13-50Hz. They found considerable inter-subject variability in the optimum stimulus type, although the

frequency range tended to fall within 8–100 Hz which is considerably higher than that used in the current study (Lee et al., 2021). Previously, the most prominent rational for the ameliorating effects of GVS was stochastic resonance which is mainly associated with RNGVS (Iwasaki et al., 2017). Stochastic resonance refers to the ability of a random noise signal to amplify the responsiveness of a non-linear biological system, such as the central nervous system, to weak, sub-threshold signals (McDonnel & Ward, 2011). Neural responsiveness to afferent signals is known to be dampened within PD (Yamamoto et al., 2005), therefore external random noise is believed to be effective as it likely causes depolarisation at random intervals which in turn render weak signals to be detectable by the system (Kim et al., 2013). However, this mechanism is not consistent with the enduring effects of CVS on PD observed in the Wilkinson et al. (2019) study which is instead more consistent with mechanisms associated with neural entrainment given the profile of the stimulation waveform. It should also be noted that in Wilkinson et al. (2019) the participants received CVS stimulation twice daily for 8 weeks which may imply that, unlike the protocol used here, repetitive stimulation at a higher frequency (between 8-100Hz) is needed to achieve neural entrainment.

Practical implications

The current study did not include any clinical assessments post-stimulation which makes it hard to know if the presence/absence of electrophysiological effects were accompanied by behavioural change. That said, several participants did provide unprompted feedback after the first session of stimulation, insinuating improvements in symptoms specific to participant. For example, one participant reported a subjective reduction in tremor, another reported increase swallowing abilities, both of which were significant main

symptoms of each participant. However, without a standardised clinical measure of these improvements, there is no definitive answer to whether these improvements were as a result of GVS or placebo effect. In order to address this, post-stimulation clinical assessments should be used in future research, most prominently those that have demonstrated improvements in previous research such as the motor and quality of life assessments used in the Wilkinson et al. (2019) and Yamamoto et al. (2005) study. In order to cover both motor and non-motor symptoms and quality of life, this thesis recommends: the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Non-Motor Symptom Scale (NMSS), the Montreal Cognitive Assessment (MoCA), Timed-up-and-go (TUG), the Hospitalised Anxiety and Depression Scale (HADS) and the Parkinson's Disease Questionnaire (PDQ-39).

The SRT task hoped to tap into a behavioural measure of participant's cognitive symptoms. Previous research, although in its infancy, has hinted at the potential for GVS to improve PD participants RT (Yamamoto et al., 2005; Lee, Smith, Lee &McKeown, 2021) however, analysis of participants RT from this thesis yielded no significant difference between sham and active GVS. A problem cited in the previous literature highlights that as bradykinesia is a key symptom of PD, SRT studies are unable to disentangle whether RT results are a reflection on decision-making or on movement speed (Lee et al., 2021). Reaction time within this thesis was measured only using behavioural response, as such the ability to disentangle the different components of sensory integration, decision making and production of movement in response to this type of task was not possible. In order to disentangle SRT data, EEG analysis of other event related potentials (ERPs) in addition to the MRCPs observed in this study could be recommended (Lee et al., 2021). Firstly, visuospatial attention can be measured by analysing the N2 component which is an index target detection and is observed in occipito-temporal electrode sites 200-350ms post stimulus onset (Folstein & Van

Petten, 2008). Further insight into the effects of GVS on higher order cognitive functioning, specifically the allocation of attentional resources and working memory, could be achieved by analysing ERP component P3 (Duncan-Johnson, 1981). P3 is observed to occur 300ms after stimulus onset and is reported as maximal over lateralised inferior-parietal regions – electrodes P3 and P4 (Polich, 2007). By observing the GVS-related effects on both N2 and P3 it would allow for the disentangling of the cognitive and motor aspects associated with the SRT used.

Although the current thesis failed to find evidence of GVS modulation on specific MRCPs, the BP and the MP, it remains possible that other physiological processes that were not measured did show change. One such physiological marker is heart rate variability (HRV). HRV refers to the fluctuations of time in between successful heartbeats and is a direct insight into an individual's autonomic nervous system (ANS) health through assessing the parasympathetic modulation of cardiac activity (Shaffer & Ginsberg, 2017; Heimrich, Lehmann, Schlattmann, & Prell, 2021). Heimrich, Lehmann, Schlattmann, and Prell (2021) conducted a meta-analysis of forty-seven HRV studies in PD populations and concluded that there was some evidence to suggest impaired parasympathetic regulation positively correlated with disease advancement. This conclusion corresponds with the assumption that the vagus nerve becomes increasingly damaged throughout the course of PD (Walter et al., 2018; Braak et al., 2004). The notion that vestibular stimulation could influence HRV is supported by the direct vestibulo-cardiac reflex which refers to rapid cardiovascular changes to maintain blood pressure and distribution after a change in posture is detected by the vestibular system. This association is evidenced by those with vestibular deficits who fail to demonstrate evidence of this rapid effect on heart rate during small backwards drops (Radtke, Popov, Bronstein & Gresty, 2000). Despite this, the effectiveness of VS on HRV is disputed. Research has indicated that AC GVS reportedly alters the RR interval variability in young adults (Tanaka

et al., 2012, 2014); conversely several studies using CVS have reported no difference in HRV of neurologically healthy individuals (Ziarati, Taziki, & Hosseini, 2020; Kasbekar et al., 2010). This variation in results may be due to the differences in the type of VS used as studies predominantly reporting no effects on HRV used CVS. Comparatively studies using AC GVS and nGVS report significant findings in both healthy controls and in participants with neurodegenerative autonomic failure (Hidaka, Nozaki & Yamamoto, 2000; Hidaka et al., 2001; Yamamoto et al., 2002). Studies investigating the impact of GVS on HRV in PD is in its infancy. Currently there is only one study highlighting GVS' potential therapeutic applications in PD populations as it was shown to modulate autonomic cardiovascular function through HRV analysis (Yamamoto et al., 2005). Building upon this finding, research similar to that of the current thesis could focus on HRV as a biological marker of change to highlight the effects of GVS in a PD sample via an explanation of modulating the autonomic nervous system.

Other markers of changes to consider the effects of VS in a PD population is cortical excitability associated with beta event-related dyssynchronisation (ERD). Beta ERD refers to the attenuation of beta frequency synchronization that occurs immediately preceding and during voluntary movements (Pfurtscheller, 1997). Analysis of changes in cortical excitability relating to beta rhythm event-related synchronisation and desynchronisation (ERS and ERD respectively) could be examined specifically ERD prior to movement onset and ERS post. Research in PD populations and animal models suggests that dopamine depletion induces an excessive synchronization in the beta range (15–30 Hz) in the basal ganglia and associated circuits (Neumann et al., 2017). Beta oscillations in the subthalamic nucleus are coherent with oscillations in ipsilateral sensorimotor (SM), adjacent premotor cortex, SMA, dorsolateral prefrontal cortex and M1 in PD (Priori and Lefaucheur, 2007; Lalo et al., 2008; Marsden et al., 2001). Beta ERD and ERS have been shown to significantly reduce with the

admission of L-dopa and deep brain stimulation in PD populations (Kühn et al., 2008; Brown et al., 2001). Importantly, transcranial alternating current stimulation (tACS) has also been shown to temporarily attenuate these excessive beta oscillations observed during EEG and magnetoencephalography (MEG) of a PD sample (Del Felice et al., 2019; Krause et al., 2014). Furthermore, these studies identified a significant reduction in motor symptoms, measured by the MDS-UPDRS III mimicking the effects of L-dopa and DBS in PD. These findings are of particular interest because, like GVS, tACS also involves the application of external sinusoidal electrical currents (Helfrich et al., 2014). Furthermore, the current thesis only performed analysis involving evaluation of the motor cortices (electrodes C3, Cz, C4) as previously reported (REFERENCES). However, this is a more complex picture that involves temporal changes over the much broader area of the sensorimotor system. Of specific interest, would be activity within the somatosensory cortices (Melnick et al., 2017) in relation to the integration of the sensory stimulus. It would therefore be interesting to assess whether GVS is able to replicate the previously stated findings and attenuate these excessive beta oscillations during stimulation as well as observe if these effects persisted after repeated stimulation resulting from neuroplastic change.

Limitations and future research

The unintended recruitment of only 17 participants (and too few controls to analyse) is likely a major limiting factor and may in part explain the absence of statistically significant main effects or interactions. An even smaller sample of participants – seven – completed the SRT which raises similar concerns about lack of statistical power. Another methodological limitation, to consider is the length of the sessions; the stimulation sessions proved to be exceptionally long, lasting around 2.5-3 hours each. The negative effects of fatigue on EEG

are well known (Li et al., 2020) and it should be noted that some participants fell asleep during the recording sessions.

Currently, there is no research on how disease sub-type, chronicity and severity affect the BP in PD. which raises the possibility that GVS can moderate the MRCP but only in a subset of participants not recruited in sufficient number here. Lee, Smith, Lee and McKeown (2021) found large interpersonal differences in how GVS affected simple reaction time that depended on the frequency of stimulation applied (between 8-100Hz). They suggested that GVS is probably not a one-size-fits all technique and instead will be most beneficial when personalised across a range of clinical and demographic characteristics. To return to the point made above the baseline clinical characteristics of the sample used for the current thesis may have affected the extent to which participants were responsive to GVS. In general, participants scored mid to high scores on the miniBEST with only four demonstrating severe balance impairment. Of those four participants, three demonstrated an increase in negativity of their MP during active stimulation compared to sham. Given that vestibular system is crucial in balance function, PD individuals with balance problems may be particularly responsive to vestibular stimulation. Indeed, there is evidence to suggest that PD with postural instability represents a discrete sub-type of PD (Factor, Steenland & Payami, 2011). Future studies should investigate the GVS effects on the MRCPs from these PD individuals with the postural instability sub-types.

Another significant study limitation is the absence of an age-matched neurologically healthy control group. Recruitment of the control group was halted due to the nationwide lockdown in response to the COVID-19 pandemic and there was insufficient time leftover to recruit both the remaining patients and controls. As a consequence, there was no clear baseline of the early-, late-BP or MP from with which to identify potential variance in this activity within the PD sample. Previous studies investigating the BP in PD have demonstrated

that it is diminished in relation to the BP of a normal, healthy control group (Cunnington et al., 1999; Dick et al., 1989; Jahanshahi et al., 1995), but specific estimates were needed here to be of use. Thus, it was not possible for this study to identify if GVS has the potential to boost the BP of PD participants to 'healthy aged-matched control' levels given that to compare to.

Conclusion

In summary, this thesis did not find an electrophysiological marker of change to better understand the mechanisms behind the alleviating effects vestibular stimulation has previously demonstrated in Parkinson's disease. Exploratory analysis revealed some interesting correlations suggesting that the effects of GVS on MRCPs may be modulated by certain clinical characteristics, however due to a lack of significance these conclusions cannot be definite. These results lead to suggest that inter-personal differences must be considered when exploring vestibular stimulation as a potential treatment for Parkinson's disease and other neurological conditions. This thesis was limited by its small sample size and lack of neurologically healthy control group. Future research must explore the effect of vestibular stimulation on other mechanisms of effect and how inter-personal differences may affect responsivity towards different vestibular stimulation frequencies.

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Appendix A

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problems.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild:	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

R ☐

L ☐

SCORE

3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problem.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.
2: Mild:	Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.
3: Moderate:	Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

R ☐

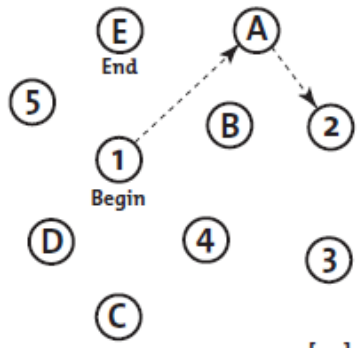
L ☐

Appendix B

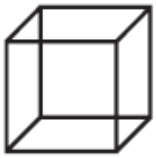
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



[ ]

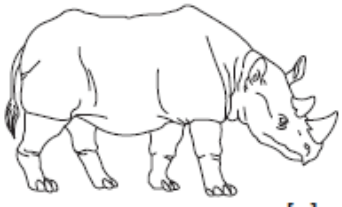


Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands — /5

NAMING

[ ]



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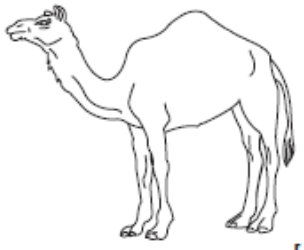

[ ] — /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 — /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] — /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — /2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

— /5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — /6

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Normal ≥ 26 / 30

TOTAL — /30

Add 1 point if ≤ 12 yr edu

Appendix C

ANTICIPATORY ***SUB SCORE:*** /6

1. SIT TO STAND

Instruction: "Cross your arms across your chest. Try not to use your hands unless you must. Do not let your legs lean against the back of the chair when you stand. Please stand up now."

(2) Normal: Comes to stand without use of hands and stabilizes independently.
(1) Moderate: Comes to stand WITH use of hands on first attempt.
(0) Severe: Unable to stand up from chair without assistance, OR needs several attempts with use of hands.

2. RISE TO TOES

Instruction: "Place your feet shoulder width apart. Place your hands on your hips. Try to rise as high as you can onto your toes. I will count out loud to 3 seconds. Try to hold this pose for at least 3 seconds. Look straight ahead. Rise now."

(2) Normal: Stable for 3 s with maximum height.
(1) Moderate: Heels up, but not full range (smaller than when holding hands), OR noticeable instability for 3 s.
(0) Severe: $\leq$ 3 s.

3. STAND ON ONE LEG

Instruction: "Look straight ahead. Keep your hands on your hips. Lift your leg off of the ground behind you without touching or resting your raised leg upon your other standing leg. Stay standing on one leg as long as you can. Look straight ahead. Lift now."

Left: *Time in Seconds Trial 1:_____Trial 2:_____*
(2) Normal: 20 s.
(1) Moderate: < 20 s.
(0) Severe: Unable.

Right: *Time in Seconds Trial 1:_____Trial 2:_____*
(2) Normal: 20 s.
(1) Moderate: < 20 s.
(0) Severe: Unable

To score each side separately use the trial with the longest time.
To calculate the sub-score and total score use the side [left or right] with the lowest numerical score [i.e. the worse side].

Appendix D

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Appendix E

Perception of Stimulation Questionnaire

Participant Number	Date of Assessment	Experimenter Initials
	____/____/_____	

1) Did you notice the stimulation (*please circle*): Yes/No

If **NO**, you may give this questionnaire back to the experimenter.

If **YES**, please answer the following:

2) Did you feel any physical sensations (*select more than one if needed*)?
   - ☐ Itching (behind ears)
   - ☐ Prickling (behind ears)
   - ☐ Warming sensation (behind ears)
   - ☐ Tingling (behind ears)
   - ☐ Other: _____

3) Did it feel like you were moving?
   - ☐ Swaying
   - ☐ Vibration
   - ☐ Rotation
   - ☐ Other: _____

4) Which way were you moving?
   - ☐ Through the head and feet (=Yaw)
   - ☐ Through the nose and occiput (=Roll)
   - ☐ Through both ears (Pitch)
   - ☐ Other:_____

5) Was it just your head or your whole body that felt like it was moving?
   - ☐ Your whole body
   - ☐ Only your head

6) Did you feel anything else (*please describe in the box below*)?