The Electrophysiological Effects of Vestibular Stimulation in Parkinson's Disease

Kamyla Marques

School of Psychology

University of Kent

Acknowledgments

First and foremost, I would like to thank Professor David Wilkinson and Dr Shelley Duncan for being the best supervisors. It was with their encouragement, support and guidance that I was able to overcome the many challenges inherent to this project. I would also like to thank Professor Heather Ferguson for all the technical expertise she provided, particularly during the first year of this project.

Secondly, my thanks also go to my colleagues Charlotte Wheeler and Jade Fawkes who kindly helped in the development, data collection and analysis of this project. Their problem-solving skills, positive attitude and sharp wit made working on this project so much more interesting than if I undertook it on my own. I would also like to thank my closest friends: Christie Marsh, Amelia Turrell, Sapna Gupta, Vaida Jakubauskaite and Rhona Lonergan. With them, I shared many of the most difficult and proudest moments of this project, filled with tears of both sorrow and laughter. I would also like to give special mention to my family and fiancé, Jack Hoayun, who were always there to pick me up after a bad day and to make a good day brighter.

Lastly but never the least, I would like to extend my warmest thanks to the participants of Study 3, who so kindly and selflessly provided their data. I am so happy to have met such wonderful people. My hope is that this project can help make a difference to individuals like them in the future.

Contents

COVID-19 Statement

The completion of data collection for Study 3 in this thesis was prevented because of the nationwide lockdown that started on March 2020 in response to the global pandemic of COVID-19. The original plan for Study 3 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 decided to cease data collection and report the data already collected from 10 PD participants in 2019.

Abstract

A recent study showed that vestibular stimulation can produce long-lasting alleviation of motor and non-motor features in Parkinson's disease (PD). The improvements observed in motor symptoms were of particular note and may provide an indication as to one of the underlying physiological mechanisms of action for vestibular stimulation. An electrophysiological marker known to be abnormal in PD is the Bereitschaftpotential (BP) of the movement-related cortical potentials (MRCPs). One aim of this thesis was to observe the effects of galvanic vestibular stimulation (GVS) on MRCPs in PD to better understand its underlying physiological mechanisms. Many studies measuring the electrophysiological response to GVS have employed pre- versus post-GVS protocols, limiting observations to only after stimulation. The investigation of the mechanisms during GVS is limited by the large artifacts that contaminate the electroencephalograph (EEG). Previous studies have described pre-processing strategies to remove the GVS-related artifact, but these have many limitations. Thus, another aim of this thesis was to describe an artifact removal strategy using a novel approach of employing Independent Components Analysis (ICA) to identify, quantify and eliminate the GVS-related artifact from the EEG data. Study 1 (n = 11) validated this strategy by successfully removing the GVS-related artifact from MRCP data when manipulating the GVS frequency. Study 2 (n = 9) provided further validation by showing successful removal of the GVS-related artifact associated with a higher GVS intensity. Study 3 applied the methodology validated in the first two studies to a PD sample and found a significant increase in the early BP associated with GVS. This suggests that vestibular stimulation may improve motor features in PD through modulation of underlying pathological oscillations associated with motor dysfunction.

The Electrophysiological Effects of Vestibular Stimulation in Parkinson's Disease

Overview

Stimulating the vestibular system via caloric or thermal currents has been shown to alleviate the symptoms of several neurological conditions such as hemi-spatial neglect, episodic migraine and Parkinson's disease (PD) (Wilkinson et al., 2014; Wilkinson et al., 2019; Wilkinson, Kilduff, McGlinchey & Milberg, 2005). The most robust and long-lasting effects have been observed in PD (Wilkinson et al., 2019). A recent clinical study found that an eight-week treatment of caloric vestibular stimulation (CVS) delivered to patients diagnosed with PD produced significant and long-lasting amelioration from motor and non-motor features of PD (Wilkinson et al., 2019). The motor improvements were especially notable with significant and enduring reductions being observed in the motor aspects of daily living and motor examination of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Other studies have also demonstrated the therapeutic potential of galvanic vestibular stimulation (GVS) in PD (Khoshnam et al., 2018; Yamamoto et al., 2005). As of yet, there have been very few formal investigations into the underlying physiological mechanisms of action during vestibular stimulation. The reductions in motor symptoms by vestibular stimulation in PD may provide a useful indication as to one of the underlying mechanisms. An electrophysiological marker known to be abnormal in PD is the Bereitschaftpotential (BP) component of the movement-related cortical potentials (MRCPs). The effect of vestibular stimulation on the BP in PD may provide a preliminary understanding of its underlying mechanisms of action. One recent study showed that GVS affected MRCPs in healthy participants (Lee, 2015). This study and many of the other studies on the effects of vestibular stimulation on responses within the electroencephalograph (EEG) have generally employed a pre- versus post-stimulation paradigm, precluding observations during the

stimulation period (Lee, Pan & Yoon, 2016; Lee et al., 2014). As of yet, it is unclear if the therapeutic effects of vestibular stimulation on motor symptoms may partly stem from mechanisms occurring during stimulation as opposed to afterwards. The investigation of EEG responses during vestibular stimulation is limited by the large artifacts that contaminate the data during concurrent recording of EEG and application of electrical stimulation via GVS (Lee, McKeown, Wang & Chen, 2018). Only five previous studies have measured EEG responses during GVS and employed different pre-processing strategies to remove the GVS-related artifact from the EEG data. These studies have several limitations, one of which is failing to report the effects of the processing strategy itself on the EEG data, which prevents replication. Another is that participants' data were only measured at rest, instead of during a specific task. Thus, there is a need to observe MRCPs elicited by motor tasks during GVS in PD. Investigating this will enable us to begin to understand the vestibular stimulation mechanisms of action on the motor symptoms in PD observed previously (Wilkinson et al., 2019).

The overall aims of this thesis are 1) to develop and evaluate a novel methodology to conduct concurrent GVS-EEG studies to obtain MRCP data and 2) to observe the direct effects of GVS on MRCPs in a PD and neurologically healthy, age-matched population[1]. Both aims related to the wider goal of finding the underlying therapeutic mechanisms of vestibular stimulation. Achieving the first aim involved evaluating the use of Independent Components Analysis (ICA) to identify, quantify and ultimately remove the GVS-related artifact from the EEG data. This facilitated the effective observation of MRCPs during GVS in PD participants and healthy individuals. Observing the direct effects of MRCPs in PD may help to explain the improvements

[1] However, due to the COVID-19 pandemic, we were unable to complete data collection for the healthy, age-matched control group.

in motor features of PD previously reported (Khoshnam et al., 2018; Wilkinson et al., 2019). Providing data for a potential mechanism of action may facilitate obtaining regulatory approval for the use of vestibular stimulation in clinical conditions. Moreover, once a clinically relevant mechanism of action is known, studies can then manipulate dosage with the aim of maximizing benefits for patients. This may involve identifying best responders in terms of physiological responsivity, which in turn can help in determining treatment response.

This thesis begins with a literature review outlining the vestibular system, vestibular stimulation, and its potential influence on the pathological mechanisms of PD. Next is a section on methodological development describing the single-case pilot studies conducted to help determine appropriate GVS parameters used in the subsequent group studies. Next are Studies 1 and 2 which directly addressed the first aim of this thesis. The main aim of Study 1 was to evaluate the effectiveness of the processing strategy to remove the GVS-related artifact from EEG data in a group of 11 participants. One objective of Study 1 was to manipulate the GVS frequency applied during EEG recording. The aim of Study 2 was the same as Study 1, however, the GVS intensity was manipulated by increasing it from 0.20-0.30 mA to 0.30-0.40 mA to determine whether the GVS-related artifact could be removed when using a higher GVS magnitude. An additional objective of Study 2 was to assess the feasibility of implementing a foot tapping task to the experimental protocol. Study 3 evaluated the feasibility of applying the processing strategy employed in Studies 1 and 2 to a PD population.

Vestibular system

The vestibular system has traditionally been associated with autonomic functions that lie largely outside of our conscious control such as balance, postural control and ocular control during head movements (Grabherr, Macauda & Lenggenhager, 2015; Clark, 1970). The vestibular sensory

organs within the inner ear consist of the fluid-filled semi-circular canals and the otolith organs (saccule and utricle), which detect rotational head motion, linear acceleration and gravitational forces (Fitzpatrick & Day, 2004). Recent research suggests the vestibular system also plays an important role in higher-order functions involved in cognition, emotion and volitional movement (Bent, Inglis & McFadyen, 2004; Bigelow & Agrawal, 2015; Cullen, 2012; Smith & Zheng, 2013; Smith, 2017; Smith, 2018). This finding stems from three lines of enquiry: neuropsychological, anatomical and neuromodulatory. This growing body of evidence helps explain the growing number of studies that investigate vestibular stimulation as a potential adjunctive or alternative therapy for neurological disorders such as PD, prosopagnosia, episodic migraine and hemi-spatial neglect (Wilkinson et al., 2014; Wilkinson et al., 2017; Wilkinson et al., 2019; Yamamoto et al., 2005). Harnessing these interactions between the vestibular system and higher-order brain regions may help alleviate the dysfunction that emerges from damage to these brain regions (Black & Rogers, 2020).

The role of the vestibular system in cognition and emotion is often highlighted when there is a loss of vestibular function. For example, it has long been known that there is a strong relationship between vestibular disturbances and affective disorders (Grabherr et al., 2015). Many epidemiological studies have reported the high prevalence of anxiety and panic disorders, phobias, traumatic stress, obsessive disorders and depression in patients presenting with vertigo syndrome, peripheral vestibular loss (BVL) and postural-perceptual dizziness (PPPD) (Best, Eckhardt-Henn, Tschan & Dieterich, 2009; Eagger et al., 1992; Staab, 2016). Conversely, individuals suffering from psychiatric disorders such as depression, anxiety, schizophrenia and phobias frequently complain of balance problems, dizziness and vertigo – symptoms associated with vestibular dysfunction (Best, Bense & Dieterich, 2007; Hallpike, Harrison & Slater, 1951; Jacob, Moller,

Turner & Wall, 1985; Nagaratnam & Bou-Haidar, 2005). These studies suggest a link between the vestibular system and limbic networks associated with emotional processing (Rajagopalan et al., 2017). Indeed, many animal studies have provided evidence for indirect pathways linking the vestibular system to structures within the limbic system such as the hypothalamus and amygdala (Rajagopalan et al., 2017). Extreme vestibular conditions such as hypo- or hyper-gravity environments or rapid accelerations of the head have been shown to activate the stress response, specifically activating the hypothalamo-pituitary-adrenocortical (HPA) axis (Horowitz, Blanchard & Morin, 2004; Murakami et al., 2002). Markia, Kovacs and Palkovits (2008) found that this stress response may be underpinned by a pathway from the medial vestibular nucleus to the hypothalamic paraventricular nucleus (PVN). Other possible indirect pathways between the vestibular system and the amygdala have also been proposed, with neural tracer viruses injected into vestibular neurons spreading rapidly to amygdala cells in the Mongolian gerbil (Metts, Kaufman & Perachio, 2006). The role of the amygdala in emotion regulation has been extensively studied, particularly in terms of its connections to the prefrontal cortex which if compromised can lead to pathological anxiety (Kim et al., 2011).

Further supporting this link are studies showing that artificial vestibular stimulation can alter mood states and emotions as well as possibly alleviating the psychiatric disorder mania (Grabherr et al., 2015; Rajagopalan et al., 2017). Positive mood ratings have been shown to decrease during left ear caloric vestibular stimulation (CVS) when compared to sham stimulation in neurologically healthy participants (Preuss, Hasler & Mast, 2014). Moreover, in the nineteenth century, artificially activating the vestibular system using spinning chairs was a common therapeutic intervention for mania (Grabherr et al., 2015). A recent study indeed confirmed that placing healthy participants in a spinning chair can improve mood states with participants reporting

feeling ‘relaxed’ and ‘calm’ (Winter et al., 2013). A small clinical study also found that manic delusions in three schizophrenic patients were transiently reduced following CVS of the left ear (Levine et al., 2012). It is possible that vestibular information modulates emotion via regulation of thalamocortical circuits, limbic function and/or autonomic responses (Rajagopalan et al., 2017).

There is also much evidence to suggest that the vestibular system modulates cognitive processes especially those involved in spatial memory (Bigelow & Agrawal, 2015; Dilda, MacDougall, Curthoys & Moore, 2012). Indeed, some studies have suggested indirect connections from the vestibular system to brain regions associated with memory, such as the hippocampus (Hitier, Besnard & Smith, 2014; Smith, 1997). At an anatomical level, the vestibular nerve projecting from the peripheral vestibular labyrinth – containing the semi-circular canals and otolith organs – sends sensory information to the vestibular nucleus complex (VNC) in the brainstem and cerebellum (Stiles & Smith, 2015). The VNC contains two types of vestibular neurons: the vestibular-ocular reflex (VOR) neurons and the vestibular only (VO) neurons (Cullen, 2012). Whilst VOR neurons are associated with oculomotor control of eye movements, the VO neurons project to motor neurons at the cervical and thoracic levels of the spinal cords and to higher-level level brain regions such as the thalamus and hippocampus (Smith, 1997; Stiles & Smith, 2015). Indeed, lesioning the vestibular nerve in rats has been shown to produce changes in hippocampal theta rhythms and eliminating vestibular signals can cause disruption in the firing rate of head direction cells in the rat hippocampus (Russell et al., 2006; Stackman, Clark & Taube, 2002). These indirect connections may play a role in the severe spatial memory deficits observed in patients with bilateral vestibular loss (BVL), as evidenced by their poor performance on the virtual Morris water maze compared to healthy controls (Brandt, Dieterich & Strupp, 2005). The link between the vestibular and cognitive systems has also been demonstrated in neurologically intact

individuals with many studies showing enhancing or disrupting effects of vestibular stimulation on tasks measuring memory (Wilkinson et al., 2008). In this way, the vestibular system may play an important role in the representation of the body's position in space with the abolishment of vestibular signals leading to spatial memory deficits in both humans and animals (Baek, Zheng, Darlington & Smith, 2010; Brandt et al., 2005). Maintaining a good representation of one's position in space is crucial for navigation in 3-dimensional space which in turn affects motor function such as gait coordination (Lacour & Borel, 1993). Language and visual attention are other cognitive processes affected by vestibular stimulation (Dilda et al., 2012; Lenggenhager, Lopez & Blanke, 2008, Wilkinson, Morris, Milberg & Sakel, 2013).

Vestibular stimulation

The findings outlined above give reason to believe that the vestibular system can be harnessed as a therapeutic pathway to brain regions damaged by acquired injury or degeneration. Indeed, investigations of whether vestibular stimulation produces clinical benefits in neurological conditions have yielded many promising results. Caloric and galvanic vestibular stimulation (CVS and GVS, respectively) have shown particularly favourable results. CVS involves applying thermal currents to the external auditory canal, which leads to stimulation of the vestibular nuclei in the brainstem (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). CVS was traditionally used to assess balance and brainstem function by irrigating the external auditory canal with warm or cold water (or air) (Been et al., 2007). However, this procedure elicited some unpleasant side effects such as nausea, dizziness and vomiting and was not amenable for home use by patients (Been et al., 2007; Black et al., 2016).

This led to the recent development of a solid-state CVS device consisting of a wearable headset fitted with ear-probes that warm and cool, which has proved more feasible for chronic, therapeutic use and tolerable for patients (Black et al., 2016). On the other hand, GVS involves the application of gentle electrical currents to the mastoid processes via transcutaneous electrodes attached to a stimulation device (Fitzpatrick & Day, 2004). It functions by activating the vestibular nerve via polarisation effects of the eighth cranial nerve projecting from both the semi-circular canals and the otolith organs in such a way as to emulate natural head motion (Fitzpatrick & Day, 2004; Goldberg, Smith & Fernandez, 1984; Utz, Dimova, Oppenlander & Kerkhoff, 2010).

Caloric vestibular stimulation (CVS) has been shown to affect pain, hemi-spatial neglect, episodic migraine, minimally conscious states, and PD (Moon, Lee & Na, 2006; Ramachandran, McGeoch & Williams, 2007; Vanzan et al., 2017; Wilkinson, Podlewska & Sakel, 2016; Wilkinson et al., 2017; Wilkinson et al., 2019). A clinical case study of two patients with post-stroke, thalamic pain showed that CVS via irrigation produced immediate and sustained reductions in self-reported pain that lasted for several weeks following the end of treatment (Ramachandran et al., 2007). CVS has also been shown to transiently alleviate the attentional bias towards the ipsilesional visual field associated with hemi-spatial neglect resulting from stroke (Moon et al., 2006). This was evidenced by increased spontaneous exploration of the contralesional side of space as well as improved performance on tests of visual neglect such as line crossing, in which participants are asked to cross lines slanted at various angles on a page (Ruben, 1985). Additionally, two recent case studies employing the solid-state CVS device developed by Black et al. (2016) demonstrated improvements in post-stroke aphasia ($n = 3$) and increases in voluntary responses of individuals in a minimally conscious state ($n = 2$) (Vanzan et al., 2016; Wilkinson, Morris, Milberg & Sakel, 2013). These findings were followed by two randomised-controlled trails (RCTs) that recruited

larger sample sizes. 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. Moreover, CVS appears to have a significant and lasting effect on PD symptoms. A single-case study by Wilkinson, Podlewska and Sakel (2016) found significant and lasting improvements in standardised neuropsychological evaluations of motor, cognitive, affective and independent function following a 3-month treatment protocol of CVS for a 70-year-old male diagnosed with PD. A recent RCT replicated these findings in a larger sample, showing significant and long-lasting reductions in motor and non-motor symptoms in PD patients receiving active CVS as opposed to a placebo group receiving sham stimulation (Wilkinson et al., 2019). These effects were found to last up to five months following the end of the treatment period, and I return to them later.

Galvanic vestibular stimulation (GVS) has also yielded promising results in terms of its therapeutic potential in neurological conditions. Preliminary findings for the clinical benefit of this approach has been demonstrated for prosopagnosia, with a single-case study of a patient left unable to recognise faces following right hemisphere damage, showing significantly improved performance in a face matching task during application of GVS (Wilkinson et al., 2005). Moreover, a recent RCT 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). This was demonstrated by significant improvements in diagnostic outcomes and quality of life (QoL) as measured by the Behavioural Inattention Test (BIT) and the Barthel Index (BI) from pre-stimulation baseline assessments. As with the PD results for CVS, GVS was also shown to have a lasting effect on attentional deficit beyond the stimulation

period in this RCT (Wilkinson et al., 2014). This enduring effect persisted regardless of the number of GVS sessions (1, 5 or 10) received by participants, suggesting that a single session of vestibular stimulation is sufficient to produce long-lasting changes.

Putative mechanisms of vestibular stimulation

The investigation into the clinical effects and feasibility of vestibular stimulation has preceded our understanding of its underlying mechanisms. The few studies that have investigated mechanisms focus on its effect on central brain activations, employing the use of functional imaging methods such as PET and fMRI. These studies have revealed the increases and decreases in activation as measured by the BOLD signal during stimulation of the vestibular system. These studies demonstrated that signals from the vestibular system can influence a widespread network of structures. To cite examples, changes produced by vestibular stimulation have been observed in the putamen, caudate nucleus, insula, temporo-parietal junction, thalamus, hippocampus and premotor regions of the frontal lobe (Bense et al., 2001; Bottini et al., 1994; Bucher et al., 1998; Della-Justina et al., 2015; Emri et al., 2003; Lobel et al., 1998; Stephan et al., 2005; Vitte et al., 1996). Despite this, the functional relevance of these activations remains unclear as these imaging studies are frequently conducted whilst participants are at rest without engaging in a task and participants are usually neurologically healthy. To explain the clinical effects of vestibular stimulation, studies need to employ functionally, and clinically relevant markers elicited by equally relevant tasks such as reaction time (RT) tasks (Dick et al., 1984) in individuals with a brain disorder.

The use of EEG may have several advantages over functional imaging methods in the investigation of the underlying mechanisms of vestibular stimulation. EEG measures the moment-to-moment voltage fluctuations produced by the synchronous activity of millions of pyramidal

cortical cells from the scalp (Luck, 2014). In this way, the electrophysiological responses associated with a specific task can be recorded with a high temporal resolution (Luck, 2014). Thus, EEG can be employed to observe the effects of vestibular stimulation on the time course of brain activity associated with a specific task – so-called event-related potentials (ERPs). This is different to functional imaging methods whose high spatial resolution limits the investigation of the effects of vestibular stimulation to which brain areas are affected. Due to the time sensitive nature of GVS and CVS, these imaging methods do not have the temporal power to unpack the temporal fluctuations in neural activity. Moreover, given that any given brain area is associated with many different functions (Price & Friston, 2002), it is difficult to interpret the findings of widespread activations produced by vestibular stimulation in relation to its clinical effects. However, by employing ERPs, researchers can explore how vestibular stimulation affects the moment-to-moment brain processing occurring during a functionally and clinically relevant task. Despite these strengths, the exploration of the effects of vestibular stimulation on electrophysiological markers has been limited.

Most studies investigating the effects of vestibular stimulation on EEG or ERPs employ GVS, as opposed to CVS, as the stimulation method. Pre- versus post-stimulation studies in normal controls have shown that GVS can influence ERPs associated with visual processing and decision-making and EEG power of different frequency ranges (Ko et al., 2020; Lee et al., 2014; Lee et al., 2016). Lee et al. (2016) found an increased amplitude and earlier latency of both the N100 and P300 elicited by a visual oddball paradigm following a GVS period of 10 minutes in healthy participants. These results suggest both an increase in attentional resources but also more efficient information processing (Luck, 2014) as a result of GVS. Moreover, these changes were mostly observed over the prefrontal and frontal cortices, suggesting vestibular influences on cognitive

decision-making (Manes et al., 2002). In a study measuring participants' memory recall of different visual stimuli, it was found that following a period of GVS, participants' error rate significantly decreased. This improvement in behavioural performance was accompanied by decreases and increases in alpha and beta frequency bands, respectively associated with the active GVS condition (Lee et al., 2014). Tasks that require more cognitive control and attention, such as memory recall, have been associated with alpha inhibition and beta increases (Egner & Gruzelier, 2001; Lee et al., 2014) which may suggest that GVS can modulate oscillatory activity. A recent study found that alpha power in the motor cortex was suppressed during walking following GVS in both healthy participants and patients with bilateral vestibular hypofunction (BVH) (Ko et al., 2020). The authors speculated that these changes in EEG power during walking were due to neuroplasticity occurring in the human vestibular cortex (left and right parietal lobes) caused by GVS. Specifically, these neuroplastic changes may consist of vestibular long-term potentiation (LTP) and long-term depression (LTD), the former defined as an enhancement and the latter as an inhibition in synaptic efficiency (Grassi & Pettorossi, 2001).

Putative mechanisms underlying improvement in PD during vestibular stimulation

The GVS effects on EEG frequencies hint that vestibular stimulation may function by altering oscillatory states within different areas of the brain (Kim et al., 2013; Smith, 2018). This is particularly meaningful because some of the most robust and enduring therapeutic effects of vestibular stimulation have been observed in PD (Wilkinson et al., 2016; Wilkinson et al., 2019) – a condition associated with pathological brain oscillations (Hammond, Bergman & Brown, 2007; Heinrichs-Graham et al., 2014). Before discussing whether vestibular stimulation may alleviate certain PD symptoms via modulation of these oscillatory states, I will first describe PD and the clinical effects that have been seen in PD during vestibular stimulation.

Parkinson's disease (PD) is a neurodegenerative condition characterised by the loss of cells in the substantia nigra which results in motor symptoms such as postural instability, slowness of movement, motor rigidity and tremor (Davie, 2008). Equally or if not more debilitating, there are also non-motor symptoms such as sleep disturbances, memory impairments, digestive problems, chronic pain, depression and anxiety (Wilkinson, 2021). Wilkinson et al. (2019) conducted a randomised, double-blind and placebo-controlled study which showed that the active treatment with a solid-state CVS device was associated with clinically significant improvements in both motor and non-motor symptoms of PD. The study included 33 individuals diagnosed with PD in accordance with the UK Parkinson's Disease Society Brain Bank Criteria and who experienced self-reported difficulties in activities of daily living (ADLs). Following a baseline assessment period, the participants were randomised to either an active or placebo 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. Follow-up assessments of clinically relevant outcomes were administered at the end of the eight-week active treatment, then at five and 24 weeks following treatment cessation. Some of the outcome measures evaluated in this study included the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Non-Motor Symptom Scale (NMSS) for PD, the Modified Schwab and England ADLs Scale, the Timed-Up-and-Go test and the 10-metre self-paced walking test (Chaudhuri et al., 2007; Goetz et al., 2008; Podsiadlo & Richardson, 1991; Schwab, 1969; Steffen & Seney, 2008). Compared to baseline evaluation, the motor symptom scores on Part II

(motor aspects of daily life) and Part III (motor examination) of the MDS-UPDRS were significantly greater for the active treatment group compared to the placebo group. Non-motor features as measured by the NMSS were also significantly reduced for the active treatment group compared to placebo. Many of these improvements exceeded a previously determined minimal clinically important difference (MCID) (Horvath et al., 2017) and persisted to the 5- and 24-week follow-ups. The active treatment arm was also associated with significant improvements on the Schwab and England ADLs Scale, the 10-metre walking test and the Timed-Up-and-Go test. 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 or cerebrovascular coupling (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. The robustness of these effects is perhaps the strongest justification for a thorough investigation into the physiological mechanisms of action of vestibular stimulation.

Galvanic vestibular stimulation (GVS) has also been shown to improve motor symptoms in PD. Most of these studies have focused on the motor symptom of postural instability but there are a few that also show improvements on fine motor tasks, gait, and some non-motor symptoms such as autonomic responsiveness. The first of these studies found that a 24-hour treatment with stochastic or noisy GVS improved autonomic responsiveness, rest-to-active transitions and motor execution in PD as evidenced by increased heart rate frequency fluctuations, trunk activity and reduced RT in a Go/No-Go task, respectively (Yamamoto et al., 2005). Another study of patients with akinesia resulting from PD or multiple-system atrophy (MSA) found that noisy GVS was

associated with greater rates of switching between higher and lower levels of wrist activity, suggesting a reduction in hand akinesia (Pan, Soma, Kwak & Yamamoto, 2008). Many other studies have found improvements by GVS on PD postural instability as evidenced by reductions in sway using centre-of-pressure measures and increased balance maintenance following perturbation using the pull test of the MDS-UPDRS and/or dynamic balance mats (Kataoka et al., 2016; Pal, Rosengren & Colebatch, 2009; Samoudi, Jivegård, Mulavara & Bergquist, 2015; Tran et al., 2018). Some recent studies have targeted more specific features in PD such as the characteristic stooped posture, visuomotor difficulties as well as gait and fine motor control disturbances. Okada et al. (2015) found that 20 minutes of direct current (DC) GVS significantly improved the posture of PD patients with severe camptocormia as shown by a reduction in their anterior bending angle during standing. Another study found that visuomotor processing in PD was improved during application of noisy GVS as evidenced by increased accuracy in the tracking of a visual stimulus using a joystick (Lee et al., 2015). The most recent study on the effects of GVS in PD found improvements in symptoms associated with both upper and lower limb extremities (Khoshnam et al., 2018). Slowing of gait and tremor during walking was improved following direct current GVS as evidenced by faster completion of the Timed-Up-and-Go test of the MDS-Unified Parkinson's Disease Ratings Scale and reduction in tremor frequency. Upper limb improvements were characterised by reductions in tremor and in the duration of manual motor blocks (MMBs) during a finger tapping task. This body of work supports a positive relationship between the use of CVS and GVS and behavioural improvements in PD, suggesting that vestibular stimulation in PD may produce disease modification through genuine physiological mechanisms of action.

To date, many of the putative mechanisms underlying the positive effects of vestibular stimulation in PD are based on the hypothesis that aberrant oscillations underlie the motor

symptoms in PD (Black & Rogers, 2020). The proposed theory is that vestibular stimulation can alter or correct these pathological oscillations, thereby leading to concomitant improvements in motor function (Black & Rogers, 2020; Smith, 2018). Moreover, the underlying mechanisms proposed are frequently reported as related to the type of stimulation applied. In many previous studies, the application of stochastic or noisy GVS to PD assumes that it can lead to stochastic resonance or facilitation (Cai et al., 2018; Lee et al., 2015; Pal et al., 2009; Samoudi et al., 2005; Yamamoto et al., 2005). This refers to the ability of a random noise signal (be this vestibular or otherwise) to amplify the responsiveness of a non-linear biological system, such as the central nervous system (CNS), to weak, sub-threshold signals (McDonnell & Ward, 2011). The external random noise signal likely causes depolarization at random intervals which in turn render the weak signals detectable by the system (Kim et al., 2013). This may be effective in PD, where neural responsiveness to reafferent signals is dampened (Yamamoto et al., 2005). However, this mechanism may not explain the dramatic and enduring effects of CVS on PD reported by Wilkinson et al. (2019). Their findings may be more consistent with mechanisms associated with neural entrainment (Black et al., 2016; Black & Rogers, 2020).

Neural entrainment refers to the synchronisation of underlying neural oscillations to an externally applied sinusoidal current (Khatoun, Asamoah & Laughlin, 2019; Krause et al., 2019; Schutter, 2016). The assumption is that the frequencies of the underlying cortical oscillations will align with the frequency of the externally applied oscillations. Indeed, neuromodulation using alternating currents (AC), as in transcranial alternating current stimulation (tACS), has been shown to alter cortical oscillations (Helfrich et al., 2014). Importantly, tACS has been shown to temporarily attenuate the excessive beta oscillations observed during EEG and magnetoencephalography (MEG) of a PD sample (Del Felice et al., 2019; Krause et al., 2014).

Despite this, the therapeutic gains of tACS in PD have been minimal, with only two studies showing transient relief from tremor, bradykinesia and mild cognitive impairment following a treatment of tACS (Brittain, Probert-Smith, Aziz & Brown, 2013; Del Felice et al., 2019). This may be attributed to the non-endogenous and highly localized method of induction for tACS, with stimulating electrodes being placed directly on the scalp above the targeted brain areas. Whilst tACS may certainly alter the activity of the regions underneath the electrodes, it may not necessarily match the naturally occurring oscillatory patterns intrinsic to those regions. Cortical entrainment in this way may only partially explain the effects of vestibular stimulation in PD. This may be because tACS and vestibular stimulation differ in their mode of induction, such that tACS targets regions of interest on the scalp whereas vestibular stimulation 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 means by which vestibular stimulation activates central nervous function has been described as a method of ‘sensory neuromodulation’ which refers to the modulation of cortical oscillations via the artificial, bottom-up activation of sensory receptors. Other examples include visual, auditory and somatosensory stimulation (Black & Rogers, 2020). The assumption here is that although the external signal applied may be artificial, the sensory network processes it in the same way as a naturally occurring sensory stimulus. Thus, sensory neuromodulation may function by strengthening endogenous, naturally developed protective oscillations in a manner that is consistent with innate mechanisms. In pathological networks as in PD, Black and Rogers (2020) speculated that sensory neuromodulation may bring brain networks closer to a naturally developed state via neuroplastic change. The vestibular system may be an ideal candidate for this process because of its widespread influence on many brain regions, including areas pertaining to other

sensory modalities (Lopez & Blanke, 2011). In support of this model, two recent studies have shown that vestibular stimulation may entrain cortical structures. Black et al. (2016) showed that CVS engendered oscillations in cerebral blood flow velocity in a migraine subject in a manner that may be consistent with entrainment of the pons, a structure known to receive direct projections from vestibular nuclei in the brainstem (Balaban, Jacob & Furman, 2011). Given that this study employed the same time-varying CVS method as that used by Wilkinson et al. (2019) on a smaller scale, it is possible that alterations in oscillatory dynamics may explain the CVS effects on PD. Furthermore, a recent EEG study found abnormal cortical coupling of theta, alpha and gamma frequency bands between motor cortex (M1), supplementary motor areas (SMA) and premotor areas in PD participants compared to a healthy control group (Lee, Liu, Wang & McKeown, 2019). However, the oscillatory patterns of these frequency bands in PD became more similar to that of the control participants when sinusoidal GVS was applied. This suggests that GVS may have 'normalised' the pathological oscillations associated with PD, consistent with the hypothesis that sensory neuromodulation strengthens naturally developed protective activity.

This body of work suggests that the mechanisms of action underlying vestibular stimulation may be related to cortical entrainment, which in turn may modulate the abnormal oscillations that underpin the motor dysfunction in PD. Thus, investigating the electrophysiological activity associated with motor function in PD may provide further clarification of the mechanisms in action during vestibular stimulation.

Movement-Related Cortical Potentials

The aberrant EEG oscillations associated with PD may underpin other abnormalities of electrophysiological markers previously observed in PD. Specifically, the Bereitschaftpotential (BP), a component of the broadly defined movement-related cortical potentials (MRCPs), has

repeatedly been shown to be reduced in PD compared to healthy controls (Cunnington, Iansek & Bradshaw, 1999; Dick et al., 1989; Jahanshahi et al., 1995; Praamstra, Jahanshahi & Rothwell, 2002). Many studies have linked MRCPs with oscillatory patterns, specifically beta event-related desynchronization (ERD), showing that they share many generator sources (SMA and other premotor regions) and follow similar time courses (Toro et al., 1994). Beta ERD refers to the attenuation of beta frequency synchronization that occurs immediately preceding and during voluntary movements (Pfurtscheller, 1997). In PD, this attenuation is often not present, hence the excessive beta oscillations previously observed (Hammond et al., 2007; Heinrichs-Graham et al., 2014). Moreover, the reduced amplitude of the BP in PD is consistent with the difficulties experienced by patients with movement initiation (Verleger, 2012). Given their association with movement-related oscillatory activity and abnormalities in PD, MRCPs are appropriate markers to investigate the electrophysiological mechanisms underlying the effects of vestibular stimulation in PD.

Movement-related cortical potentials (MRCPs) refer to the cortical activity recorded around the time course of movement (Colebatch, 2007). The components associated with it reflect the different phases preceding and during movement. Two core MRCP components are that of the contingent negative variation (CNV) and the Bereitschaftspotential (BP). The BP and CNV are functionally different in their association with volitionally generated movements and responses to external cues, respectively (Jahanshahi & Hallett, 2003). For the purpose of this research, focus is given to Bereitschaftspotential (BP) or readiness potential (RP) which refers to a slowly rising negativity starting one to two seconds prior to movement onset (Shibasaki & Hallett, 2006). It has generally been investigated using simple movements such as finger extensions or ankle dorsiflexion, self-paced and self-initiated in the absence of external triggers (Colebatch, 2007;

Jahanshahi & Hallett, 2003). The BP consists of two different phases associated with different preparatory functions: the early and late BP (Shibasaki & Hallett, 2006). The early BP is the earliest component initiating one to two seconds prior to movement onset and showing maximal activation at the vertex (Cz). Its topographical distribution is widespread across the scalp and symmetrical across hemispheres regardless of movement side. Its generator sources have frequently been reported as the SMA and premotor regions (Shibasaki & Hallett, 2006) and it was traditionally said to reflect preconscious readiness for the oncoming movement because it was reported to precede participants' reported decision to perform a voluntary movement (Libet, Gleason, Wright & Pearl, 1983). However, this view has recently been challenged with some authors arguing that it likely reflects the negative voltage deflections of slow cortical oscillations closely associated with self-initiated movements (Schmidt, Jo, Wittmann & Hinterberger, 2016). Following the early BP is the late BP consisting a steep rise in the negativity 400-500 milliseconds prior to movement onset. The maximal site of the late BP has been observed at Cz but it is also frequently reported as maximal at sites contralateral (C1, C2, C3 or C4) to movement side, particularly for finger movements (Shibasaki & Hallett, 2006). The late BP has been reported to reflect the intense interaction of the SMA and M1 in the selection of appropriate muscles immediately preceding movement (Neshige, Luder & Shibasaki, 1988). At the highest peak of the rising negativity and co-occurring with the movement at approximately 100-200 milliseconds is the motor potential (MP) reflecting the recruitment signals being sent to the peripheral nerves prior to an observable movement response (Deecke, Eisinger & Kornhuber, 1980; Shibasaki & Hallett, 2006).

The BP is known to be deficient in PD and this is generally interpreted as an impairment in the preparation for a voluntary movement. Specifically, Dick et al. (1989) first found that the early BP elicited by finger extensions was significantly diminished in PD compared to healthy,

age-matched individuals. Given that the BP reflects preparatory activity preceding a movement, this suggests PD is associated with a specific deficit in movement preparation. This was confirmed by Cunnington, Iansek, Johnson and Bradshaw (1997) in a study that isolated the movement preparation and execution processes by comparing the MRCPs from real and imagined movements performed by PD participants. Imagined movements are said to recruit movement preparation-related activity more than motor execution processes (Decety, 1996). The results showed that only the pre-movement component (CNV) was reduced in PD and not the movement-execution activity. Thus, these findings suggest that PD is associated with a specific deficit in the preparatory activity preceding movement. Moreover, the BP is also more closely related to the preparation for voluntary, purposeful movements as opposed to externally cued movements, which are associated with the CNV (Cunnington et al., 1999). Both PD and control participants have shown a greater BP preceding self-initiated compared to externally triggered movements (Cunnington et al., 1999). However, the amplitude of the BP was only significantly smaller in PD compared to control for the internally generated movements, not for the externally triggered movements. This is consistent with PD clinical presentation in which more difficulties are experienced when initiating voluntary compared to externally cued movements (Verleger, 2012).

The findings described above support the measurement of MRCPs, and particularly the BP, to investigate the underlying mechanisms of vestibular stimulation in PD. To date, there has only been one study to investigate the effects of vestibular stimulation on MRCPs. Lee (2015) measured MRCPs elicited by left thumb abductions before and after participants received GVS using a triangular waveform for 10 minutes. The waveform was triangular shaped in morphology with decreases in amplitude immediately following increases in amplitude and vice versa continuously. The main results were a significant increase in the amplitude of the late BP ipsilateral to movement

(C3) and in the amplitudes of the late BP and MP contralateral to movement (C4) from pre- to post-GVS. These findings suggest that GVS may affect the late-stage preparation for a forthcoming movement (late BP) as well as motor execution itself (MP). However, the extent to which these results reflect GVS effects on volitionally generated movement-related activity is questionable as MRCPs were elicited in response to images and were not self-initiated by participants as is conventionally done (Jahanshahi & Hallett, 2003). Moreover, this study and many others that employed EEG have followed a pre- versus post-stimulation design (Lee et al., 2014; Lee et al., 2016). However, to progress the understanding of the physiological mechanisms of vestibular stimulation, an investigation of its ongoing, spontaneous effects on electrophysiological activity is required. This would build on the imaging findings of widespread activations during vestibular stimulation (Bottini et al., 1994; Della-Justina et al., 2015; Emri et al., 2003; Vitte et al., 1996) as electrophysiological markers can be linked to clinically and functionally relevant tasks such as RTs or movement tasks. Thus, there is a need for a study to observe changes in MRCPs elicited by self-initiated movements during application of vestibular stimulation in both a healthy and PD population.

Problem of concurrent GVS-EEG studies

The focus for the remainder of this thesis will be on GVS instead of CVS. This is because sub-sensory stimulation can be more easily achieved via GVS, as opposed to CVS, therefore allowing the blinding of participants to the sham and active stimulation conditions (Utz et al., 2010). Moreover, the solid-state CVS devices employed in the clinical trial conducted by Wilkinson et al. (2019) were not available for use at the time of data collection for the studies in this thesis. To date, there have only been five studies that have observed EEG during GVS. The first of these found an increase in the amplitude of N170 ERP and in the power spectra within the

delta and theta frequency bands associated with the active, sub-sensory DC GVS condition compared to the sham (Wilkinson, Ferguson & Worley, 2012). Next, Kim et al. (2013) observed spectral changes in all frequency bands of interest (theta, alpha, beta and gamma) in participants at rest receiving zero-mean, linearly detrended noisy GVS. Another study administered imperceptible GVS using AC to participants whilst they performed an auditory oddball task (Schmidt-Kassow, Wilkinson, Denby & Ferguson, 2016). They found the amplitude of the P300 ERP elicited by the oddball task was increased by GVS, but only when the stimulation frequency matched that of the tones played. Recently, Lee et al. (2019) found that pathological cortical coupling between theta, alpha and gamma frequency bands in PD became more 'normal' when applying AC GVS. This was shown by the oscillatory dynamics in PD participants becoming more similar to that of the control participants. These findings suggest that many different EEG markers are affected during GVS, which further supports the focus on investigating its electrophysiological mechanisms.

The scarcity of studies observing EEG effects during GVS is partly attributed to the large, stimulation-related artifacts introduced into the continuous EEG during simultaneous EEG-GVS (Lee et al., 2018). These electrical artifacts associated with the GVS are sufficiently large to obscure the 'true' electrophysiological responses stemming from the brain. The studies described above employed different strategies to remove the GVS-related artifact that contaminated the EEG data. Wilkinson et al. (2012) and Schmidt-Kassow et al. (2016) employed the same strategy of bandwidth filters: 0.3-30 Hz and 0.6 Hz, respectively. This was done despite the application of two different types of current (DC and AC, respectively). The problem with this strategy is that the electrical activity associated with the stimulation artifacts frequently overlaps with the underlying oscillatory activity of the signals of interest (Lee et al., 2018). Thus, it is unlikely that simple

filtering techniques are sufficient to completely remove the electrical noise from the ERP data. These studies reported the successful acquisition of the ERPs of interest suggesting that the filtering technique employed was effective at removing the GVS-related artefact – but no evidence was presented to demonstrate this. Furthermore, a thorough account of the effect the filtering had on the EEG data and the GVS-related artefact was not reported so replication is not possible. Thus, the extent to which the application of the bandwidth filters may have removed underlying activity associated with the signals of interest is unknown. The study by Kim et al. (2013) also has a similar limitation with their use of QR decomposition to remove the GVS-related artifact. QR decomposition is a regression method (*qr* function in Matlab) in which a matrix of the concatenated EEG data is aligned with a matrix of the artifactual stimulus signal (Kim et al., 2013). The row corresponding to the matrix with the artifactual stimulus is set to zero thereby obtaining the EEG data with the stimulus regressed out (Kim et al., 2013). This technique has been validated previously for its artifact extraction ability (Zheng, Qi, Gao & Guan, 2012); however, it does not provide a quantifiable account of the characteristics of the GVS-related artifact. Knowing this would enable more effective discrimination between data contaminated by noise from the GVS and data stemming from genuine brain activity. Moreover, Kim et al. (2013) did not report any evidence showing that this strategy was effective at removing the GVS-related artifact from the EEG data. This highlights the need for further studies to present evidence of data before and after the GVS-removal method is applied.

Finally, the study by Lee et al. (2019) employed quadrature regression-independent vector analysis (*q*-IVA) to remove the GVS-related artifact from the EEG data. This technique involves two fundamental steps of processing, 1) high-amplitude stimulation artifact is removed using a regression model that factors both the stimulation signal and its quadrature component, and 2)

independent vector analysis (IVA), which is similar to that of an ICA, however, is a process of jointly analysing multiple data sets instead of one as in ICA, therefore overcoming the issue of permutation (Lee et al., 2019). Although this study evaluated the effects *q*-IVA had on the EEG data and characterised the quantifiable measures of the GVS-related artifact, a fundamental limitation relates to the static nature of this paradigm, where testing was conducted whilst participants were at rest. No evidence was provided that this approach could be applied to data collected whilst participants were engaged in a task. There are currently no studies that provide a thorough report of the effectiveness of an artefact rejection technique at removing the GVS-related artefact without interfering in the acquisition of ERPs. The findings from these concurrent GVS-EEG studies are difficult to interpret in terms of the clinical effects of GVS observed previously (Khoshnam et al., 2018; Wilkinson et al., 2019) because they have not employed functionally or clinically relevant markers. In this way, they are no different to the functional imaging studies previously mentioned (Bense et al., 2001; Bottini et al., 1994; Bucher et al., 1998; Della-Justina et al., 2015; Emri et al., 2003; Lobel et al., 1998; Stephan et al., 2005; Vitte et al., 1996).

Aims

This thesis built on the work of previous concurrent GVS-EEG studies in two ways. First, the strategy for the removal of the GVS-related artifact employed Independent Components Analysis (ICA) to identify and quantify the GVS-related artifact. This builds upon the use of only bandwidth filters (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012) by characterising the effects both the GVS-related artifact and the strategy for removal of the artifact had on the EEG data. Second, this strategy was evaluated in terms of its ability to remove the GVS-related artifact without compromising the acquisition of MRCPs. This builds upon the studies by Lee et al. (2019) and Kim et al. (2013) who had recorded concurrent GVS-EEG data only from participants at rest.

The studies reported in this thesis include EEG data recorded whilst participants were performing simple movements tasks and receiving GVS. The rationale behind these motor tasks was to elicit MRCPs, which would provide clinically and functionally relevant electrophysiological markers during GVS. Observing changes in MRCPs during GVS may provide an initial understanding of the therapeutic mechanisms that improve motor function in the PD sample tested by Wilkinson et al (2019).

Prior to developing and evaluating the strategy for removal of the GVS-related artifact, it was imperative to select the appropriate current type to use for the GVS stimulus. GVS can be applied using current steps (direct current stimulation), sinusoids (alternating current stimulation) or noise currents (Dlugaiczyk, Gensberger & Straka, 2019). The current type of AC or sinusoids was selected in this thesis for three reasons. First, sine waves used in AC stimulation and the CVS waveform (saw-tooth) employed in the PD clinical trial (Wilkinson et al., 2019) share the similar property of a predictable, time-varying component. Thus, employing a sinusoidal current produces a closer approximation to the stimulation parameters employed in the PD trial, despite employing different modes of induction (CVS and GVS). Second, sinusoidal currents, using both GVS and tACS, have been shown to alter oscillatory dynamics in the brains of both healthy and neurologically impaired populations (Del Felice et al., 2019; Kim et al., 2013; Krause et al., 2014; Lee et al., 2019). Lastly, at a physiological level, AC GVS produces nerve signals that mimic sinusoidal head rotation (Ezure, Cohen & Wilson, 1983; Gensberger et al., 2016; Kim, Minor, Della Santina & Lasker, 2011). Therefore, it may be more suitable as a mode of sensory neuromodulation because it can simulate natural vestibular reflexes (Black & Rogers, 2020; Dlugaiczyk et al., 2019).

The strategy for removal of the GVS-related artifact from EEG data employed in this thesis involved two fundamental steps during offline processing: 1) the application of a bandwidth filter (0.05-50 Hz), and 2) conducting an Infomax ICA on EEG data recorded during active and sham GVS conditions. The first processing step was to apply high-pass (0.05 Hz) and low-pass (50 Hz) filters. The high-pass filter of 0.05 Hz was selected based on the findings from previous studies showing that MRCPs are underpinned by slow-wave oscillations varying between 0.01-2 Hz (Armstrong, Sale & Cunnington, 2018; Schmidt et al., 2016). The low-pass filter of 50 Hz was chosen to prevent mains voltage noise from contaminating the data (Luck, 2014). The next processing step involved conducting ICA on the EEG data from both the active and sham GVS conditions.

Independent components analysis (ICA) is an artifact correction technique that functions by generating an 'unmixing matrix' from the recorded data which allows for the calculation of the time course of underlying components (Onton & Makeig, 2011). ICA uses the statistical properties of the observed data to extract maximally temporally independent components thus it is said to be a 'blind' decomposition technique as no prior knowledge of the nature of 'true' brain processes is required (Onton & Makeig, 2011). This is contrasted with source localization techniques that use the biophysics of voltage conduction to generate the unmixing matrix (Luck, 2014). When ICA is applied to observed data, the algorithm finds a set of weighted sums of the component matrix (i.e., the unmixing matrix) that can be multiplied with the observed data matrix to produce a matrix of independent components (ICs), each having a distinct time course, power spectrum and topographical map. In this way, ICA can 'learn' to distinguish between different EEG sources (ICs) such as brain-generated processes and non-brain signals (artifacts) and provide their relative amplitude and polarity at any one time point. Statistically, activations from brain and non-brain

related sources tend not to be correlated which has resulted in ICA being suitably employed to identify, characterize and eliminate several known artifacts such as eye blinks, saccadic eye movements, muscle activation and heart rate (Jung et al., 2000; Klug & Gramann, 2020). As such, the novelty of the strategy employed in this thesis lies in the employment of ICA for the identification and quantification of the GVS-related artifact in the same manner as has been previously done for other known artifacts stemming from ocular movements or muscle activation (Klug & Gramann, 2020).

One of the advantages of employing ICA for this purpose is that it becomes more than an artifact correction method. The ICs obtained from the data are the most temporally distinct portions of the data which means that ICA can clearly separate their features and allow them to be studied concurrently with brain-related activity as signals of interest in their own right. For example, ICA has been utilized to concurrently analyse EEG and EMG (a non-brain, biological source of activation), with EMG-related activations receiving equal weighting in the analysis (Onton & Makeig, 2011). This is important in the context of characterizing the GVS-related artifact during concurrent GVS-EEG recording. Another benefit of utilizing ICA in this thesis is its applicability to different populations and in particular populations whose data is more likely to be dominated by artifactual signals. For instance, ICA has been successfully applied to EEG data obtained from children whose data is often heavily contaminated by eye movements (Onton & Makeig, 2011). This is promising given that recording EEG data from clinical populations can have inherent challenges such as increased muscle tension which can increase the likelihood of collecting noisy data.

There are some technical challenges to consider when applying ICA to remove the GVS artifact from EEG data. Non-brain signal sources such as blinks, saccadic movement, etc. always

have the same topographic pattern (Onton & Makeig, 2011) that is known and recognized. However, the patterns of activation for the topographical maps to be generated for the GVS-related noise is not known which could limit identification and characterization of the GVS artifact. The contributions of the GVS signal to the EEG depend on the stimulation parameters (frequency and amplitude). Determining the appropriate stimulation parameters is paramount to prevent the GVS signal from dominating the EEG and increasing the number of temporally independent ICs related to the GVS signal. Having a high number of ICs such as these could greatly limit the ability of ICA to distinguish between distinct EEG processes (artifact or otherwise). Moreover, ICA generates the same number of ICs as the number of data channels which means that contributions from sources beyond those relating to the data channels are mixed into some or all the ICs adding a noise that is dispersed across the decomposition (Onton & Makeig, 2011). Thus, it is possible that some of the GVS-related noise may remain within the ICs that are not removed following artifact correction. This highlights the importance of having a sufficiently high number of channels with 'clean' data which can be achieved by taking measures during recording to ensure that the influence of the GVS on the recording in minimal.

Independent components analysis (ICA) was chosen for this thesis over other methods such as principal components analysis (PCA) for several reasons. PCA identifies uncorrelated principal components that account for the most possible variance in the portion of signal data that is not correlated (Onton & Makeig, 2011). PCA aims to 'lump' together the variance from signal sources into as few principal components as possible whereas ICA 'splits' the signal into various components without considering variances. Whilst PCA can be useful in preserving variance during signal decomposition it also deletes much of the remaining source activations. It was imperative to minimize the processing steps to avoid loss or distortion of data which is better

accomplished by ICA than PCA. Previous strategies used by other studies which used concurrent GVS and EEG were also not employed for a number of reasons. The band-stop method of applying filters (0.1-30Hz) utilized by Wilkinson et al. (2012) and Schmidt et al. (2016) was not employed here as it overlaps with and would therefore remove the underlying oscillatory activity (0.01-2Hz) of the MRCPs. Other methods such as combining ICA with QR decomposition, and the modified joint blind source separation (involving quadrature regression and subsequent independent vector analysis) used by Kim et al. (2013) and Lee et al. (2019), respectively, have only been validated in participants at rest and not involved in a voluntary movement task. Whereas ICA has been frequently employed as an artifact rejection technique in experiments that require functionally relevant tasks such as RT and finger movements (Luck, 2014; Onton & Makeig, 2011; Klug & Gramann, 2020). Additionally, these methods are computationally complex and frequently require advanced statistical expertise whereas ICA can be run using EEG analysis software (e.g., Brain Vision Analyser 2 and EEGLAB) making it relatively accessible.

One challenge of employing this strategy was to ensure both the amplitude and frequency of the GVS stimulation did not either overlap or swamp the EEG signal making it difficult if not impossible to evaluate potential neural activity of interest (ERPs). This was particularly important given that the sinusoidal current applied shares two of the same properties as EEG signals. Both AC GVS and EEG have the sine wave characteristic of amplitude and frequency. It was therefore imperative to distinguish the functional significance of these properties in terms of the stimulus (GVS) and measured outcome (EEG). The frequency of the GVS referred to the number of complete cycles of the sine wave applied that occurred every second of stimulation. Whereas the stimulus signal applied contains only a single sine wave, the EEG is a mixed signal composed of several sine waves of different frequencies (Luck, 2014). The stimulus frequency may overlap with

one or more of the underlying frequencies of the mixed signal EEG. Thus, the GVS frequencies of 3 Hz and 0.01 Hz were selected because they were unlikely to interact with the underlying oscillatory patterns of MRCPs (Armstrong et al., 2018; Schmidt et al., 2016). The amplitude of the AC GVS referred to the intensity of the current applied, which in signal processing refers to the size of the waveform applied from peak-to-peak. It is frequently denoted as milliamps in the literature (Dlugaiczyk et al., 2019). Because EEG contains a mixture of several sine waves of different frequencies, determining its amplitude requires decomposition of the mixed signal into its component frequencies. The pilots described in the methodological development section of this thesis utilised the frequency decomposition technique of fast Fourier transform (FFT) to deconstruct the EEG signals from the active and sham GVS conditions as a means of evaluating the effect of the offline processing strategy developed and employed within the subsequent studies.

Methodological Development

This section describes the development of a novel methodology designed to collect EEG data from any population using simultaneous GVS and EEG. The core methodological challenge within the first studies of this body of work was the development of a robust strategy for the removal of the GVS-related electrical artifact from the continuous EEG raw data. The first section describes a series of pilots conducted to characterize the effects of different GVS stimulation parameters on the continuous EEG data. The results of these pilots then aided in determining the optimal set of stimulation parameters to employ in the main studies of this thesis. Studies 1 and 2 are then described with the aim of observing the simultaneous effects of GVS on the BP and MP components of the MRCPs. Specifically, Study 1 assessed the feasibility of utilizing the novel pre-processing strategy developed during the pilots to eliminate the GVS-related artifact from EEG

data recorded during a simple finger movement task, without compromising the acquisition of the MRCPs. After validating the pre-processing strategy in Study 1, Study 2 aimed to evaluate the logistics of including an additional motor task to the experimental protocol and further refining the GVS parameters. Conducting two studies instead of one allowed initial validation of the novel methodology in Study 1 prior to further optimization in Study 2 and reduced the risk of fatiguing participants (Gandevia, 2001) with a single albeit prolonged session. The results of these studies conducted on neurologically healthy participants then informed the methodology in the final study of this thesis, which focused on a PD population.

Single-Subject Pilot Data

Formal ethical approval was obtained to conduct the studies reported below by the School of Psychology Ethics Committee at the University of Kent in Canterbury, UK and could be provided upon request. The authors declare that all studies conducted on human participants for this thesis were in accordance with the Declaration of Helsinki and that all procedures were carried out with the participants' adequate understanding and written informed consent.

This section describes the process through which the stimulation parameters employed in the main studies of this thesis were justified in a series of pilots. The aim of the pilots was to characterize the effects of different GVS parameters on the continuous EEG raw data. To achieve this, EEG data was recorded from a single participant during one minute of GVS using three different intensities (0.30 mA, 0.25 mA and 0.20 mA) as well as sham GVS. Although small, these intensities were selected because measurable physiological responses such as oculomotor torsion and body roll-tilt can be observed from intensities as low as 0.1 mA (Cauquil, Faldon, Popov, Day, & Bronstein, 2003; Day, Séverac Cauquil, Bartolomei, Pastor, & Lyon, 1997; Pal et al., 2009). Moreover, using lower intensities also facilitates the blinding of participants to stimulation

conditions. Most healthy individuals and participants with a neurological condition do not report any skin sensations (itching, tingling) during receipt of sub-sensory currents with intensities around or below 0.6mA (Utz et al., 2011). The data from the four different conditions were then graphically represented using the frequency decomposition technique, FFT, and topographical distribution maps derived from ICA. The use of these techniques in the pilots enabled the first reported description and characterization of the GVS-related electrical artifact that contaminates the EEG data recorded with concurrent GVS application. It was imperative to understand the effects of the GVS-related artifact on the EEG data in a single participant prior to evaluating the efficacy of a novel pre-processing pipeline designed to remove the GVS-related artifact from movement-related cortical data, the primary aim of Study 1.

Materials

Galvanic vestibular stimulation (GVS). The stimulation device utilized for all the studies presented in this thesis consisted of a *Neuroconn DC Stimulator* (GmbH, Ilmenau, Germany), delivering a gentle alternating current (AC) to the mastoids via a pair of rubber, self-adhesive, disposable electrodes (5.1cm x 10.2cm; ComfortEase, Empi Inc.) with the anode electrode over the right mastoid and the cathode over the left. The stimulation intensity employed varied between studies from a minimum of 0.20 mA to a maximum of 0.40 mA. GVS frequency also varied between the pilots and the studies with the former employing 3 Hz and the latter using 0.01 Hz. This was a point of refinement from the pilots to Study 1 due to the high number of GVS-related IC labels identified by the ICA when using a GVS frequency of 3 Hz in the pilots. For the studies, the stimulation duration also varied (10-15 minutes per movement block) depending on the pace at which participants moved their limbs in the motor tasks.

EEG acquisition. All electro-cortical and muscle activity outlined in this thesis was recorded using an eegoTMsports 64 (ANT Neuro, Enschede, Netherlands) amplifier. EEG data was recorded from a 32-channel electrode cap (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC1, FC2, 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). A DELL tablet connected to the amplifier allowed for online monitoring of EEG. 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 AFz as ground. Impedance was kept below 10 kΩ throughout EEG recording.

Procedure

All procedures reported in this thesis were conducted in a quiet, temperature-controlled laboratory. Prior to start, the subject provided written and verbal informed consent to participate. Four EEG recording conditions, each lasting one minute, were conducted whilst the participant received sub-sensory, binaural AC to the mastoid processes at three different intensities (0.2 mA, 0.25 mA, 0.3 mA) as well as a sham stimulation period. In keeping with the aim of recording movement-related data, all GVS currents were delivered at a frequency of 3 Hz in the pilot. During all stimulation periods, the participant was seated upright in a comfortable chair with eyes open and gazing at a fixation point on a computer screen to minimize the effect of ocular artifacts during EEG recording. The participant was instructed to relax and remain at rest for the duration of the conditions to minimize the effects of muscle artifacts on the EEG. The skin over the mastoid processes was prepared using alcohol wipes and Nuprep gel prior to placement of the GVS electrodes. During sham GVS, the stimulating device was switched off and the participant was falsely informed of receipt of stimulation. The participant did not report any physical sensations (itching, prickling, etc.) during active GVS conditions as reported by informal questioning. This

is consistent with previous literature stating that stimulation intensities averaging at 0.30 mA are mostly reported as sub-sensory (Utz et al., 2011).

Data Offline Processing and Graphical Results

The same offline processing was applied to all studies reported in this thesis to maintain a consistent approach to the analysis strategy. All offline data processing was conducted using Brain Vision Analyser 2 (Brain Products, GmbH, Gilching, Germany) software and high (0.05 Hz) and low pass (50 Hz) digital filters were applied. This bandwidth was selected on the basis that it has minimal overlap with the underlying oscillatory frequencies of the MRCPs (0.01-2 Hz) (Armstrong et al., 2018; Schmidt et al., 2016). 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. Previous MRCPs studies have employed linked earlobes or mastoids as reference electrodes (Dick et al., 1989; Fattapposta et al., 2000; 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. The physical online reference of CPz was not retained for offline analysis due to its proximity to the maximal site for the BP and MP at Cz so data was re-referenced to an offline average reference.

FFTs obtained from the EEG data after application of bandwidth filters and re-referencing to an average showed the presence of a peak in amplitude within the delta frequency range observable in all channels (see Figure 1). Given that this peak between 2-5 Hz is present during all active GVS conditions (see Figure 1a for the example of 0.30 mA intensity) but absent in the sham GVS condition (shown in Figure 1b), it is likely related to the 3 Hz GVS frequency applied. Moreover, the larger amplitude peaks observed in bilateral C3 and C4 channels compared to Cz provides further evidence that these artifacts are GVS-related, as bilateral channels are more

affected by GVS-related noise due to their proximity to the GVS electrodes placed over the mastoid processes. As can be seen in Figure 1 the application of bandwidth filters alone is not effective at removing the GVS artifact from the EEG data. The next step in the attempt to disentangle the effects of the GVS artifact from the EEG was to apply the signal decomposition technique known as ICA.

Prior to ICA decomposition, the data were segmented into four one-minute intervals, each corresponding to the different GVS intensities applied (0.20 mA, 0.25 mA, 0.30 mA) and the sham GVS. ICAs using the Infomax (Gradient) restricted algorithm were then conducted on each segment separately and each analysis returned 30 maximally independent components. As illustrated in Figure 2, ICA decomposition enabled successful identification of the independent components (ICs) associated with the GVS-related artifact. Figure 2a contrasts two examples of ICs classified as GVS (F00) and ocular (F24) artifacts in the 0.30 mA GVS condition. The number of ICs associated with the GVS-related artifact exceeded those related to neural activity (28 out of the 30 components returned). This increase was indicative of the 3 Hz frequency of the GVS having an impact on the overall signal quality which therefore may obscure the slow-wave oscillations that underlie the MRCPs (0.01-2Hz) when participants are performing the voluntary movements in Studies 1 and 2. This increase in artifactual ICs has also been observed in EEG data recorded during experiments in which participants are more physically active, with the number of brain ICs diminishing whilst the number of movement-related ICs increasing (Klug & Gramann, 2020). Removing all 28 ICs associated with the GVS-related noise would risk removing a large portion of underlying neural activity of interest as well as introducing a high degree of bias to the analysis strategy. This further demonstrated the significant influence the GVS signal has on the

signal and the difficulty in disentangling noise-related variance from variance derived from 'true' neural data.

Figure 2 illustrates the characteristics of the ICs classified as relating to the 0.30 mA GVS (F00) and those relating to ocular artifacts (F24). The topographical map (F00) depicted in Figure 2b illustrates the characteristic pattern of activation associated with the GVS-related artifact, which consists of bipolar and temporally lateralized activity. This is consistent with the GVS electrode placement at the mastoid processes, with temporal channels being most affected by the GVS-related noise because of their proximity to the mastoids. The GVS IC label (F00) in Figure 2c further clarifies the influence of the GVS magnitude applied on the EEG amplitude. The power spectra range for the GVS artifact (F00) in Figure 2c pertains to the 0.30 mA intensity, showing amplitudes ranging from -272.21 μV to 297.97 μV. Whilst the two other GVS intensities applied resulted in comparatively lower amplitude ranges, -173.03 μV to 157.96 μV for 0.20 mA and -211.71 μV to 190.14 μV for 0.25 mA. These characteristics of the topographical distribution (see Figure 2b) and power spectra (see Figure 2c) pertaining to the GVS-related IC (F00) could be distinguished from the standardized characteristics of the ocular (F24) IC label. The identification of these standardized IC labels for ocular artifacts by ICA makes the identification of the GVS-related IC label more robust. Once these characteristics were identified, the ICs pertaining to the GVS-related artifact could be excluded from further analyses.

Figure 3 shows the FFT graphs from the EEG data during GVS at an intensity of 0.30 mA and during sham GVS following exclusion of ICs associated with the GVS-related artifact and ocular artifacts as per conventions. The FFT graphs obtained for concurrent GVS-EEG data in Figure 3a no longer show the high amplitude peak within the delta frequency range that was present in Figure 1a. Figure 4 shows the example snapshot of an 8000-millisecond segment of data prior

to and after removal of the GVS-related artifact using ICA. These figures suggest that ICA signal decomposition was successful at removing the 2-5 Hz artifactual peak attributed to the influence of the GVS signal on the EEG data. Therefore, this offline processing pipeline will be carried over into all subsequent studies. However, it is important to note that given the high number of GVS-related ICs associated with the GVS-related noise, the GVS parameters would need to be modified to prevent the variance associated with the GVS noise from dominating the signal decomposition as it did in the pilot. Moreover, reducing the number of ICs related to the GVS noise by altering the stimulation parameters may result in the ICA returning fewer noise-related ICs and thus reduce the likelihood of removing variance associated with the neural activity of interest.

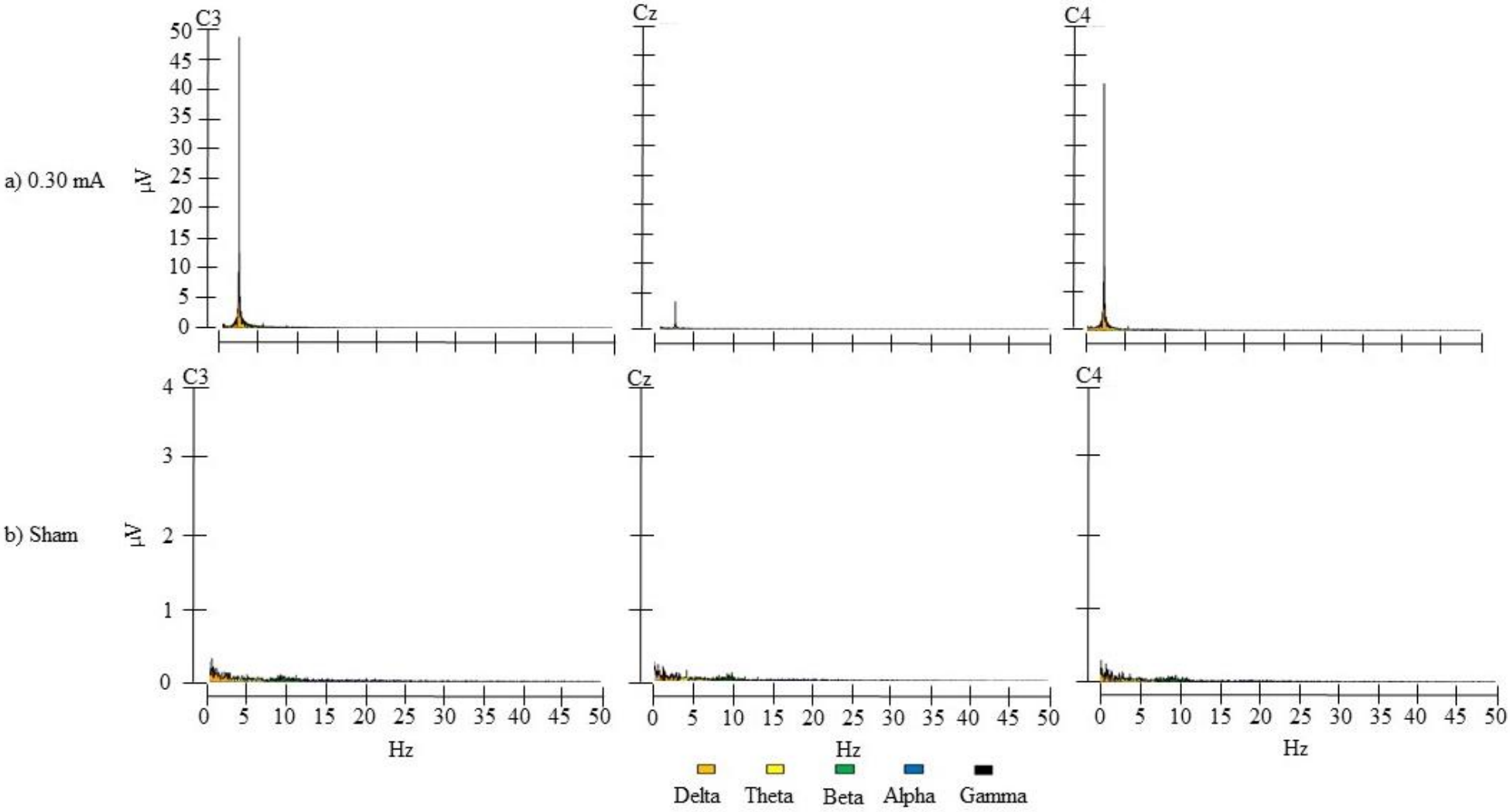


Figure 1. Row a) shows an example of the FFTs obtained (as a result of all GVS amplitudes tested) from EEG data contaminated by the GVS artifact after application of bandwidth filters and an average reference. The FFTs for each electrode clearly shows a high amplitude peak in the delta frequency range. Row b) shows the comparable FFTs obtained from EEG data recorded during sham stimulation.

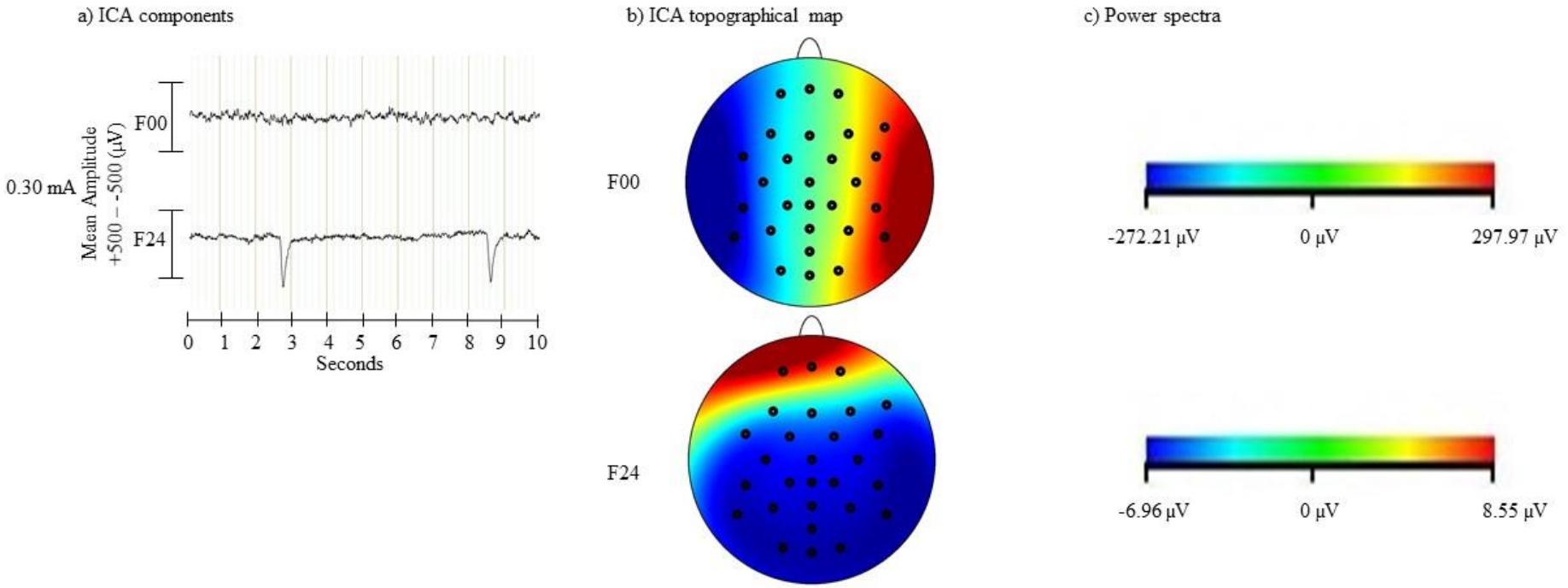


Figure 2. Column a) shows three examples of components returned by the ICA that are associated with the GVS artifact (F00) and blinks (F24). Column b) shows the characteristic topographical map of the distribution of activation elicited by the GVS (F00) and ocular (F24) artifacts. Column c) shows an example of the range of amplitude associated with the stimulation artifact elicited by the GVS at an intensity of 0.30 mA and that elicited by eye blinks.

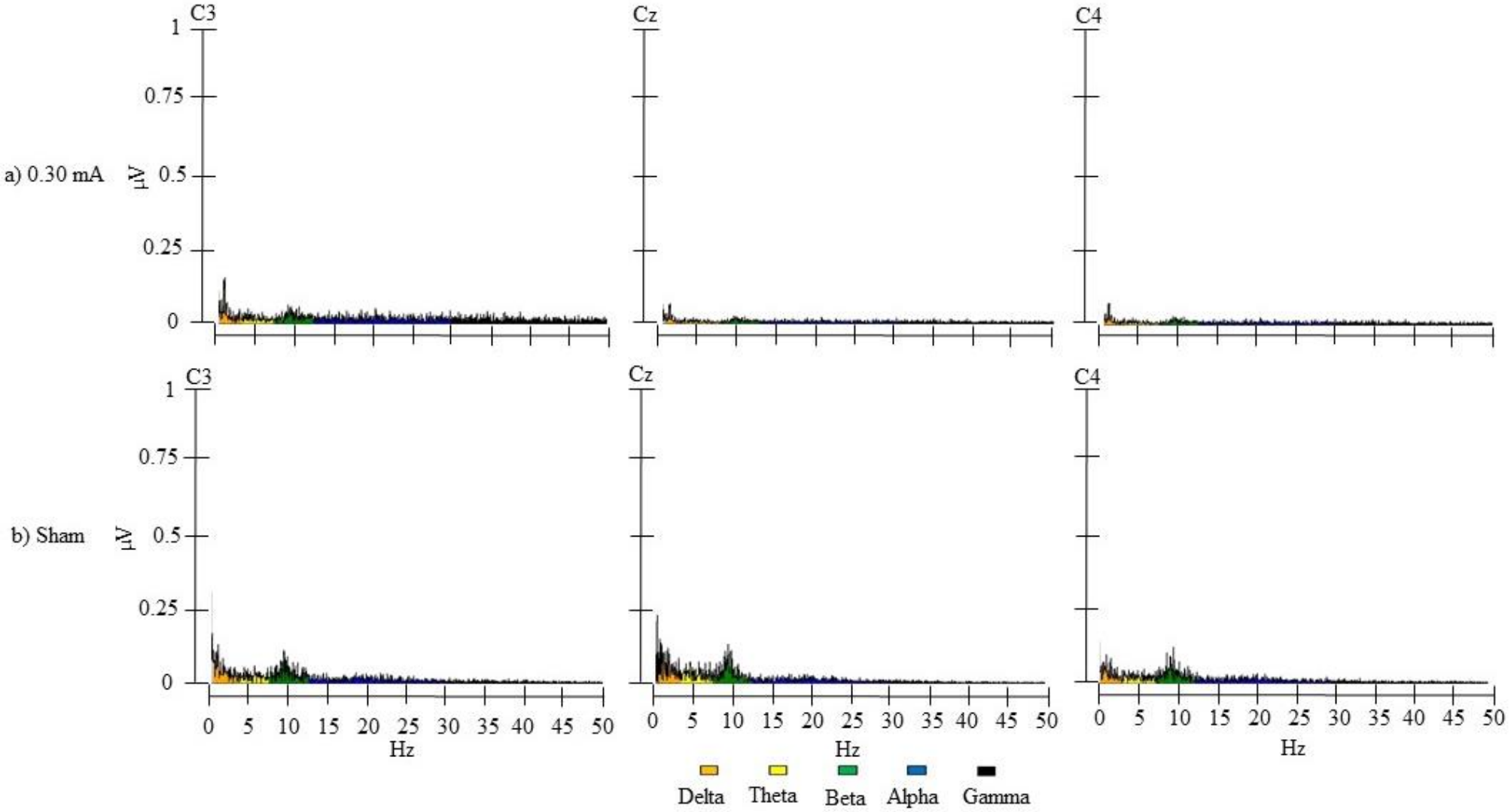


Figure 3. Row a) shows an example of the FFT graphs obtained from EEG data recorded during GVS application following the removal of the ICA components associated with the GVS artifact. The high-amplitude peak within the delta frequency range observed in Figure 1a) is absent here but some residual activity in the lower end of the delta frequency range remains. Row b) shows comparable FFT graphs obtained from EEG data recorded during sham GVS following removal of ICA components associated with blinks and saccadic eye movements as per convention.

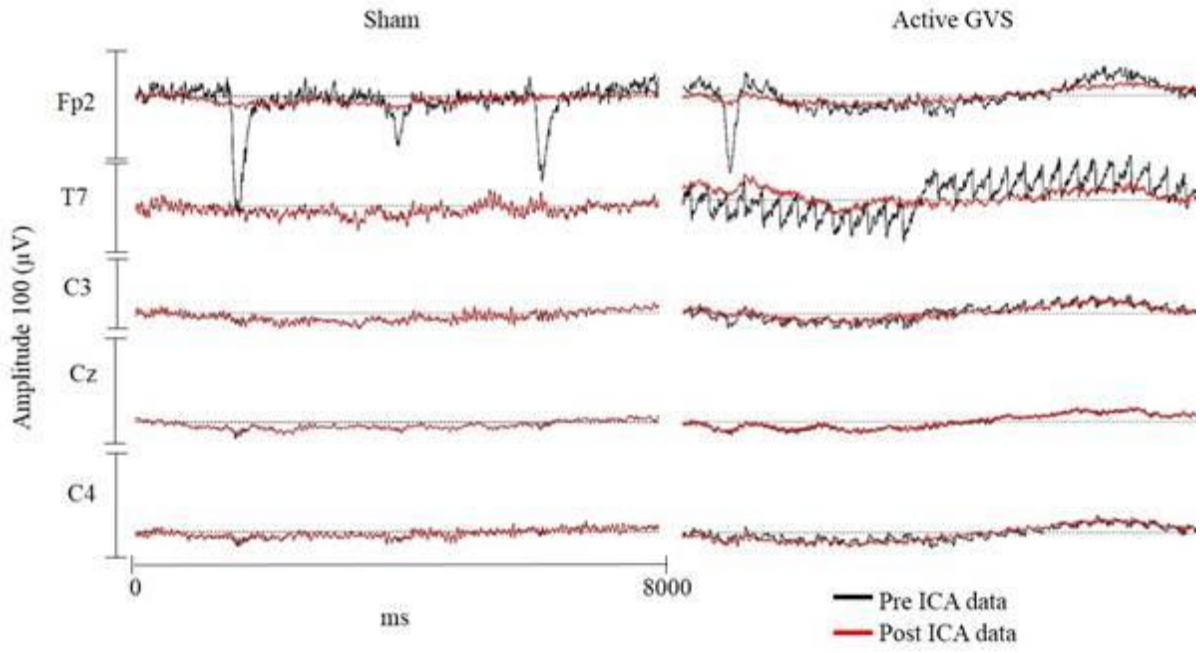


Figure 4. Snapshot (8000 ms) of data before and after ICA. Post data represents the data after both IC's associated with the electrooculogram (EOG) and GVS have been removed.

Study One

Study 1 was a proof-of-concept investigation to evaluate the feasibility and logistics of collecting MRCP data from a healthy student population using concurrent EEG and GVS. The main aim was to successfully remove the GVS-related artifact from the continuous EEG without compromising the acquisition of the MRCPs. One point of difference in this study from the GVS parameters in the pilots was the change to a GVS frequency of 0.01 Hz instead of 3 Hz. This decision was based on the finding in the pilots that a frequency of 3 Hz led to the number of IC labels associated with the GVS-related artifact to exceed those associated with neural activity (28 out of 30). Thus, 0.01 Hz was selected to determine whether altering the GVS frequency would reduce the number of GVS IC labels identified by ICA, and because it is unlikely to interact with the underlying oscillatory frequency of MRCPs (0.01-2 Hz) (Armstrong et al., 2018; Schmidt et al., 2016). Moreover, there is no evidence or theoretical reason to think that employing this low frequency may reduce the therapeutic strength of GVS effects. Study 1 also evaluated whether

removal of the GVS-related artifact by ICA would disrupt the ability to obtain MRCPs from concurrent GVS-EEG data. An experimental protocol comprising of simple, self-paced, voluntary finger movements was employed, whilst participants received GVS and EEG was recorded. Self-initiated finger tapping is an established motor task employed in many previous studies to elicit MRCPs (Deecke, Grozinger & Kornhuber, 1976; Deecke, Scheid & Kornhuber, 1969) and crucially is a task identified in the UPDRS to evaluate the diagnosis and pathogenesis of PD (Goetz et al., 2008).

Participants

Sample Size Justification. The sample size obtained for the three studies was based on several factors. A power analysis was conducted for studies 1 and 2 using GPower 3.1 (Faul, Erdfelder, Lang & Buchner, 2007) with power set (1-β err prob) at 0.95 and $\alpha = 0.05$. To obtain a large effect size of 0.40 ($\eta_p^2 = 0.14$) as previously reported in the literature (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012) a sample size of $n = 12$ was required for studies 1 and 2. A power analysis for study 3 was also conducted using the same parameters but accounting for two groups (PD and control group) and yielded a sample size of $n = 12$ for each group. An optimal sample size of $n = 12$ was treated as a minimum for Study 3 with the PD and control participants as there was sufficient justification from the literature to increase this to 20 in each group (Wilkinson et al., 2019). The target sample sizes were also based on resource constraints and feasibility as they were influenced by limited access to populations, particularly access to the PD population. Another factor that made recruitment more difficult was the intensive nature of the experimental protocol itself. Nevertheless, I note that similar studies that have used GVS, EEG and EMG have also recruited sample sizes ranging from 10-23 participants (Kim et al., 2013; Lee at al., 2019; Schmidt-Kassow et al., 2016).

Study 1 Participants. Eleven students (10 females, M_{age} = 18.75, age range = 18-20 years) from the University of Kent were recruited via the School of Psychology Research Participation Scheme (RPS). All participants were eligible to participate with none having skin abrasions/lesions behind the ears; any history of neurological disorder; any metallic objects or electronic implants in the body/head or currently taking any anti-depressive or anti-anxiety medication. Participants were compensated for their participation with course credits.

Materials

Galvanic Vestibular Stimulation (GVS). The stimulation device utilized in this study was the same as for the pilots (see page 36 for more information). The sham stimulation condition was conducted identically to the active stimulation condition except the device was turned off and participants were falsely informed that they were receiving stimulation. This blinding procedure has been routinely used in previous GVS studies (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012). The stimulation frequency employed in this study was altered from 3 Hz to 0.01 Hz following the results from the pilots. The amplitude of the sinusoidal current used in Study 1 oscillated between 0.20-0.30 mA. The pilots supported the feasibility of employing these intensities in terms of the successful removal of the GVS-related artifact using ICA. Moreover, measurable vestibular responses have been reported from low intensities such as these (Day et al., 1997; Cauquil et al., 2003; Pal et al., 2009) and this will also facilitate the blinding of participants to stimulation conditions (Utz et al., 2011).

EEG and EMG Acquisition. EEG data in this study was recorded identically to that of the pilots (see pages 36 for more information). Surface muscle activity was recorded using self-adhesive, disposable EMG electrodes (34.93mm, SilveRestTM, Vermed®, Buffalo, New York) via

a bipolar channel adaptor connected to the amplifier. A bandwidth filter of 20-249Hz and a 50Hz notch filter was applied to EMG data during recording.

Procedure

Participants provided written and verbal informed consent prior to being seated upright in a comfortable chair with their right forearm resting on a cushion beside them and facing a black computer screen. To minimise the effect of blink and saccadic eye movement-related artifact, participants were asked to fixate on a cross positioned in the centre of the computer screen.

First, the skin over the mastoids and the extensor digitorum communis (ED) muscle of the right forearm was prepared using sterilizing alcohol wipes and Nuprep® (Weaver and Company, Colorado, USA) skin prep gel. This muscle is reported to effectively detect and provide quantification for movement-related activity within the fingers (Leijnse et al., 2008). The GVS electrodes were then placed over the mastoids behind each ear. The EMG electrodes were placed over the ED muscle group in a bipolar montage with the ground electrode over the wrist, according to the European SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) recommendations (Hermens et al., 1999). EMG and EEG were recorded within the same software (same sampling rate), enabling time-locking of movement-related EEG activity in association with EMG phase (movement onset) (Shibasaki & Rothwell, 1999). Here, the first action of movement, also known as EMG onset, is utilized as a fiducial point to observe MRCPs during a simple finger tapping movement. This is particularly pertinent for the pre-movement potentials which need to be closely tied to the earliest physiological indication of movement onset (Shibasaki & Rothwell, 1999). Finally, an EEG cap was then fitted to the participant's head and electroconductive gel was used to maintain impedance below 10 kΩ throughout data collection. EEG and EMG preparation lasted approximately 40 minutes.

Participants were then provided with verbal instructions for the finger tapping task. They were instructed to perform voluntary extensions of the right index finger at their own pace without relying on any external cues. They were provided with five minutes to practice whilst an experimenter monitored their EMG trace on the tablet screen and provided feedback about the timing, magnitude and velocity of movements. If movements were occurring too close together in time (under one to two second intervals), participants were instructed to slow down. Additionally, only movements that commenced from complete muscle relaxation (steady-state EMG) were considered acceptable. These measures facilitated the offline assignment of markers that time-locked EEG epochs to EMG onset and ensured that there was sufficient time between movements to allow for the successful acquisition of the BP and MP. The negative slope of the BP is said to commence 1.5 seconds prior to muscle activation onset and the negative deflection associated with the MP is reported to peak around 200 milliseconds post movement onset (Shibasaki & Hallett, 2006; Colebatch, 2007). Moreover, ensuring a sufficient epoch length of 2-5 seconds also minimised the impact of potential overlap in the ERP waveforms. Overlap can cause a jittering or smearing effect on the data that can lead to misinterpretation. As an ERP can last several seconds, the inter-stimulus interval (ISI) must account for this (Luck, 2014), hence the minimum period of 2-5 seconds for movement. The participants were also instructed to maintain their gaze on the fixation cross of the computer screen for the duration of the motor task to minimize ocular artifacts. This was monitored by the experimenters whilst the participants performed the task with participants being instructed to return their gaze to the fixation cross if their eyes deviated away from it. Finally, they were instructed to avoid any muscle activation (jaw-clenching, fidgeting, head and shoulder movements), other than the finger tapping, to minimize muscle-related artifacts.

EEG data was then recorded in blocks as illustrated in the Figure 5. The order of condition blocks was as follows: at rest with eyes open during active GVS; participants performing 150 finger taps during active GVS; at rest with eyes open during sham GVS and finally participants performing 150 finger taps during sham GVS. Experimenters counted movements as participants executed them. Rest blocks were included as a means of providing a baseline to determine and optimise characterisation of GVS-related artifact during offline processing.

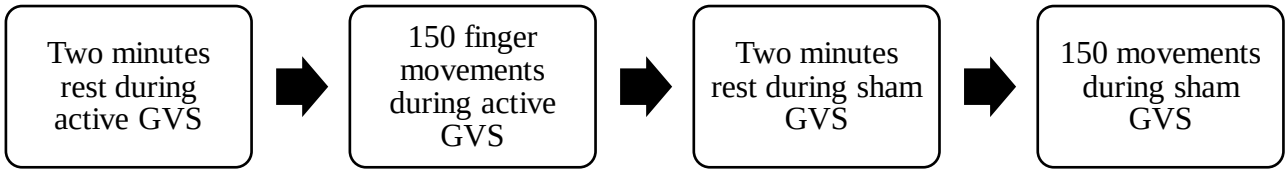


Figure 5. Schematic of procedure for Study 1.

Following completion of the last block of movements, participants filled out a perception of stimulation questionnaire to report any GVS-related physical sensations they may have experienced during the session (see Appendix A). The participants were then provided with a full verbal and written debrief of the experiment and were thanked for their participation. This study lasted approximately two hours.

Data Offline Processing and Analysis

The offline processing strategy employed in Study 1 was the same as that used in the pilot except that ICA was conducted on concatenated data. For each participant, 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 were excluded from further analysis.

Each participants' data was segmented into epochs time-locked to EMG onset. The method for determining EMG onset was the manual placement of markers upon visual inspection. Markers

were placed prior to the earliest rise in the trace amplitude beyond the steady state. EMG traces from trials that did not show an abrupt and clear deviation from the steady state EMG were not included in the segmented epochs. Visual determination of EMG onset is widely used in studies evaluating the temporal properties of EMG and its accuracy has been shown to equal that of statistical methods (Hodges & Bui, 1996). Epoch length was 1000ms following and 1500ms prior to EMG onset. On average, 2% (n = 37) of trials in the active GVS condition and 3% (n = 49) in the sham GVS condition were excluded because the EMG trace did not show an abrupt and clear deviation from the steady state EMG to accurately determine movement onset. Data was then baseline corrected to the first 200ms of the epoch time-window. Grand averages were calculated using 98% and 97% of trials for the active (n = 1609) and sham GVS (n = 1586) conditions, respectively. For the EMG results, the peak-to-peak amplitude of the averaged EMG traces were used to compute the rectified EMG amplitude for the active and sham GVS conditions. A paired-sample t-test was conducted to compare the rectified EMG amplitudes in the active and sham GVS conditions, with a p value of <.05 being considered statistically significant. Effect sizes for pairwise comparisons were measured using Cohen's d, with magnitudes of d = 0.2, d = 0.5 and d = 0.8 being considered small, medium and large effects, respectively (Cohen, 2013).

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 the largest voltage deflections identified in the grand collapsed averaged data and topographical maps and 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 – 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 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, with a p value of $< .05$ being considered statistically significant. Effect sizes for the ANOVAs were measured using partial eta squared, with magnitudes of $\eta_p^2 = .01$, $\eta_p^2 = .06$ and $\eta_p^2 = .14$ being considered small, medium and large effects, respectively (Miles & Shevlin, 2001). Post-hoc comparisons conducted on the electro-cortical data were Bonferroni corrected with a p value of $< .01$ being considered statistically significant for when three comparisons were conducted. Effect sizes for pairwise comparisons were measured using Cohen's d, with magnitudes of $d = 0.2$, $d = 0.5$ and $d = 0.8$ being considered small, medium and large effects, respectively (Cohen, 2013).

Study 1 Results

The results from the Perception of Stimulation Questionnaire showed that only one out of the 12 participants experienced an itching/prickling sensation behind the ears during active GVS.

Independent Component Identification

The IC labels identified in Study 1 (see Figure 6) were consistent with those identified in the pilots. The use of a 0.01 Hz GVS frequency also proved successful in reducing both the number

of IC labels associated with the GVS-related artifact (1 out of 30) and the power spectrum associated with it. This is in comparison to the high number found in the pilots (28 out of 30) when a higher GVS frequency (3 Hz) was employed. As Figure 5 shows, the GVS-related IC label differs from other standardized IC labels (eye blink, saccade, and brain). This is evidenced by its characteristic temporally polarized topographical distribution of activation, which can be differentiated from the frontal and frontotemporal localised activations during eye blinks and saccadic eye movements, respectively. Along with its characteristic topographical map, the GVS-related IC label show a higher power spectrum (-10.20 μV – 8.85 μV) compared to that the brain-related IC label (-2.5 μV – 1.5 μV).

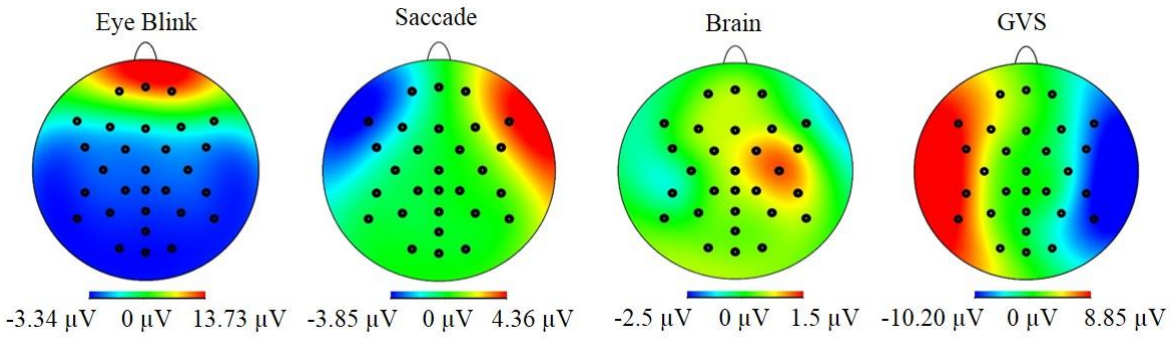


Figure 6. Four examples of components returned by ICA associated with EOG, brain activity and the new GVS-related artifact components.

EMG Results

A paired-samples t-test revealed no significant difference between mean EMG amplitude across active (M = 13.20 μV, SD = 7.85) and sham (M = 13.79 μV, SD = 7.94) GVS conditions (t (10) = 0.43, p = 0.68; d = -0.13).

ERP Results

Early BP. The ANOVA for the early BP yielded a significant main effect of Electrode Site (F = 4.34; p = 0.03; η_p^2 = 0.30) but not Stimulation (F = 0.50; p = 0.50; η_p^2 = 0.05), nor was there

a significant interaction between Electrode Site and Stimulation (F = 1.37; p = 0.28; η_p^2 = 0.12). (see Table 1 and Figures 7 and 8). Pairwise comparisons for the main effects of Electrode Site revealed no significant differences between amplitudes at C3, Cz and C4 following Bonferroni correction (C3 and Cz: t (10) = 2.61; p = 0.03; d = 1.65; C3 and C4: t (10) = 0.59; p = 0.57; d = 0.37; Cz and C4: t (10) = -2.57; p = 0.03; d = -1.63).

Late BP. A significant main effect of Electrode Site was found for the late BP ANOVA (F = 6.91; p = 0.01; η_p^2 = 0.41) but not Stimulation (F = 0.00; p = 0.98; η_p^2 = 0.00), nor was there significant interaction between variables (F = 1.22; p = 0.32; η_p^2 = 0.11). Pairwise comparisons for the main effect of Electrode Site, revealed that the late BP amplitude was significantly greater at Cz (M = -1.31 μV, SD = 0.82) than at both C3 (M = -0.60 μV, SD = 0.79) and C4 (M = -0.55 μV, SD = 0.58), (t (10) = 3.35; p = 0.01; d = 2.12, t (10) = -3.70; p = 0.00; d = -2.34, respectively) and there was no difference between late BP amplitudes at C3 and C4, (t (10) = -0.17; p = 0.87; d = -0.11).

MP. The ANOVA for the MP yielded a significant main effect of Electrode Site (F = 15.67; p = 0.00; η_p^2 = 0.61), but not Stimulation (F = 0.10; p = 0.76; η_p^2 = 0.01), nor was there a significant interaction (F = 1.59; p = 0.23; η_p^2 = 0.14). (see Table 1 and Figures 7 and 8). Pairwise comparisons of the mean MP amplitudes across C3, Cz and C4 revealed that the MP amplitude was significantly greater at Cz (M = -3.11 μV, SD = 1.54) than at both C3 (M = -1.45 μV, SD = 1.38) and C4 (M = -1.16 μV, SD = 0.94), (t (10) = 4.93; p = 0.00; d = 3.12, t (10) = -5.68; p = 0.00; d = -3.59, respectively) and there was no difference between MP amplitudes at C3 and C4, (t (10) = -0.66; p = 0.52; d = -0.42).

Table 1

Table of mean amplitude of MRCPs components within both GVS conditions for all electrodes.

MRCP Component	Electrode Site	Stimulation Condition	Mean Amplitude μV (SD)
Early BP	C3	Active GVS	0.05 (0.39)
		Sham GVS	-0.15 (0.26)
	Cz	Active GVS	-0.29 (0.42)
		Sham GVS	-0.33 (0.18)
	C4	Active GVS	-0.15 (0.20)
		Sham GVS	-0.07 (0.26)
Late BP	C3	Active GVS	-0.47 (1.05)
		Sham GVS	-0.72 (0.65)
*	Cz	Active GVS	-1.32 (1.14)
		Sham GVS	-1.31 (0.81)
*	C4	Active GVS	-0.68 (0.66)
		Sham GVS	-0.43 (0.65)
MP	C3	Active GVS	-1.30 (1.55)
		Sham GVS	-1.59 (1.31)
*	Cz	Active GVS	-3.19 (1.63)
		Sham GVS	-3.04 (1.66)
*	C4	Active GVS	-1.31 (1.02)
		Sham GVS	-1.00 (1.01)

Note: * indicates statistical significance at the $p < .01$ level.

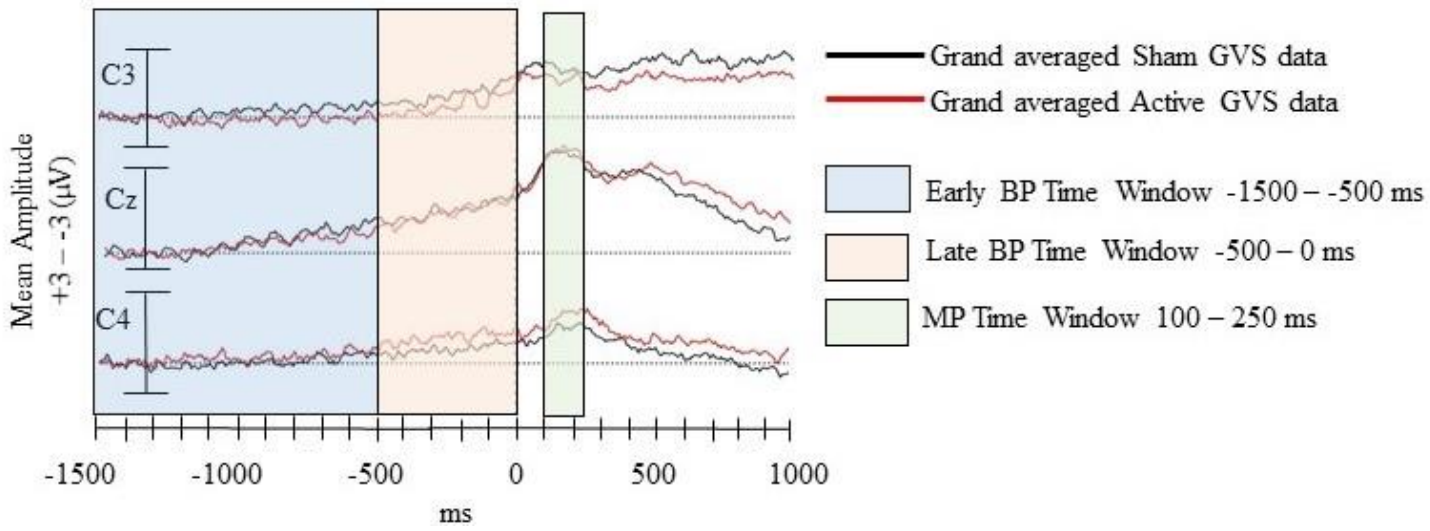


Figure 7. MRCP waveforms of Study 1 results.

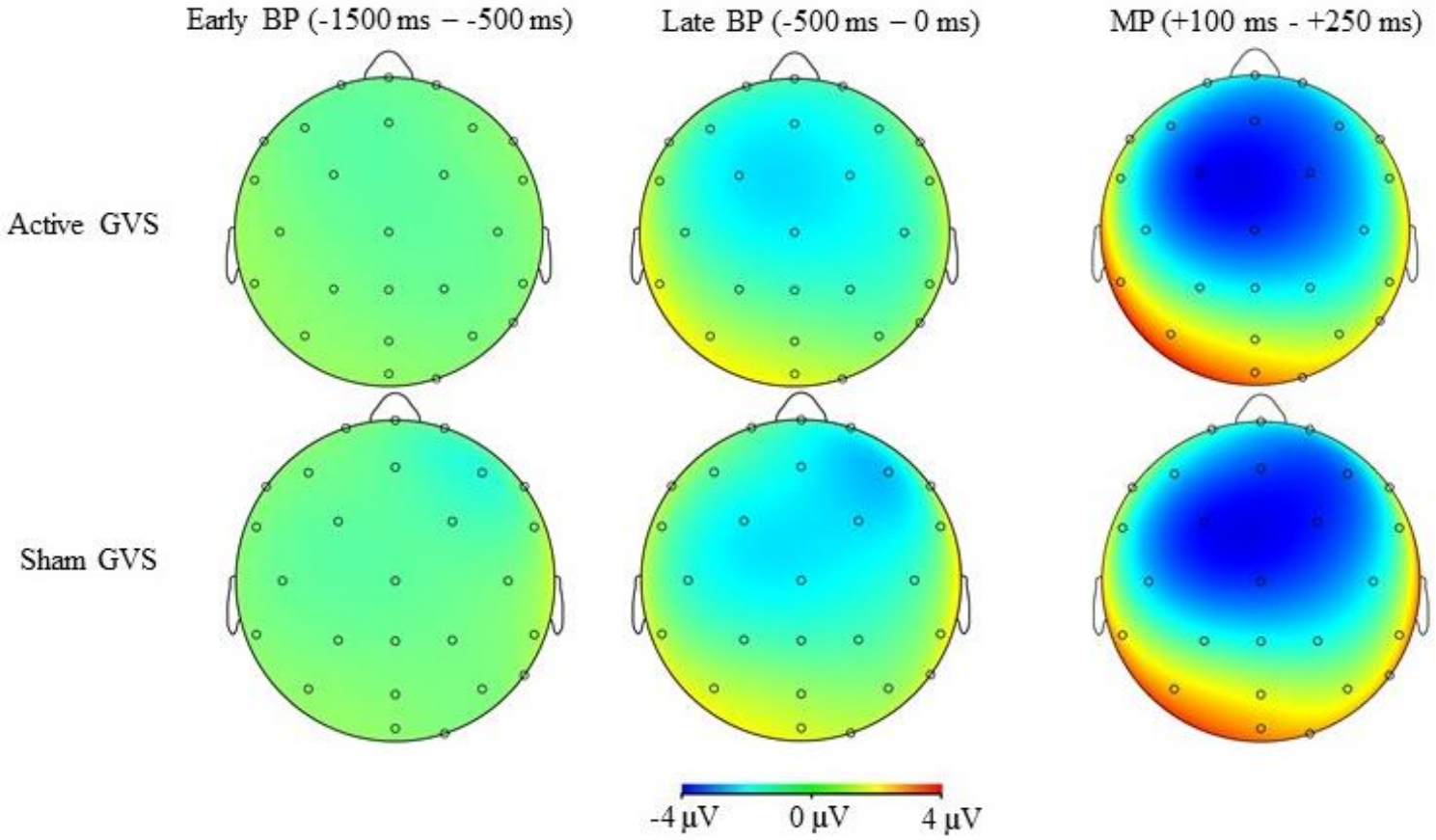


Figure 8. Topographical maps of Study 1 results.

Study 1 Discussion

The aim of Study 1 was to develop and evaluate a pre-processing pipeline to remove the GVS-related artifact introduced during concurrent EEG and GVS from the EEG raw data, without compromising the acquisition of MRCPs. The results showed no significant difference in the mean amplitudes of the early BP, late BP and MP components across active and sham GVS conditions for the three central electrodes. These statistical findings and the consistency of the MRCP waveforms and topographical distributions across active and sham stimulation conditions provides validation of the analysis strategy used to remove the GVS-related artifact. Post-hoc analyses of differences found between electrodes Cz and C4 in the late BP and MP amplitude is also consistent with previous reports on the progression of activity within Cz during movement preparation and execution.

In contrast to the findings observed within this study, previous findings report an effect of GVS on ERPs and EEG power. Specifically, GVS has been reported to increase the amplitudes of the P3 elicited by the oddball paradigm and the N170 during a visual discrimination task (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012). Wilkinson et al. (2012) also observed elevated delta and theta activity during the active stimulation condition compared to sham, whilst Kim et al. (2013) reported stimulus-dependent changes in all frequency bands related to the GVS intensity applied. However, the differences in results between this current and previous research may reflect variances in methodological approach. For example, this study obtained MRCPs as the electro-cortical activity of interest whereas the previous studies reported on the P3, N170 and frequency band power. These markers differ in terms of the functions associated with them as well as their reported location. For example, the P3 in the previous study was associated with auditory processing using an oddball paradigm task whereas MRCPs were associated with motor function

in this study through the use of a movement task. Furthermore, P3 location is generally reported over parietal regions whereas MRCPs are associated with central regions, likely reflecting activations of the motor cortex (Linden, 2005; Shibasaki & Hallett, 2006). Additionally, it is suggested that the results in this current study are reflective of a ceiling effect associated with the participant cohort being from a neurologically healthy sample. Therefore, the effects of GVS may not have been sufficiently large to induce changes in motor cortical activity. Indeed, there is evidence to suggest that the corticomotor effects of non-invasive stimulation in healthy individuals may be small compared to those in neurologically impaired individuals (Bastani & Jaberzadeh, 2012). The authors suggest that the enhanced effects of non-invasive brain stimulation in individuals with neurological disease may reflect the rapid changes in cortical plasticity following damage. It is worth noting here that the therapeutic value of the GVS parameters employed in this study have not yet been assessed. Another potential explanation for the absence of stimulation effects is that the employment of ICA in the analysis may have removed any meaningful effects of GVS on MRCPs. Every preprocessing step applied offline inherently adds a level of bias and for each extraction process such as ICA there is always potential for underlying neural activity of interest to be removed, hence the need to remove the least number of ICs as possible. If the GVS effect is small for example, the removal of the GVS-related ICs may in fact reduce the parameters of the components of interest. Hence, significant effort was made in the processing analysis to maintain a minimal number of offline steps (only filters and ICA) to mitigate the potential effects of the analysis on the results (Gramman and Klug, 2020), but such a possibility cannot be dismissed.

Post-hoc comparisons revealed significantly larger activation of the late BP and MP components at Cz compared to C4. The mean amplitudes becoming increasingly larger from the late BP to the MP at Cz, whilst remaining relatively stable at C4 (see Table 1), which suggests that

these results are likely driven by the progression of motor activity that is reported to be maximal at Cz (Colebatch, 2007). This is consistent with previous literature reporting the negativity becoming increasingly steeper as the corticomotor phase progresses from preparation (late BP) to execution (MP) at Cz. The late BP phase likely reflects the interaction between the supplementary motor area (SMA) and the motor cortex (M1) during selection of the appropriate muscles for activation, whilst the MP reflects the actual recruitment of these muscles during movement (Neshige et al., 1988; Deecke et al., 1980).

In sum, the aim of Study 1 was to assess the validity of a novel methodology to remove the GVS artifact from concurrent GVS and EEG data, without compromising the acquisition of the MRCPs from finger tapping data. Moreover, the use of a lower GVS frequency to that employed in the pilots also successfully reduced the number of GVS-related IC labels identified by ICA in Study 1 compared to the pilots. The findings of Study 1 support the validation of the novel methodology as the consistency of the early and late BP and the MP across the active and sham stimulation conditions indicate the successful removal of the GVS artifact without interfering with underlying neural activity. The methodology validated in Study 1 was then implemented within Study 2 with the aims of further refining the GVS parameters and observing MRCPs elicited during a foot movement task.

Study Two

Study 1 applied a novel methodology of using simultaneous GVS and EEG to a previously established approach of obtaining MRCPs through simple finger movements. The EEG processing pipeline successfully eliminated the GVS-related artifact from the continuous EEG without compromising the BP and MP components acquired from voluntary finger movement. The aims of Study 2 were to build on the methodology developed in Study 1 by evaluating the feasibility of adding foot movements to the experimental paradigm and to further optimize the GVS parameters. To achieve this, Study 2 evaluated the feasibility of obtaining MRCPs derived from foot movements using a concurrent GVS and EEG experimental protocol. Additionally, Study 2 assessed the efficacy of the EEG processing pipeline in successfully removing the GVS-related artifact derived from a higher intensity GVS stimulus.

As in finger movements, MRCPs have been reported preceding and during voluntary foot movements (Brunia & van de Bosch, 1984; Shibasaki, Barrett, Halliday & Halliday, 1981). However, foot movements have been shown to elicit MRCPs of earlier onset and larger amplitude than finger movements (Brunia & van de Bosch, 1984). Differences between scalp distribution of finger and foot movements have also been reported. Finger movements seem to consistently induce MRCPs of larger amplitudes over the hemisphere contralateral to movements, whereas MRCPs derived from foot movements show larger amplitudes in the midline or in the hemisphere ipsilateral to movement (Brunia & van de Bosch, 1984; Shibasaki et al., 1981). These findings have been explained by the distinct cortical representational areas of each limb within the motor cortex, with the medial location of the foot area resulting in dipoles orienting to more central or ipsilateral areas of the scalp (Böcker, Brunia & Cluitmans, 1994).

The implementation of foot tapping in this study was also justified because of its clinical relevance to the foot tapping tasks in the MDS-UPDRS used for the diagnosis of PD (Goetz et al., 2008). Foot tapping as a motor task has also been employed previously for the measurement of lower limb function in PD with high reliability (Gunzler et al., 2009). Indeed, it is likely that foot tapping may be a more valid approximate measure of gait disturbances such as freezing of gate (FOG) than finger tapping because it may share mechanisms with locomotion (Delval, Defebvre & Tard, 2017; Gunzler et al., 2009). Moreover, previous studies have reported discrepancies in PD symptoms between upper and lower limbs in PD. One study showed that whilst upper limb spinal reflexes (SR) remain relatively intact during locomotion in PD, SR of the lower limbs was attenuated compared to that of healthy, age-matched participants (Dietz & Michel, 2008). This abnormality is likely related to reduced activation of the leg extensor muscles required for walking (Dietz & Colombo, 1998). Another study found subtle discrepancies in the variability and rhythm of rest tremors between upper and lower limbs, suggesting different underlying mechanisms (Scanlon et al., 2013). Hence the importance of measuring MRCPs from both upper and lower limbs.

Refinement of the GVS parameters in this study consisted of increasing the current intensity from the 0.20-0.30 mA employed in Study 1 to 0.30-0.40 mA. Previous studies have demonstrated that higher galvanic stimulation intensities produce larger ocular and postural effects (Coats, 1973). For example, Cauquil, Gervet and Ouaknine (1998) found that larger head movements and body sway during standing could be elicited by increasing GVS intensity. GVS intensities between 0.10 mA and 0.70 mA have been shown to produce postural and ocular responses of similar characteristics, i.e., these low currents produce body sway and torsional slow phase eye movement towards the anode (Day et al., 1997; Cauquil et al., 2003). Moreover,

increasing current intensities appear to influence more parts of the peripheral vestibular system. Zink et al. (1998) showed that whilst lower intensities of GVS current stimulated the otolith organs, higher intensities additionally induced semicircular canal responses indicated by an increase in horizontal-rotatory nystagmus. Based on these findings, it is possible that the therapeutic utility of GVS may be increased if the stimulation intensity range is widened.

The experimental protocol for Study 2 remained identical to that utilized in Study 1 to ensure consistency, except for the inclusion of short breaks within movement blocks to reduce the effects of physical and/or cognitive fatigue (Gandevia, 2001). As in Study 1, finger movements consisted of self-paced, voluntary right index finger extension. The foot movement blocks that followed finger movements consisted of self-paced, voluntary ankle dorsiflexion. Participants were provided with identical instructions for both movement tasks to ensure movements were standardized.

Participants

Nine students (5 females, M_{age} = 18.78, age range = 18-20) from the University of Kent were recruited via the School of Psychology RPS. All participants were eligible to participate with none having skin abrasions/lesions behind the ears; any history of neurological disorder; any metallic objects or electronic implants in the body/ head or currently taking any anti-depressive or anti-anxiety medication. Participants were compensated for their participation with course credits.

Materials

All materials used in Study 2 were identical to those utilized in Study 1 with one exception in the GVS parameters. A sinusoidal current oscillating between 0.30-0.40mA was applied during active GVS. All other GVS parameters remained the same as in Study 1.

Procedure

The experimental procedure for Study 2 was identical to that of Study 1 with two alterations. First, the foot tapping task was included following the finger tapping task (see Figure 9). Participants were instructed to perform 150 dorsiflexions with their right foot at their own pace without any external cues. Surface EMG of the tibialis anterior muscle (TA) was recorded during foot movements with the ground electrode over the right ankle, according to the European SENIAM recommendations (Hermens et al., 1999). The TA was chosen based on its use in previous physiological studies and for the fact that it is identified as one of the two main muscles (TA and gastrocnemius) that is used to detect contractile-related movement at the onset of dorsiflexion (Albani et al., 2003). This is pertinent within a PD population, specifically in relation to the capacity to measure and quantify the different phases of walking (e.g., gait initiation) (Elble, Moody, Leffler & Sinha, 1994) and leg muscle activity in lower limb movements (den Otter, 2005; Taniguchi, Peper & Shimokawa, 2018). Second, 30s breaks were introduced within each movement block after every 50 movements (see Figure 10). Participants also completed the same perception of stimulation questionnaire as in Study 1 (see Appendix A). Each session lasted approximately three hours.

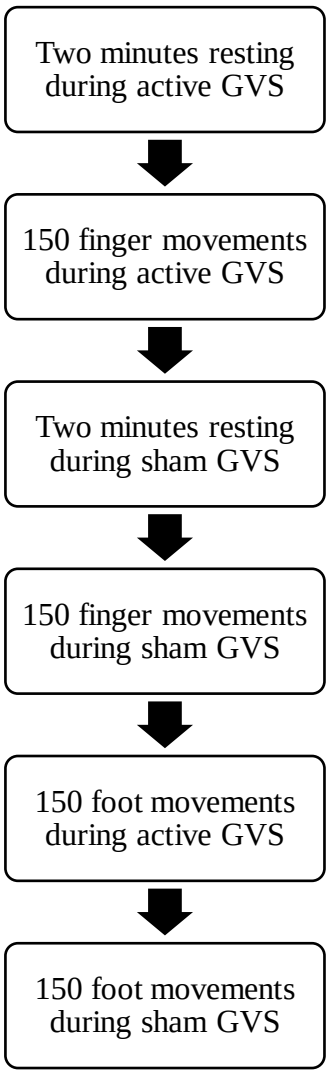


Figure 9. Schematic of procedure for Study 2.

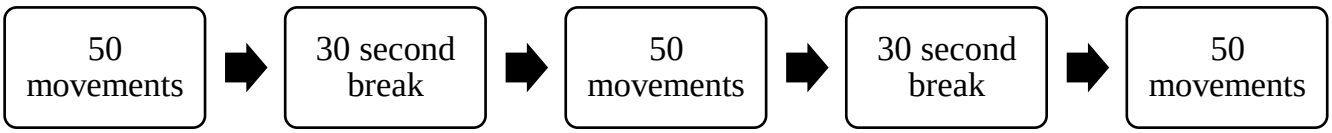


Figure 10. Schematic of movement blocks in Study 2.

Data Offline Processing and Analysis

The offline processing strategy employed in Study 2 was identical to that used in Study 1 (see pages 48-51). Segmentation into epochs was conducted using the same method for EMG onset determination employed in Study 1, with epochs being the same length. On average for finger movements, 1% (n = 32) of trials in both the active and the sham GVS conditions were excluded because EMG onset could not be accurately determined. Thus, for finger movements the grand averages for both stimulation conditions were calculated using 99% (n = 2659) of trials following baseline correction to the first 200 ms (-1500 - -1300 ms) of the epoch. Fewer than 1% (n = 6) of foot movement trials in both stimulation conditions were excluded due to inaccurate EMG onset determination, which meant that over 99% (n = 2671) of foot movement trials were used to calculate the grand average amplitudes for the foot active and sham GVS conditions. The rectified EMG amplitude was used to compare the mean EMG amplitude across the active and sham GVS conditions. A paired sample t-test was conducted to compare the rectified EMG amplitudes from the active and sham GVS conditions for the finger EMG data. The same comparison was applied to the foot EMG data. A p value of $< .05$ was considered statistically significant for this analysis and Cohen's d was also used to determine effect sizes (Cohen, 2013).

MRCP waveforms for both finger and foot movements were defined in the same way as in Study 1 finger MRCP waveforms (see pages 48-50). Mean amplitudes of the early and late BP and the MP were computed for each limb (finger and foot), stimulation condition (active and sham GVS) and electrode site (C3, Cz, C4). The same statistical analysis was applied to data obtained from finger and foot movements. For finger movement data, three separate, repeated measures 2x3 ANOVAs were conducted for each MRCP component – using 2 (stimulation: active and sham GVS) x 3 (electrode site: C3, Cz, C4) within-subjects ANOVA, with a p value of $< .05$ being

considered statistically significant. The same statistical analysis was applied to the foot movement data. A second set of analyses was conducted to compare finger and foot movement for each MRCP using a three-way 2 (limb: finger and foot) x 2 (stimulation: sham and active GVS) x 3 (electrode site: C3, Cz, C4) within-subjects ANOVA. Adding limb as a variable was to investigate any differences between finger and foot movements in relation to their activation distribution (electrode site) and response to stimulation.

As with Study 1, ANOVA effects with a p value of $< .05$ were considered statistically significant and partial eta squared was used to measure effect sizes, with magnitudes of $\eta_p^2 = .01$, $\eta_p^2 = .06$ and $\eta_p^2 = .14$ being considered small, medium and large effects, respectively (Miles & Shevlin, 2001). Post-hoc comparisons were considered statistically significant at a p value of $< .01$ when conducting three comparisons and $p < .05$ with one comparison. Cohen's d was used to measure effect sizes, with magnitudes of $d = 0.2$, $d = 0.5$ and $d = 0.8$ being considered small, medium and large effects, respectively (Cohen, 2013).

Study 2 Finger Movement Results

In this study, eight out of the nine participants reported itching/prickling sensations on the Perception of Stimulation Questionnaire during the active GVS conditions.

Independent Components Identification

As demonstrated in Figure 11, the GVS-related IC labels showed a similar topographical distribution across finger and foot movements, both separately and when combining their data.

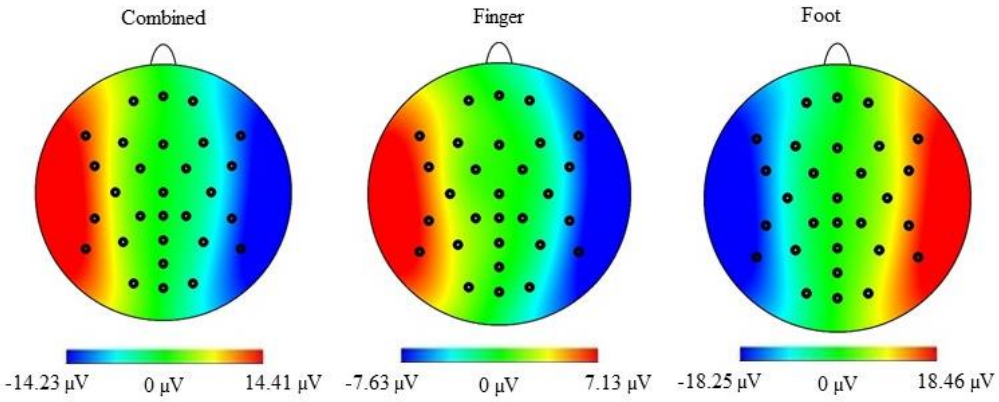


Figure 11. Three examples of the GVS-related components returned by ICA associated with the combined and individual finger and foot movement data in Study 2.

EMG Results

A paired-sample t-test comparing the mean EMG amplitudes of the active (M = 17.30 µV, SD = 12.32) and sham (M = 16.58 µV, SD = 13.54) GVS conditions revealed no significant differences (t (8) = -0.62, p = 0.55; d = 0.21).

ERP Results

Early BP. The ANOVA for the early BP yielded a significant main effect of Electrode Site (F = 4.02; p = 0.04; η_p^2 = 0.33), but no significant main effect of Stimulation (F = 1.89; p = 0.21; η_p^2 = 0.19) nor was there an interaction (F = 2.53; p = 0.11; η_p^2 = 0.24). (see Table 2 and Figures 12 and 13). Pairwise comparisons for the main effects of Electrode Site revealed no significant differences between amplitudes at C3, Cz and C4 following Bonferroni correction (C3 and Cz: t (8) = 1.71; p = 0.13; d = 1.21; C3 and C4: t (8) = -1.02; p = 0.34; d = -0.72; Cz and C4: t (8) = -3.00; p = 0.02; d = -2.12).

Late BP. The ANOVA for the late BP yielded a significant main effect of Electrode Site (F = 5.80; p = 0.01; η_p^2 = 0.42), but no significant main effect of Stimulation (F = 1.09; p = 0.33; η_p^2 = 0.12) nor was there an interaction (F = 0.67; p = 0.52; η_p^2 = 0.08). Pairwise comparisons for the

main effect of Electrode Site revealed a significant difference between Cz (M = -1.01 μV, SD = 0.82) and C4 (M = -0.16 μV, SD = 0.76) such that the late BP mean amplitude was greater at Cz compared to C4 (t (8) = -3.42; p = 0.01; d = -2.42). No significant differences were found between late BP mean amplitudes at electrodes Cz and C3 (M = -0.94 μV, SD = 0.73), (t (8) = 0.22; p = 0.83; d = 0.16). The difference between C3 and C4 trended towards significance following Bonferroni correction, (t (8) = -3.17; p = 0.01; d = -2.24) (see Table 2 and Figures 12 and 13). This suggests an increase in mean amplitude associated with the Electrode Site contralateral to the finger movement on the right side.

MP. The ANOVA for the MP yielded a significant main effect of Electrode Site (F = 17.09; p = 0.00; η_p^2 = 0.68), but no significant main effect of Stimulation (F = 1.12; p = 0.54; η_p^2 = 0.04) nor was there an interaction (F = 0.33; p = 0.73; η_p^2 = 0.05). Pairwise comparisons of the main effect of Electrode Site revealed significant differences between electrodes C3 (M = -3.25 μV, SD = 1.71) and C4 (M = -0.10 μV, SD = 1.13) (t (8) = -5.55; p = 0.00; d = -3.92), and between Cz (M = -2.27 μV, SD = 1.41) and C4 (t (8) = -4.27; p = 0.00; d = -3.02), but not between Cz and C3, (t (8) = -1.70; p = 0.13; d = -1.20). This showed an increase in mean amplitude associated with the Electrode Site contralateral to the finger movement on the right side (see Table 2 and Figures 12 and 13).

Table 2

Table of mean amplitude of MRCPs components obtained from finger movements in Study 2.

MRCP Component	Electrode Site	Stimulation Condition	Mean Amplitude μV (SD)
Early BP	C3	Active GVS	-0.10 (0.24)
		Sham GVS	-0.10 (0.40)
	Cz	Active GVS	-0.14 (0.43)
		Sham GVS	-0.36 (0.35)
	C4	Active GVS	0.11 (0.29)
		Sham GVS	-0.12 (0.26)
Late BP	C3	Active GVS	-0.92 (0.64)
		Sham GVS	-0.96 (1.10)
	Cz	Active GVS	-0.82 (0.79)
		Sham GVS	-1.21 (1.07) *
	C4	Active GVS	-0.04 (0.79)
		Sham GVS	-0.29 (0.78)
MP	C3	Active GVS	-3.15 (1.47)
		Sham GVS	-3.35 (2.05)
	Cz	Active GVS	-2.01 (1.08)
		Sham GVS	-2.53 (1.80) * *
	C4	Active GVS	0.12 (1.35)
		Sham GVS	-0.32 (0.)

Note: * indicates statistical significance at the $p < .01$ level.

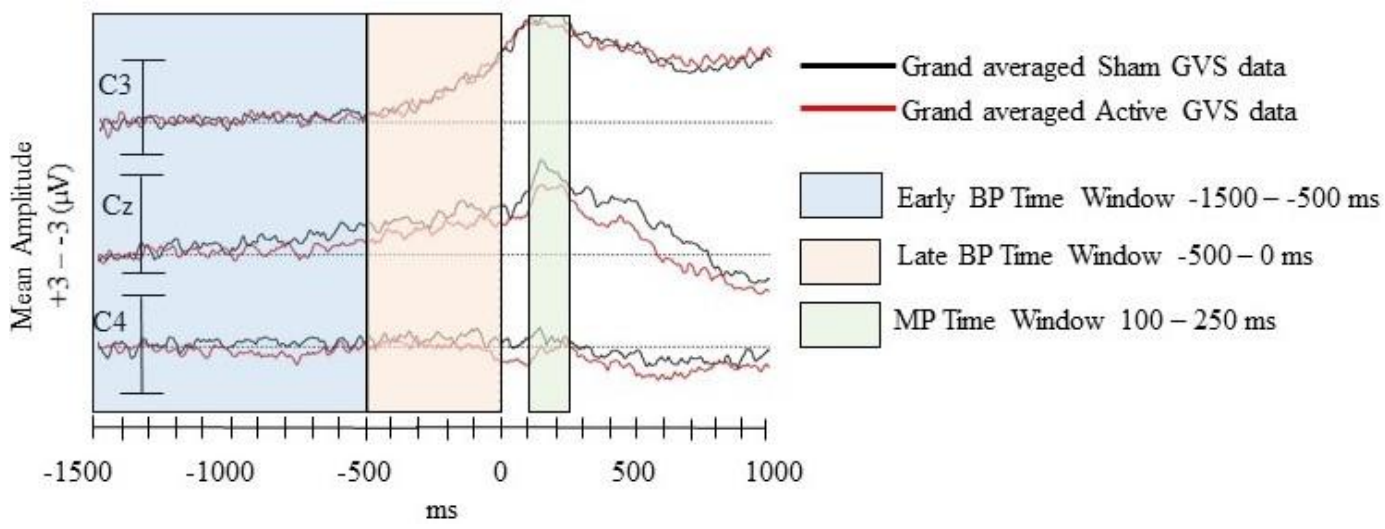


Figure 12. MRCP waveforms obtained from finger movements in Study 2.

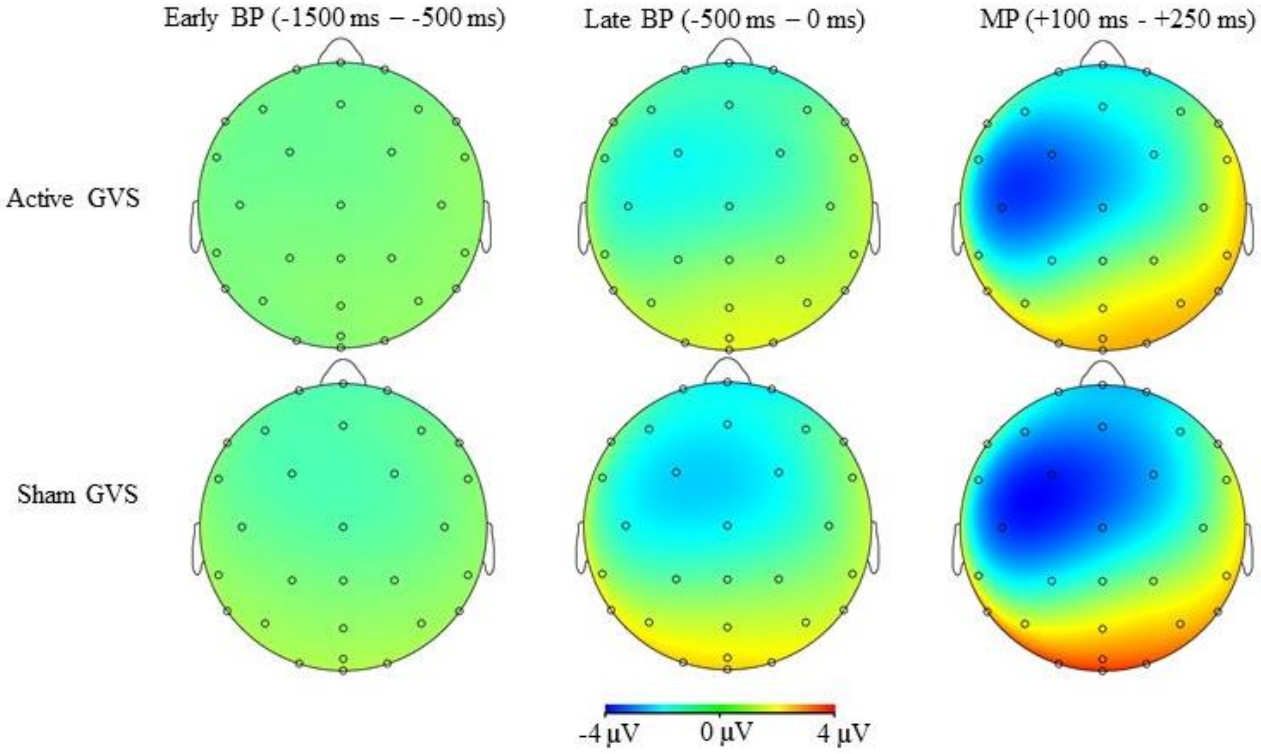


Figure 13. Topographical distribution of MRCPs obtained from finger movements in Study 2.

Study 2 Foot Movements Results

EMG Results

A paired-sampled t-test revealed no significantly different mean EMG amplitudes across the active (M = 52.94 μV, SD = 36.98) and sham (M = 52.27 μV, SD = 26.08) GVS conditions for foot movements (t (8) = -0.13, p = 0.90; d = -0.09).

ERP Results

Early BP. The ANOVA for the early BP yielded a significant main effect of Electrode Site (F = 4.65; p = 0.03; η_p^2 = 0.37), but no significant main effect of Stimulation (F = 1.31; p = 0.29; η_p^2 = 0.14) nor was there an interaction (F = 0.09; p = 0.92; η_p^2 = 0.01). (see Table 3 and Figures 14 and 15). Pairwise comparisons for the main effect of Electrode Site revealed no significant differences between amplitudes at C3, Cz and C4 following Bonferroni correction (C3 and Cz: t (8) = 2.09; p = 0.07; d = 1.48; C3 and C4: t (8) = -0.36; p = 0.73; d = 0.25; Cz and C4: t (8) = -2.98; p = 0.02; d = -2.11).

Late BP. The ANOVA for the late BP yielded a significant main effect of Electrode Site (F = 25.26; p = 0.00; η_p^2 = 0.76), but no significant main effect of Stimulation (F = 0.04; p = 0.85; η_p^2 = 0.01) nor was there an interaction (F = 0.25; p = 0.78; η_p^2 = 0.03). Pairwise comparisons revealed three significant results. Late BP mean amplitude was significantly greater at Cz (M = -4.96 μV, SD = 2.85) compared to at C3 (M = -0.17 μV, SD = 0.49) and C4 (M = -1.16 μV, SD = 0.74), (t (8) = 5.18, p = 0.00; d = 3.66 and t (8) = -4.99, p = 0.00; d = -3.53, respectively). Significant differences between C3 and C4 mean amplitudes were also found (t (8) = 3.39, p = 0.01; d = 2.40). These results showed that the late BP was maximal at Cz for foot movements and that an increase in mean amplitude was associated with the Electrode Site ipsilateral to foot movements on the right side (see Table 3 and Figures 14 and 15).

MP. The ANOVA for the MP yielded a significant main effect of Electrode Site ($F = 38.04$; $p = 0.00$; $\eta_p^2 = 0.83$), but no significant main effect of Stimulation ($F = 0.00$; $p = 0.98$; $\eta_p^2 = 0.00$) nor was there an interaction ($F = 0.63$; $p = 0.55$; $\eta_p^2 = 0.07$). Pairwise comparisons revealed three significant results. MP mean amplitude was significantly greater at Cz ($M = -11.90$ μV, $SD = 5.10$) compared to at C3 ($M = 0.24$ μV, $SD = 1.16$) and C4 ($M = -2.83$ μV, $SD = 1.56$), ($t\,(8) = 6.26$, $p = 0.00$; $d = 4.43$ and $t\,(8) = -6.64$, $p = 0.00$; $d = -4.70$, respectively). Significant differences between C3 and C4 mean amplitudes were also found ($t\,(8) = 3.79$, $p = 0.01$; $d = 2.68$). These results showed that the MP was maximal at Cz for foot movements and that an increase in mean amplitude was associated with the Electrode Site ipsilateral to foot movements on the right side (see Table 3 and Figures 14 and 15).

Table 3

Table of mean amplitude of MRCPs components obtained from foot movements in Study 2.

MRCP Component	Electrode Site	Stimulation Condition	Mean Amplitude μV (SD)
Early BP	C3	Active GVS	-0.21 (0.30)
		Sham GVS	-0.08 (0.28)
	Cz	Active GVS	-0.84 (0.93)
		Sham GVS	-0.72 (0.91)
	C4	Active GVS	-0.30 (0.39)
		Sham GVS	-0.11 (0.39)
Late BP	C3	Active GVS	-0.27 (0.52)
		Sham GVS	-0.07 (0.61)
*	Cz	Active GVS	-4.88 (3.19)
		Sham GVS	-5.04 (2.79)
*	C4	Active GVS	-1.21 (0.77)
		Sham GVS	-1.10 (0.92)
MP	C3	Active GVS	0.08 (1.06)
		Sham GVS	0.39 (1.34)
*	Cz	Active GVS	-11.64 (5.54)
		Sham GVS	-12.17 (5.04)
*	C4	Active GVS	-2.92 (1.78)
		Sham GVS	-2.73 (1.55)

Note: * indicates statistical significance at the $p < .01$ level.

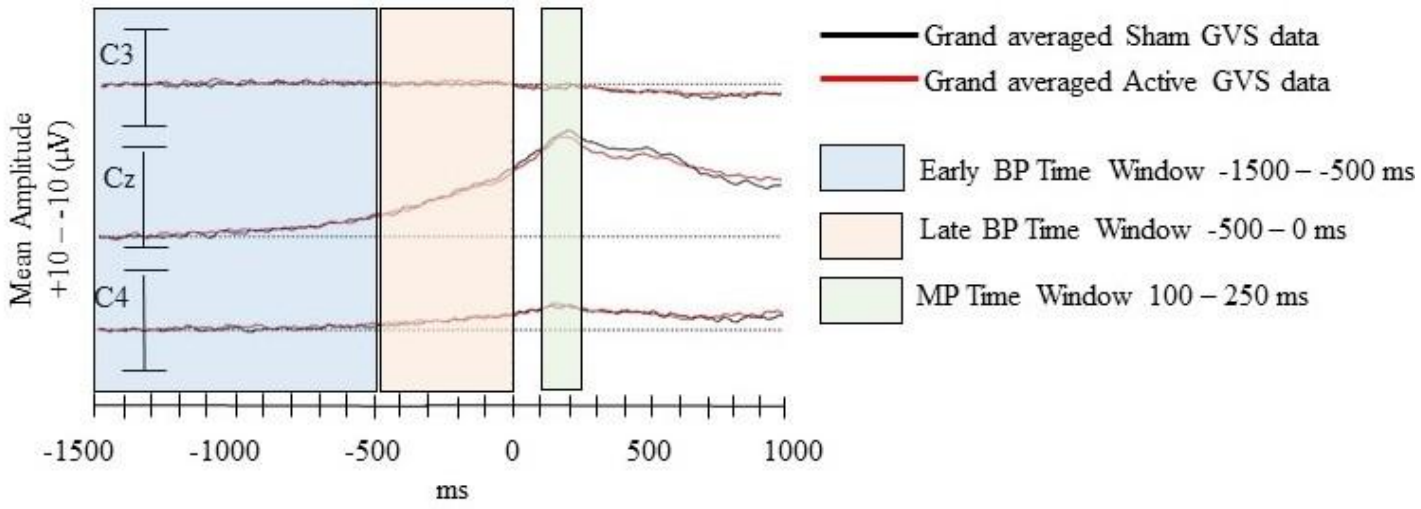


Figure 14. MRCP waveforms obtained from foot movements in Study 2.

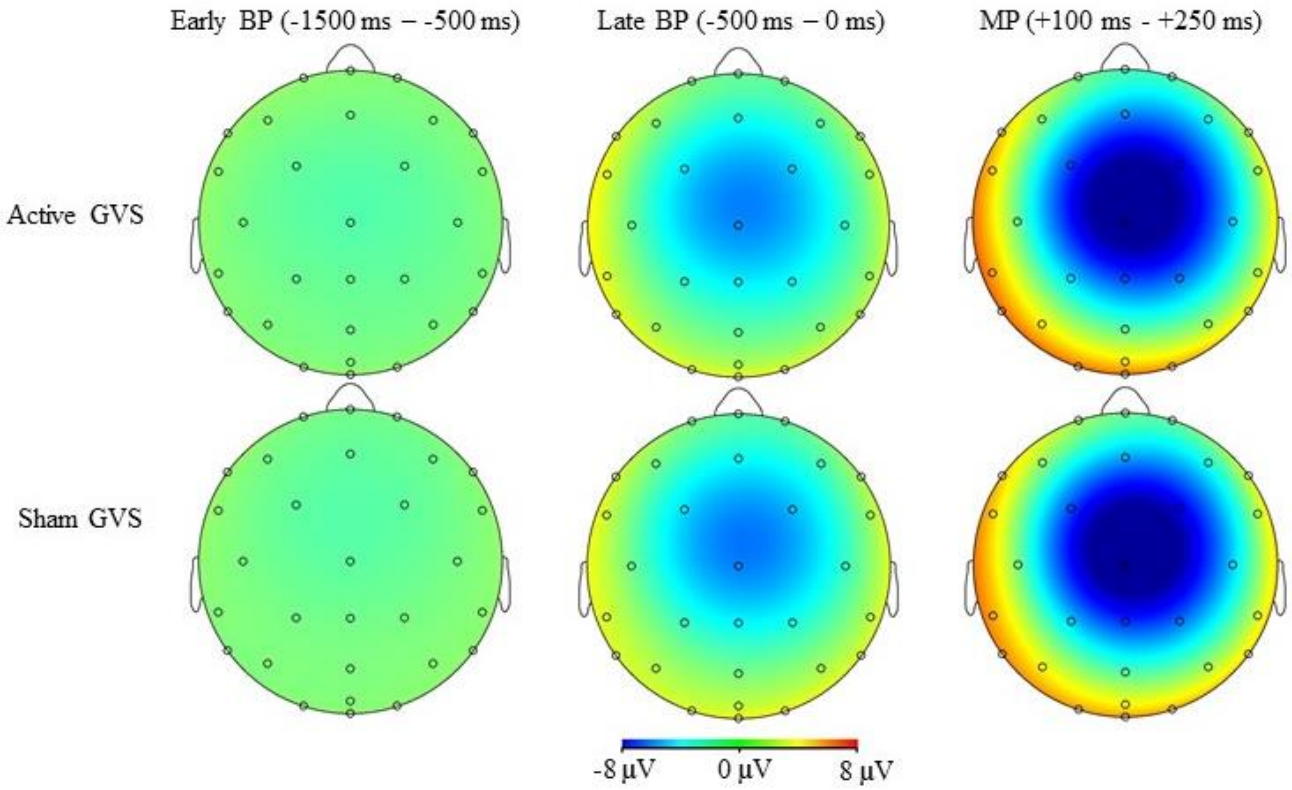


Figure 15. Topographical distribution of MRCPs obtained from foot movements in Study 2.

Study 2 Finger and Foot ERP Results

Early BP

The three-way ANOVA for the early BP yielded a significant main effect of Electrode Site ($F = 8.26$; $p = 0.00$; $\eta_p^2 = 0.51$) and of Limb ($F = 5.31$; $p = 0.05$; $\eta_p^2 = 0.51$), however, there was no main effect of Stimulation ($F = 0.00$; $p = 0.97$; $\eta_p^2 = 0.00$). There was no three-way interaction ($F = 0.86$; $p = 0.44$; $\eta_p^2 = 0.10$), nor were there any two-way interactions between Limb and Electrode Site ($F = 1.76$; $p = 0.20$; $\eta_p^2 = 0.18$), between Limb and Stimulation ($F = 3.59$; $p = 0.10$; $\eta_p^2 = 0.31$) or between Electrode Site and Stimulation ($F = 0.75$; $p = 0.49$; $\eta_p^2 = 0.09$).

Pairwise comparisons of the main effect of Electrode Site revealed a significant difference between early BP mean amplitude at Cz ($M = -0.51$ μV, $SD = 0.50$) and C4 ($M = -0.10$ μV, $SD = 0.22$), (t (8) = -3.33, $p = 0.01$; $d = -2.35$), but not C3 ($M = -0.12$ μV, $SD = 0.15$) and Cz (t (8) = 2.93, $p = 0.02$; $d = 2.07$), nor C3 and C4 (t (8) = -0.20, $p = 0.85$; $d = 0.14$). This showed that a greater mean amplitude of the early BP was found at the vertex (Cz) when combining finger and foot movements. The main effect of Limb showed a greater mean amplitude of the early BP in the foot ($M = -0.38$ μV, $SD = 0.38$) compared to the finger ($M = -0.11$ μV, $SD = 0.23$).

Late BP

The three-way ANOVA for the late BP found a significant interaction between Limb and Electrode Site ($F = 20.34$; $p = 0.00$; $\eta_p^2 = 0.72$), but not between Limb and Stimulation ($F = 0.76$; $p = 0.41$; $\eta_p^2 = 0.09$), nor between Electrode Site and Stimulation ($F = 1.01$; $p = 0.39$; $\eta_p^2 = 0.11$). A three-way interaction was also not found ($F = 0.02$; $p = 0.98$; $\eta_p^2 = 0.00$). There were also significant main effects of Limb ($F = 21.29$; $p = 0.00$; $\eta_p^2 = 0.73$) and Electrode Site ($F = 24.90$; $p = 0.00$; $\eta_p^2 = 0.76$), but not of Stimulation ($F = 0.24$; $p = 0.64$; $\eta_p^2 = 0.03$).

Pairwise comparison of the significant interaction between Limb and Electrode site, revealed that late BP mean amplitude was significantly larger at Cz during foot movements compared to finger movements (t (8) = 4.61, p = 0.00; d = 3.26). Pairwise comparisons of the main effect of Electrode Site revealed that the mean late BP amplitude at Cz (M = -2.99 μV, SD = 1.69) was significantly greater than at C3 (M = -0.55 μV, SD = 0.46) and C4 (M = -0.66 μV, SD = 0.63), (t (8) = 5.04, p = 0.00; d = 3.56 and t (8) = 0.74, p = 0.48; d = 0.52, respectively). No significant differences were found between C3 and C4 (t (8) = 0.74, p = 0.48; d = 0.52). These results showed that the late BP was maximal at the vertex (Cz) irrespective of the limb used. These results were consistent with the greatest late BP mean amplitude being associated with electrode Cz during foot movements (M = -4.96 μV, SE = 0.95). The main effect of Limb revealed a significant difference between finger (M = -0.70 μV, SD = 0.60) and foot (M = -2.10 μV, SD = 1.20) movements in terms of late BP mean amplitude. This indicated that foot movements were associated with a greater mean amplitude of the late BP compared to finger movements.

MP

The three-way ANOVA for the MP found a significant two-way interaction between Limb and Electrode Site (F = 36.73; p = 0.00; η_p^2 = 0.82), but not between Limb and Stimulation (F = 1.11; p = 0.32; η_p^2 = 0.12), nor between Electrode Site and Stimulation (F = 1.25; p = 0.31; η_p^2 = 0.14). There was also no significant three-way interaction between the variables (F = 0.21; p = 0.81; η_p^2 = 0.03). There were also significant main effects of Limb (F = 42.16; p = 0.00; η_p^2 = 0.84) and Electrode Site (F = 34.10; p = 0.00; η_p^2 = 0.81), but not of Stimulation (F = 0.65; p = 0.45; η_p^2 = 0.08).

The interaction between Limb and Electrode Site revealed a significant difference between finger (M = -1.87 μV, SD = 1.07) and foot (M = -4.83 μV, SD = 1.90) movements in terms of mean

MP amplitude. This indicated that foot movements were associated with a great mean MP amplitude compared to finger movements. Pairwise comparisons of the main effects of Electrode Site revealed that the mean MP amplitude at Cz (M = -7.09 μV, SD = 3.01) was significantly greater than at C3 (M = -1.51 μV, SD = 0.89) and C4 (M = -1.46 μV, SD = 1.19), (t (8) = 5.76, p = 0.00; d = 4.07 and t (8) = -6.78, p = 0.00; d = -4.79, respectively). No significant differences were found between C3 and C4 (t (8) = -0.09, p = 0.93; d = -0.06). These results showed that the MP was maximal at the vertex (Cz) irrespective of the limb used. This is consistent with the greatest mean MP amplitude being associated with electrode Cz during foot movements (M = -11.90 μV, SE = 1.70).

Study 2 Discussion

The first aim of Study 2 was to assess the feasibility of implementing a foot movement task into the experimental protocol developed and validated in Study 1. This was achieved by the successful acquisition of MRCPs from both finger and foot movements that were consistent with previous reports (Shibasaki et al., 1981). Related to this is the additional finding that the EEG processing pipeline was effective at removing the GVS-related artifact from both finger and foot data. The second aim was to evaluate the effectiveness of the EEG processing pipeline at removing the GVS-related artifact when using a stimulus current of a higher magnitude. Whilst this study demonstrated the successful removal of the GVS-related artifact associated with a higher GVS magnitude, the use of a higher intensity of GVS current was sensed by the majority of participants. This is problematic given the need to use a sub-sensory GVS stimulus to mitigate the influence of confounding factors within Study 3.

As in Study 1, the statistical and graphical results in Study 2 demonstrated the success of the methodological design and EEG processing pipeline in measuring MRCPs from both finger

and foot movements. This was also supported by the finding of no differences in the components on interest (early BP, late BP and MP) across stimulation conditions (sham compared to active GVS) for both finger and foot movements. This further validates the methodology because it demonstrates the potential for its multi-modal application. The mean amplitude data demonstrated that most of the components of interest were maximal at Cz for both finger and foot movements, which is consistent with the results from Study 1 and previous literature (Colebatch, 2007; Shibasaki et al., 1981). The only exception was the maximal MP at C3 for finger movements which was also larger than the MP at C3 for foot movements. Given that the only difference in logistical set-up between the finger and foot conditions was the placement of the EMG electrodes on the ED and TA muscles, respectively, this difference in cortical activation may be attributed to the recruitment of these different muscles. Indeed, previous literature has reported more lateral activations for finger compared to foot movements (Shibasaki, et al., 1981). The explanation for this may be the more lateralized representational area for the fingers compared to the feet, according to the somatotopic organization of the human sensorimotor cortex (Penfield & Boldrey, 1937). The potential reason this was observed during only Study 2 may be due to the enhanced magnitude of GVS (0.30-0.40 mA) that was applied in this study compared to Study 1.

The separate analyses for the finger and foot movements further highlighted their differences in terms of the late-phase movement preparation (late BP) and motor execution (MP). Although the late BP was maximal at Cz for both finger and foot movements, the mean amplitude data showed a bilateral inverse effect for the two limbs. For finger movements, the late BP was larger at C3 compared to C4, although this difference did not reach significant following corrections. By contrast, the late BP was significantly larger at C4 compared to C3 for foot movements. This inverse distribution was partially observed for the MP. For finger movements,

the MP was associated with a larger amplitude contralateral to the right-sided movement. For foot movements, although the MP was maximal at Cz, it was also a significantly larger at C4 compared to C3. The use of the right-sided limb may explain the greater contralateral activation at C3 for finger movements, but not the greater activation at C4 for foot movements. This may be better explained by the more medial location of the representational area of the foot within the motor cortex, which results in dipoles that orient to more central or ipsilateral areas of the scalp (Böcker et al., 1994). These findings corroborate the results of Brunia and van de Bosch (1984), which showed opposite lateralized distributions prior to and following finger and foot movements, irrespective of movement side. However, these findings did not persist when directly comparing the finger and foot movements in the three-way ANOVA. Rather, when combining the data from the finger and foot movements, the consistent finding was that the mean amplitude for all the MRCPs were greatest at Cz for foot movements. This finding corroborated previous reports of foot movements eliciting larger MRCPs (Colebatch, 2007).

The results of this study showed that there was no difference between active and sham GVS conditions in terms of mean MRCP amplitude. As in Study 1, this finding confirms the second aim of this study, which was to evaluate the effectiveness of the EEG processing pipeline in removing the GVS-related artifact produced by a GVS current of a larger magnitude (0.30-0.40 mA). However, 8 out of the 9 participants reported cutaneous sensations such as itching/prickling behind the ears during the active GVS conditions. This may not have directly affected the results of the current study given the consistency of effects across the sham and active GVS conditions. However, it is possible that this reflects the participant sample of young adults (age range = 18-20) as studies have shown that the threshold for sensory perception of transcutaneous electrical stimulation is significantly lower for younger compared to older adults (de Jesus Guirro et al., 2015).

Notwithstanding, the blinding of participants to stimulation conditions is imperative in the theoretical investigation of the clinical effects of a treatment (Davis, Gold, Pascual-Leone & Bracewell, 2013). Placebo-controlled experiments have been conventionally used to disentangle the specific effects of a treatment from nonspecific, incidental factors such as environment or participants' mental or physical state (Chambless & Hollon, 1998). Furthermore, it is important to note that the BP specifically has been shown to be affected by psychological factors such as intention to move, conscious pre-planning of movements as well as learning and skill acquisition (Lang, 2003). This rationale supported the decision to reduce the GVS current intensity in Study 3 given that the aim was to observe the direct effects of GVS on the brain activity of a clinical sample.

Study 2 confirmed the feasibility of implementing an additional task of foot tapping to the experimental protocol and successfully acquired MRCPs from both finger and foot movements. Moreover, even when applying a higher intensity GVS stimulus, the EEG processing pipeline was still effective at eliminating the GVS artifact, without compromising the acquisition of the MRCPs. Despite this, most participants correctly sensed when they were receiving active GVS. The findings from this study (and Study 1) informed the methodology applied in the main study of this thesis, with the aim of observing the direct effects of GVS on MRCPs in participants diagnosed with PD.

Study Three: The Effects of Vestibular Stimulation in Individuals with Parkinson's disease

This section outlines Study 3 that applied the novel methodology validated in the studies of the previous section to a clinical population of individuals diagnosed with PD. The aims of Study 3 were 1) to observe the direct effects of GVS on MRCPs in PD individuals and 2) to

evaluate the feasibility of applying the methodological design to a clinical sample. The first aim was related to the investigation of a potential underlying electrophysiological mechanism for the effects of vestibular stimulation on motor function in PD. Finding an electrophysiological mechanism could lead to further optimization of GVS protocols to improve the motor benefits already observed in PD (Khoshnam et al., 2018; Wilkinson et al., 2016; Wilkinson et al., 2019; Yamamoto et al., 2005). The methodology employed in Studies 1 and 2 informed the methods in Study 3 with modifications to accommodate for the needs of the clinical sample. These include delivering a reduced intensity of GVS (0.25-0.35 mA); dividing the experimental session into two sessions instead of one and the inclusion of a clinical assessment session.

The GVS intensity of 0.25-0.35 mA was selected because it was between the intensities used in Studies 1 (0.20-0.30 mA) and 2 (0.30-0.40 mA). Reducing the GVS magnitude applied from Study 2 ensured that the stimulation remained imperceptible to facilitate the blinding of PD participants to the GVS condition. However, increasing the intensity from that used in Study 1 was based on the rationale of strengthening any clinical effects the GVS may have on MRCPs. Also, of note is that older PD individuals may have higher sensory thresholds for detecting transcutaneous stimulation compared to a younger student sample (de Jesus Guirro et al., 2015). The GVS frequency applied in this study remained the same as in Studies 1 and 2 (0.01 Hz).

The decision to divide the study into two experimental sessions was made to 1) mitigate the potential risk of the effect of fatigue (either supra-spinal or peripheral), particularly for elderly participants (Gandevia, 2001); 2) to ensure that the PD medication remained efficacious throughout the experiment. Having two sessions meant that each experimental session was shorter in duration (two hours each) instead of the three-hour session required for Study 2. This ensured that the time of day that the sessions were conducted always coincided with participants' ON

period of medication and meant that the neural activity recorded accurately reflected participants' performance of the task during stable medication. Many individuals with PD experience motor and non-motor fluctuations in their symptoms throughout the day that correlate with their medication 'kicking in' or 'wearing off' (Schrag & Quinn, 2000; Jankovic, 2005). Although the duration of these periods can vary across individuals, most individuals report an ON period of two hours after taking medication (Hardie, Lees & Stern, 1984). A potential consequence of dividing the study into two experimental sessions was the potential after-effects of GVS on the second session. Indeed, a previous experiment conducted by our research group on the effects of GVS on motor cortical excitability revealed a reduction in TMS-elicited motor-evoked potentials (MEPs) 24 hours following GVS. To prevent any confounding effects related to this 24-hour reduction in cortical excitability, participants were asked to return for their final experimental session 48 hours after the first session. Finally, the inclusion of a clinical assessment session prior to the experimental sessions enabled the characterization of the clinical sample. This was done by administering a test battery of gold-standard, neuropsychological assessments to all participants.

The original aim for this study was to collect data from both a PD (n = 20) and control (n = 20) group of elderly, age-matched individuals. However, due to the COVID-19 pandemic, data collection was halted in March 2020 in response to the nationwide lockdown. For this reason, Study 3 was based solely on the data collected from the 10 PD subjects who had participated up until the beginning of the lockdown period.

Methods

Participants

Ten volunteers (six males, M_{age} = 62, age range = 53-76 years) diagnosed with PD were recruited either from community-based local organizations around the South East of the UK (e.g.,

Parkinson's UK) or from a database of former participants who consented to being contacted again. All PD participants fulfilled the eligibility criteria with none having co-morbid neurological conditions, scars or skin abrasions behind the ears, implanted electronic devices (e.g., DBS, pacemakers, etc.) or in receipt of dopamine or apormorphine infusion therapy. All PD participants provided documentary evidence of their diagnosis of idiopathic PD according to the UK PD society brain bank clinical diagnostic criteria, in the form of a letter from their neurologist confirming their diagnosis. Moreover, PD participants remained on their stable anti-parkinsonian medication regime for the duration of the study. Examples of anti-parkinsonian medication taken by participants include rasagiline, co-careldopa, ropinirole, sinemet and madopar. The PD sample showed a high variability in the years since PD onset (range = 1-11 years) and also in the severity of their motor symptoms (scores ranging between 16 and 49) as measured by the MDS-UPDRS Part III (see Table 4).

Table 4

Table showing clinical characteristics of PD participants in Study 3.

Participant	Years since diagnosis	MDS-UPDRS Part III	MDS-UPDRS Total	Hoehn & Yahr	MoCA	MiniBest
1	4	49	84	2	27	21
2	4	36	64	2	28	20
3	4	37	82	3	19	23
4	8	45	92	2	27	23
5	2	29	57	2	28	26
6	6	27	57	2	28	22
7	5	25	35	1	29	27
8	11	30	63	2	25	25
9	1	16	36	1	26	27
10	7	47	77	2	24	24

Materials

All materials relating to vestibular stimulation and EEG used in the main study were identical to those used in Studies 1 and 2 with only two alterations. First, the current intensity for the GVS stimulus was established as oscillating between 0.25-0.35 mA. This intensity was selected to strike a balance between delivering an intensity that was sufficient to produce large physiological effects without being too high that it would jeopardise the blinding of participants to stimulation conditions, as in Study 2. Second, the addition of a test battery of neuropsychological assessments enabled the clinical characterization of each PD participant's disease state. Experimenters gained certification for MDS-UPDRS and MoCA administration in order to carry out these assessments.

The MDS-Sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS). This scale (Goetz et al., 2008) was administered to the PD volunteers to characterize their parkinsonian

symptoms. The MDS-UPDRS has four parts and all items within these are rated on a five-point scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 = severe). Parts I and II measure non-motor and motor experiences of daily living, respectively. Part IA was administered by the experimenter in an interview format whilst Part IB and II were self-administered by the participants with or without the assistance of a spouse. For all interview and questionnaire formats of the scale, emphasis was placed on responses reflecting a global or average evaluation of the previous week. Part IA included questions about cognitive impairment, hallucinations, apathy, anxiety and depression delivered in an interview format by the experimenter. Part IB, the patient questionnaire, included questions about sleep problems, constipation, fatigue, urinary problems and others.

Part III consists of a motor examination in which participants performed a series of tasks used to assess movement, rigidity, postural stability, gait and tremor. Experimenters rated performance on these tasks based on observations during that session only (see Appendix B for example items 3.4 and 3.7 from Part III). Part IV assessed motor complications, dyskinesias and motor fluctuations associated with the OFF-state and was rated by the experimenter in an interview format. Example items included questions about time spent in the OFF state, the functional impact and complexity of fluctuations.

The Montreal Cognitive Assessment (MoCA). The MoCA (Nasreddine et al., 2005) was administered to measure mild cognitive dysfunction (see Appendix C). A total score was generated by summing subscores from the different domains and adding one point for individuals who have had 12 years or fewer years of formal education. 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. This assessment was employed as an outcome measure in Wilkinson et al.'s (2019) study to observe the effects of CVS on cognitive function.

The Mini-Balance Evaluation Systems Test (Mini-BESTest). The Mini-BESTest is a 14-item shortened version of the BESTest (Horak, Wirsley & Frank, 2009) designed to assess balance control systems for targeted rehabilitation purposes of different balance disorders (Franchignoni et al., 2010). It was used to assess five different balance domains (vestibular and non-vestibular balance, functional mobility, gait and vestibular function) in both the PD and the control group. The 14 items address four of the original six sections of the BESTest (anticipatory postural adjustments, reactive postural control, sensory orientation, dynamic gait) using a 2-level ordinal scale (2 = normal, 1 = moderate, 0 = severe) (see Appendix D for example items). The total score is 28 points and greater scores indicated normal balance functions. This assessment was selected for use in this study because of its suitability in assessing balance characteristics of PD (King et al., 2012).

Procedure

This study was conducted over three sessions on three separate days to mitigate the potential risk of the effect of fatigue (supra-spinal and peripheral) (Gandevia, 2001) and to ensure PD medication remained efficacious throughout testing. Each session was conducted 30 minutes to an hour following medication intake and lasted approximately two hours. This ensured that participants were assessed when their medication was in the same state of effectiveness each time and their motor symptoms were stable each time.

The clinical assessment session consisted of administration of the neuropsychological test battery outlined above and always preceded the experimental sessions. During this session, participants were introduced to the study and provided their informed consent. Demographic information such as age, occupational, marital and educational status was obtained as well as a list of parkinsonian and non-parkinsonian medication. Part IA of the MDS-UPDRS was then

administered by the experimenter followed by Parts IB and II which participants completed on their own or with a spouse/partner. Part III or the motor examination of the MDS-UPDRS was then administered by the experimenters followed by the MoCA and the Mini-BESTest. Participants were then instructed to avoid the consumption of caffeinated or alcoholic beverages at least 24 hours prior to the experimental sessions and avoid the use of hair products that may increase EEG impedances.

The two experimental sessions were separated by a period of 48 hours. The experimental part of this study was conducted over two sessions using a randomized and counterbalanced design (see Table 5). Participants were randomly assigned to conditions in which the order of movement task (finger or foot) and stimulation condition (active or sham GVS) was counterbalanced. 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. 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 worst side. The procedure within the movement blocks was identical to that conducted in Study 2.

Table 5

Table showing an example of the randomized and counterbalanced experimental sessions for four participants in Study 3.

	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

Data Offline Processing and Analysis

The offline processing strategy employed in this study was identical to that used in Studies 1 and 2 (see pages 48-51). Segmentation into epochs was conducted using the same method for EMG onset determination employed in Studies 1 and 2, with epochs of the same length. On average for finger movements, fewer than 2% (n = 25) of trials across both active and sham GVS conditions were excluded because EMG onset could not be accurately determined. Thus, for finger movements the grand averages for both stimulation conditions were calculated using over 98% (n = 2647) of trials following baseline correction to the first 200 ms (-1500 to -1300 ms) of the epoch. Approximately 2.5% (n = 39) of foot movement trials across both stimulation conditions were excluded due to inaccurate EMG onset determination, which meant that over 97% (n = 2925) of foot movement trials were used to calculate the grand average amplitudes for the foot active and sham GVS conditions. The mean EMG amplitudes of finger and foot movements were determined by employing the rectified EMG amplitude. A paired sample t-test was conducted to compare the rectified EMG amplitude across active and sham GVS conditions for each of the types of movements (finger and foot separately). A p value of $< .05$ was considered statistically significant for this analysis and Cohen's d was also used to determine effect sizes (Cohen, 2013).

The method for defining MRCP waveforms was the same as that employed in the previous studies (see pages 48-51). The same procedure for statistical analysis as in Study 2 was followed in this study (see pages 64-65).

Study 3 Finger Movement Results

In this study, none of the participants reported itching/prickling sensations on the Perception of Stimulation Questionnaire during the active GVS conditions.

Independent Components Identification

As demonstrated in Figure 16, the GVS-related IC labels showed a similar topographical distribution across finger and foot movements.

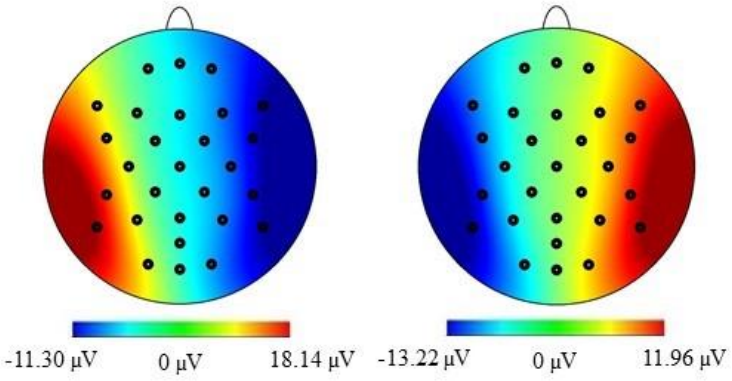


Figure 16. Two examples of the GVS-related components returned by ICA associated with the individual finger (left) and foot (right) movement data in Study 3.

EMG Results

A paired-sample t-test comparing the mean EMG amplitudes of the active (M = 35.25 µV, SD = 22.19) and sham (M = 37.33 µV, SD = 20.61) GVS conditions revealed no significant differences (t (8) = 0.64, p = 0.54; d = 0.45) for finger movements.

ERP Results

Early BP. The ANOVA for the early BP yielded no significant main effects of Stimulation (F = 1.76; p = 0.22; η_p^2 = .18) or Electrode Site (F = 0.37; p = 0.70; η_p^2 = 0.04). There was also no significant interaction between Stimulation and Electrode Site (F = 2.52; p = 0.11; η_p^2 = .24).

Late BP. The ANOVA for the late BP yielded a main effect of electrode (F = 5.94; p = 0.01; η_p^2 = 0.43), but not Stimulation (F = 0.70; p = 0.43; η_p^2 = 0.08), nor was there a significant interaction (F = 1.55; p = 0.24; η_p^2 = 0.16). Pairwise comparisons of the main effect of electrode revealed no significant differences between electrode mean amplitudes following Bonferroni correction (C3 and Cz: t (8) = 2.28; p = 0.05; d = 1.61; C3 and C4: t (8) = -1.65; p = 0.14; d = -1.17; Cz and C4: t (8) = -2.76; p = 0.03; d = -1.95).

MP. The ANOVA for the MP yielded a main effect of electrode ($F = 9.33$; $p = 0.00$; $\eta_p^2 = 0.54$), but not Stimulation ($F = 0.71$; $p = 0.42$; $\eta_p^2 = 0.08$), nor was there a significant interaction between Stimulation and Electrode Site ($F = 2.59$; $p = 0.11$; $\eta_p^2 = 0.25$). Pairwise comparisons of the main effect of electrode revealed that there was a significantly greater amplitude at Cz ($M = -3.54$ μV, $SD = 2.15$) compared to C4 ($M = -1.12$ μV, $SD = 0.99$), ($t(8) = -3.75$, $p = 0.00$; $d = -2.65$). There were no significant differences between MP mean amplitude at C3 ($M = -1.98$ μV, $SD = 1.33$) compared to Cz or C4 ($t(8) = 2.58$, $p = 0.03$; $d = 1.82$ and $t(8) = -1.99$, $p = 0.08$; $d = -1.41$, respectively).

Table 6

Table of mean amplitude of MRCPs components obtained from finger movements in Study 3.

MRCP Component	Electrode Site	Stimulation Condition	Mean Amplitude μV (SD)
Early BP	C3	Active GVS	-0.04 (0.57)
		Sham GVS	0.20 (0.45)
	Cz	Active GVS	-0.19 (0.81)
		Sham GVS	0.15 (0.82)
	C4	Active GVS	0.12 (0.39)
		Sham GVS	0.06 (0.39)
Late BP	C3	Active GVS	-0.80 (1.06)
		Sham GVS	-0.40 (0.80)
	Cz	Active GVS	-1.53 (1.64)
		Sham GVS	-1.04 (1.48)
	C4	Active GVS	-0.14 (0.93)
		Sham GVS	-0.25 (0.57)
MP	C3	Active GVS	-2.21 (1.70)
		Sham GVS	-1.74 (1.29)
	Cz	Active GVS	-3.86 (2.20)
		Sham GVS	-3.22 (2.26)
*	C4	Active GVS	-0.93 (1.33)
		Sham GVS	-1.31 (0.82)

Note: * indicates statistical significance at the $p < .01$ level.

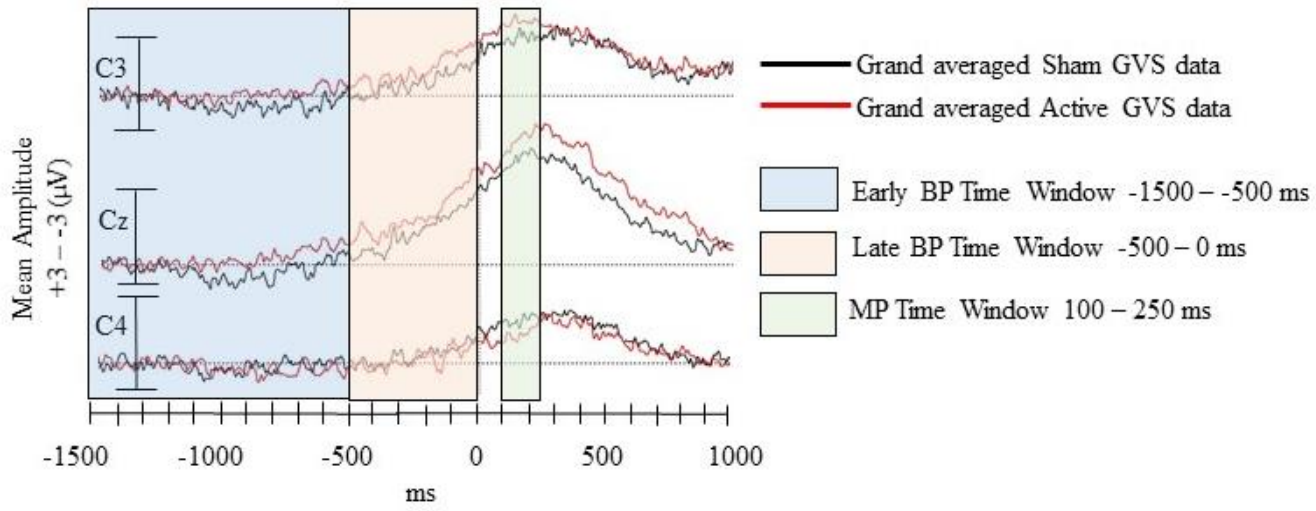


Figure 17. MRCP waveforms obtained from finger movements in Study 3.

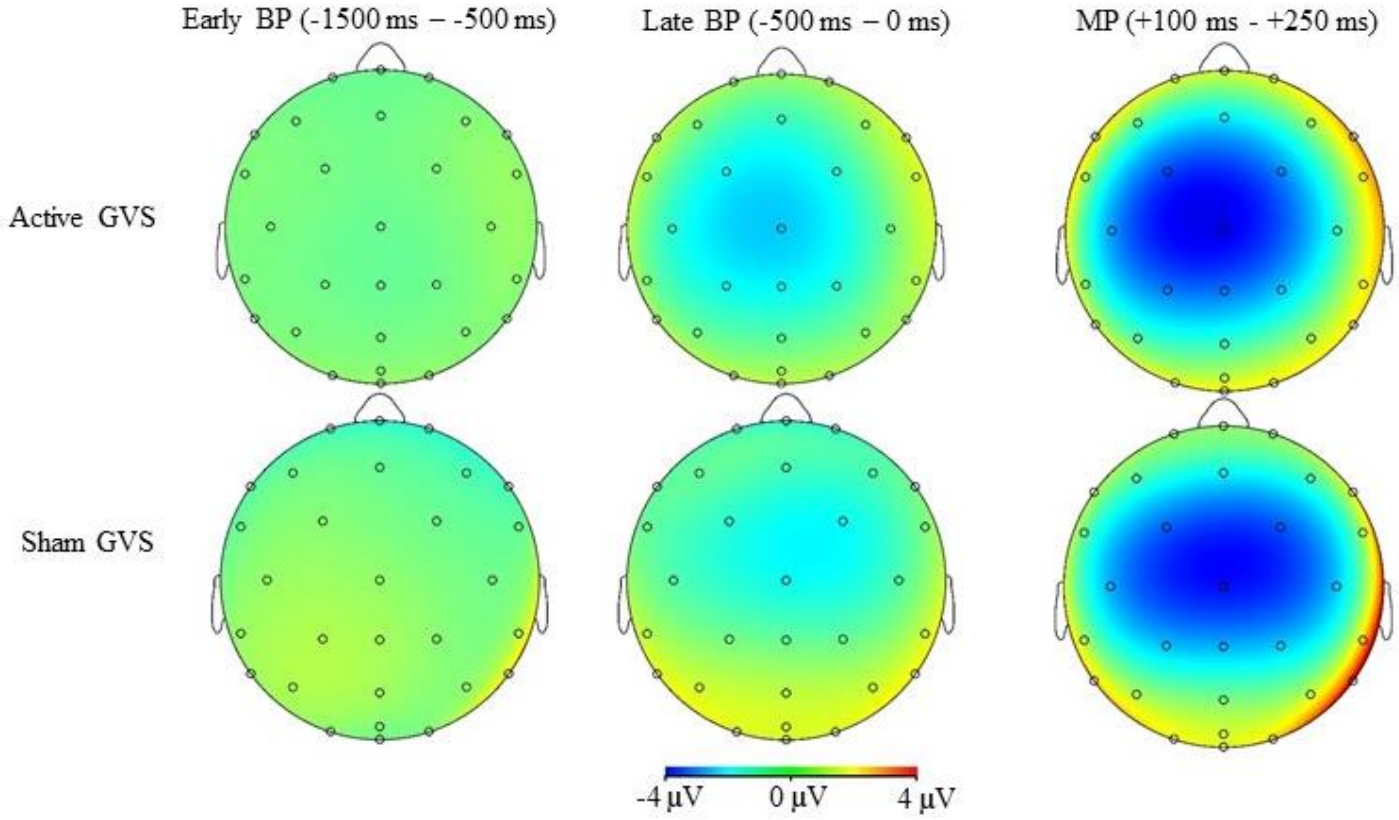


Figure 18. Topographical distribution of MRCPs obtained from finger movements in Study 3.

Study 3 Foot Movement Results

EMG Results

A paired-sample t-test comparing the mean EMG amplitudes of the active (M = 50.91 μV, SD = 15.35) and sham (M = 49.64 μV, SD = 15.35) GVS conditions revealed no significant differences (t (9) = -0.29, p = 0.78; d = -0.19) for foot movements.

ERP Results

Early BP. The ANOVA for the early BP yielded no significant main effects of Stimulation (F = 0.05; p = 0.82; η_p^2 = .01) or Electrode Site (F = 0.26; p = 0.77; η_p^2 = 0.03). There was also no significant interaction between Stimulation and Electrode Site (F = 0.12; p = 0.89; η_p^2 = .01).

Late BP. The ANOVA for the late BP revealed a significant main effect of electrode (F = 4.57; p = 0.03; η_p^2 = 0.34), but not Stimulation (F = 0.00; p = 0.97; η_p^2 = 0.00) or interaction between Stimulation and Electrode Site (F = 0.14; p = 0.87; η_p^2 = 0.02) (see Table 7 and Figures 19 and 20). To further unpack the main effect of electrode pairwise comparisons were conducted, however, following Bonferroni correction, no significant differences were found between the mean amplitudes at the three electrode sites (C3 and Cz: t (9) = 2.52; p = 0.03; d = 1.68; C3 and C4: t (9) = -0.30; p = 0.77; d = -0.2; Cz and C4: t (9) = -2.37; p = 0.04; d = -1.58).

MP. The ANOVA yielded a significant main effect of electrode (F = 14.78; p = 0.00; η_p^2 = 0.62), but not Stimulation (F = 2.25; p = 0.17; η_p^2 = 0.20) or interaction (F = 0.82; p = 0.46; η_p^2 = 0.08) (see Table 7 and Figures 19 and 20). Pairwise comparisons of the mean effect of Electrode Site showed that the amplitude of the MP was significantly greater than at Cz (M = -4.00 μV, SD = 3.04) compared to C3 (M = -1.20 μV, SD = 1.94) and C4 (M = -0.47 μV, SD = 0.86), (t (9) = 4.86, p = .00; d = 3.24 and t (9) = -4.10, p = 0.00; d = -2.73, respectively). No significant difference between C3 and C4 were found (t (9) = -1.27, p = 0.24; d = -0.85).

Table 7

Table of mean amplitude of MRCPs components obtained from foot movements in Study 3.

MRCP Component	Electrode Site	Stimulation Condition	Mean Amplitude μV (SD)
Early BP	C3	Active GVS	0.11 (0.47)
		Sham GVS	0.12 (0.43)
	Cz	Active GVS	0.17 (1.07)
		Sham GVS	0.24 (0.93)
	C4	Active GVS	0.07 (0.55)
		Sham GVS	0.06 (0.55)
Late BP	C3	Active GVS	-0.23 (1.05)
		Sham GVS	-0.19 (1.20)
	Cz	Active GVS	-1.23 (2.00)
		Sham GVS	-1.19 (1.89)
	C4	Active GVS	-0.05 (0.84)
		Sham GVS	-0.16 (1.07)
MP	C3	Active GVS	-1.11 (2.04)
		Sham GVS	-1.29 (1.94)
*	Cz	Active GVS	-3.74 (3.15)
		Sham GVS	-4.25 (2.97)
*	C4	Active GVS	-0.40 (0.95)
		Sham GVS	-0.53 (0.98)

Note: * indicates statistical significance at the $p < .01$ level.

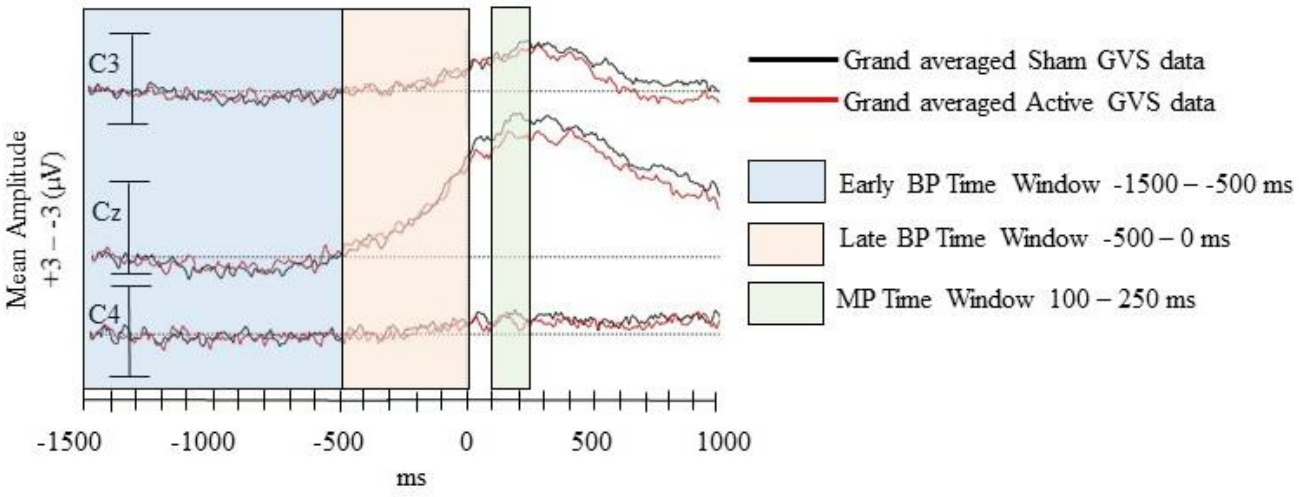


Figure 19. MRCP waveforms obtained from foot movements in Study 3.

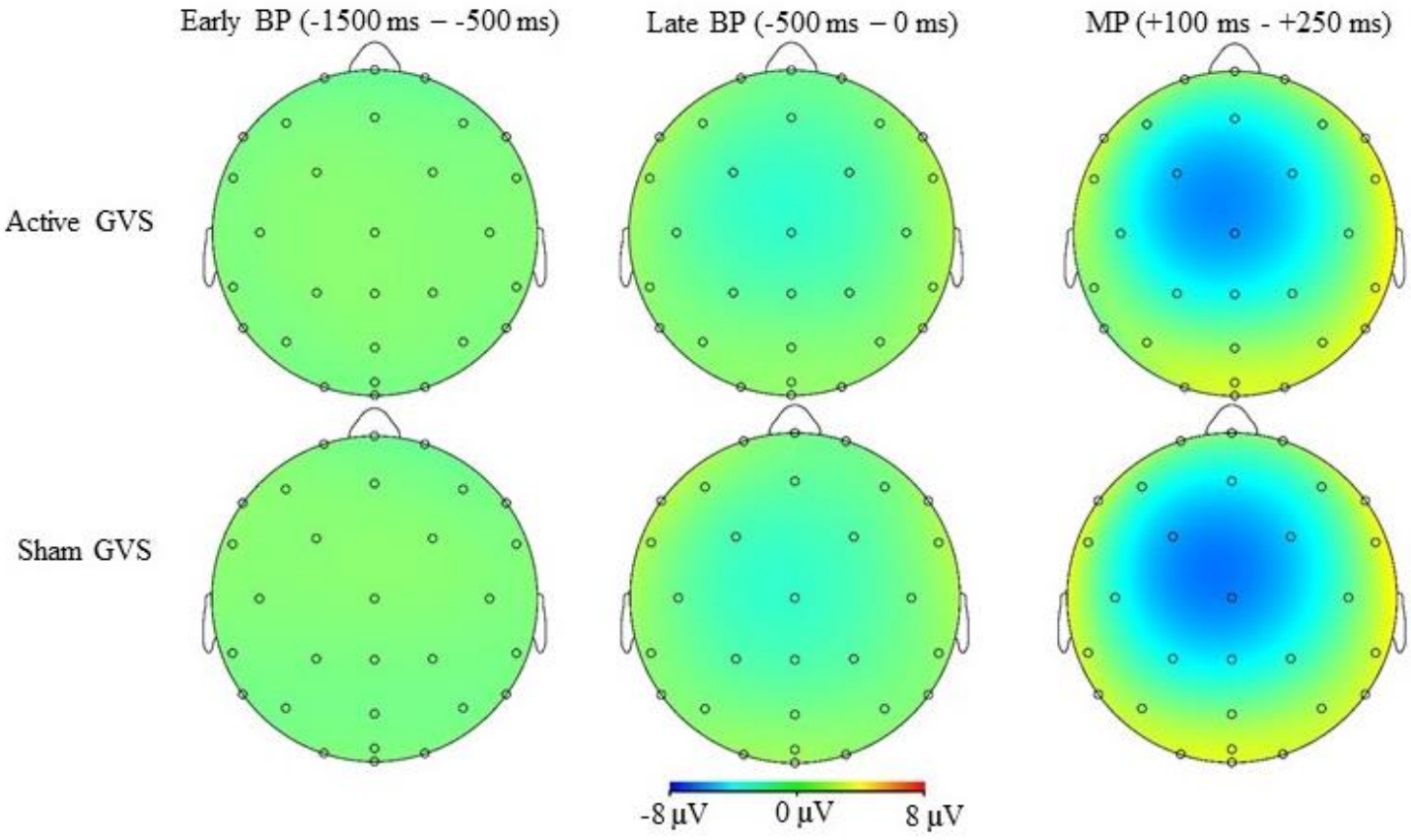


Figure 20. Topographical distribution of MRCPs obtained from foot movements in Study 3.

Study 3 Finger and Foot ERP Results

Early BP

The three-way ANOVA for the early BP yielded a significant main effect of Stimulation (F = 5.11; p = 0.05; η_p^2 = 0.39), but not of Electrode (F = 0.03; p = 0.97; η_p^2 = 0.00) or Limb (F = 0.29; p = 0.60; η_p^2 = 0.04). There was also no significant three-way interaction (F = 0.91; p = 0.42; η_p^2 = 0.10), nor were there any two-way interactions between Limb and Electrode Site (F = 1.06; p = 0.37; η_p^2 = 0.12), Limb and Stimulation (F = 0.29; p = 0.61; η_p^2 = 0.04) or between Electrode Site and Stimulation (F = 1.74; p = 0.21; η_p^2 = 0.18).

The main effect of Stimulation revealed a significant difference between early BP mean amplitude during the active GVS (M = 0.00 μV, SD = 0.70) and the sham GVS (M = 0.24 μV, SD = 0.82) conditions. This result showed a significant increase in negativity associated with the active GVS condition compared to the sham of a magnitude of 0.24 μV.

Late BP

The three-way ANOVA for the late BP found a significant main effect of Electrode Site (F = 6.11; p = 0.01; η_p^2 = 0.43) but not of Stimulation (F = 1.26; p = 0.29; η_p^2 = 0.14) or Limb (F = 0.34; p = 0.57; η_p^2 = 0.04). There was no significant three-way interaction (F = 0.58; p = 0.57; η_p^2 = 0.07), nor were there any two-way interactions between Limb and Electrode Site (F = 0.20; p = 0.82; η_p^2 = 0.02), Limb and Stimulation (F = 0.21; p = 0.66; η_p^2 = 0.03), or between Electrode Site and Stimulation (F = 1.25; p = 0.31; η_p^2 = 0.14).

Pairwise comparisons of the main effect of electrode site revealed no significant differences between electrodes following Bonferroni correction (C3 and Cz: t (8) = 2.70; p = 0.13; d = 1.91; C3 and C4: t (8) = -1.07; p = 0.32; d = -0.76; Cz and C4: t (8) = -2.78; p = 0.20; d = -1.97).

MP

The three-way ANOVA for the MP yielded a two-way interaction between Limb and Electrode Site that trended towards significance ($F = 3.08$; $p = 0.07$; $\eta_p^2 = 0.28$). There were no other significant two-way interactions between Limb and Stimulation ($F = 1.98$; $p = 0.20$; $\eta_p^2 = 0.20$) or Electrode Site and Stimulation ($F = 0.80$; $p = 0.47$; $\eta_p^2 = 0.09$). Nor was there a three-way interaction between all variables ($F = 1.10$; $p = 0.15$; $\eta_p^2 = 0.07$). A significant main effect of Electrode Site was also found ($F = 18.79$; $p = 0.00$; $\eta_p^2 = 0.70$), but not of Stimulation ($F = 0.00$; $p = 0.96$; $\eta_p^2 = 0.00$) or Limb ($F = 0.05$; $p = 0.83$; $\eta_p^2 = 0.01$).

The main interaction between Limb and Electrode Site revealed no significant difference between finger ($M = -2.21$ μV, $SD = 1.22$) and foot ($M = -2.13$ μV, $SD = 1.66$) movements in terms of the mean MP amplitude. Pairwise comparisons of the main effect of Electrode Site revealed that the mean MP amplitude at Cz ($M = -3.99$ μV, $SD = 2.22$) was significantly greater than at C3 ($M = -1.70$ μV, $SD = 1.50$) and C4 $M = -0.82$ μV, $SD = 0.84$), ($t(8) = 4.71$, $p = 0.00$; $d = 3.33$ and $t(8) = -4.89$, $p = 0.00$; $d = -3.46$, respectively). These results showed that whilst Cz was associated with a maximal mean amplitude of the MP, this did not differ significantly between finger ($M = -3.54$ μV, $SE = 0.72$) and foot ($M = -4.45$ μV, $SE = 0.95$) movements for PD participants.

Study 3 Discussion

The core aim of Study 3 was to observe the effects of GVS on MRCPs obtained from a PD population. Due to limitations relating to a small sample size, the results obtained in this study may be underpowered. The findings revealed a small increase in the negativity of the early BP at Cz associated with the active GVS condition compared to the sham, but only when the finger and foot movement data were combined. This suggests that given a larger sample size to increase power, vestibular stimulation may have an enhancing effect on the motor preparatory activity of individuals with PD. A secondary aim of this study was to evaluate the applicability of the novel

concurrent GVS-EEG methodology and processing pipeline to a clinical sample. The consistency of the MRCPs obtained in this study with those acquired in Study 1 and 2 validates the applicability of the methodology and processing pipeline to a PD population.

The results of the three-way ANOVA revealed that the active GVS condition was associated with a significant increase in the early BP at Cz compared to the sham GVS condition. This finding may begin to explain the improvements in the MDS-UPDRS scores observed previously following vestibular stimulation in PD (Wilkinson et al., 2016; Wilkinson et al., 2019). Previous studies have reported the early BP as reduced in PD whilst other components (late BP, MP) remained largely unaffected, suggesting a deficit in motor preparatory activity. Indeed, the early BP is associated with facilitation of motor pathways in 'readiness' for an upcoming movement, which is consistent with the movement initiation difficulties experienced by PD individuals (Colebatch, 2007; Shibasaki & Hallett, 2006; Verleger, 2012). Whereas the late BP and MP are related to SMA and M1 interaction in selection of appropriate muscles and recruitment of these during movement, respectively (Neshige et al., 1988; Deecke et al., 1980). The findings from this study combined with previous literature suggest that vestibular stimulation may boost deficient early-phase preparatory activity in PD. However, it is still unclear whether this enhancement of preparatory activity by GVS leads to improvements in motor function at a behavioural level, such as improvements of gait disturbances or motor blocks during upper limb movement as has been observed previously (Khoshnam et al., 2018). The current study found no differences in muscle activation (EMG) between the active and sham GVS conditions. It is likely that the limited duration of the stimulation period in this study may not have been sufficient to produce observable, behavioural effects. Previous studies showing the clinical effects of vestibular stimulation have usually employed multiple, repeated sessions (Wilkinson et al., 2014; Wilkinson et al., 2016;

Wilkinson et al., 2019). Furthermore, absence of a behavioural effect may in part be due to the study being underpowered due to a small sample size.

It is likely to that the findings of the current study were influenced by limitations relating to low power due to a small sample size. No significant differences between the active and sham GVS conditions were observed when the finger and foot movement data were analysed independently. These analyses due to the small sample size may have lacked the power with which to detect a meaningful difference. Indeed, a significant main effect of condition only emerged when the number of data points were increased in the omnibus three-way analysis of the combined finger and foot data. The original aim for this study was to collect data from both a PD (n = 20) and control (n = 20) group of elderly, age-matched individuals and this was consistent with the power calculation of a minimum sample size of 12 per group. Thus, increasing the power of the study by having a larger sample size may prove promising in terms of unveiling significant differences between active and sham GVS that are truly present but were not sufficiently demonstrated in the current study. A second limitation was the lack of a matched, neurologically healthy control group to compare to the PD sample. Recruitment of a control group was halted due to the nationwide lockdown in response to the COVID-19 pandemic. Therefore, there was no clear baseline from which to determine that the early BP in PD was in fact deficient. Although, previous studies investigating the BP in PD have all demonstrated that it was diminished in relation to the BP of a normal, healthy control group (Cunnington et al., 1999; Dick et al., 1989; Jahanshahi et al., 1995). Thus, it is unclear whether this increase in the early BP associated with the active GVS reflects a boosting of the deficient early preparatory activity in PD to 'normal' levels or if GVS affects the early BP in similar ways in PD and neurologically healthy individuals.

Study 3 supported the successful application of the concurrent GVS-EEG methodology and processing pipeline used to remove the GVS-related artifact to a clinical population. This was achieved by the successful acquisition of MRCPs that are consistent with previous literature and parallel the results from Studies 1 and 2. The descriptive and graphical results demonstrated the BP and MP to be maximal at Cz as reported previously in the literature (Shibasaki & Hallett, 2006; Colebatch, 2007). Additionally, the post-hoc comparisons revealed a significantly larger amplitude of the MP associated with Cz compared to C3 and C4, which is consistent with the MP results of Studies 1 and 2. The results for the late BP followed the same trend of maximal amplitude at Cz with main effects of electrode in the two-way ANOVAs despite not reaching significance after correction in the post-hoc comparisons. These findings further validate the effectiveness of the processing pipeline in removal of the GVS-related artifact without compromising the components of interest. Moreover, this study extends the applicability of this novel methodology to EEG data acquired from individuals with neurological conditions.

Study 3 aimed to observe the direct effects of GVS on MRCPs obtained from a PD population. The findings revealed an enhancing effect on early pre-movement preparatory activity associated with active GVS when combining data from finger and foot movements. It remains to be investigated whether this effect would persist in the individual analysis of finger and foot data from a larger sample. Nevertheless, this study provides the first step to understanding the effect of vestibular stimulation on functionally relevant electrophysiological markers in PD. Finally, this study also provided further validation for the novel methodology enabling the successful acquisition of MRCPs using concurrent GVS-EEG in a PD population. This suggests the applications of this novel methodology can be extended to other clinical populations to investigate the underlying electrophysiological mechanisms of vestibular stimulation.

General Discussion

The overall aim of this thesis was to develop and evaluate a novel methodology in the investigation of the direct effects of GVS on the electrophysiological activity associated with movement in PD and neurologically healthy individuals. Studies 1 and 2 provided validation for this novel methodology by demonstrating its effectiveness in removing the GVS-related artifact and successfully obtaining MRCPs. Specifically, Study 1 demonstrated the successful retrieval of MRCPs from finger movements performed by neurologically healthy young adults following the successful removal of the GVS-related artifact. Study 2 further validated the methodology by demonstrating the extension of its applicability to foot movements and to higher GVS intensities. Study 3 demonstrated that GVS demonstrated a small therapeutic effect on the preparatory cortical activity preceding movement in PD which may potentially be amplified if explored in larger sample sizes. The core methodological challenge when attempting to observe electrophysiological activity acquired during concurrent GVS-EEG is the presence of a GVS-related artifact that contaminates the continuous EEG. Thus, the first two studies reported in this thesis assessed the effectiveness of a strategy using ICA to extract the GVS artifact from EEG data. The novelty of this strategy was the identification and characterization of the independent components associated with the GVS-related artifact.

The pilots outlined in methodological development section of this thesis enabled the identification and characterization of the component associated with the GVS-related artifact as well as demonstrating the influence of the different GVS parameters had on the continuous EEG data. This, in turn, informed the GVS parameters used in Studies 1 and 2 to ensure the successful removal of the GVS artifact. The aim of Study 1 was to evaluate the feasibility of successfully obtaining MRCPs from finger movement data following removal of the GVS-relate artifact using

ICA as an artifact rejection technique. MRCPs were the electro-cortical activity of interest because of the strong relationship between vestibular and motor functions (Lacour & Borel, 1993; Stiles & Smith, 2015). They were also selected because the BP component of the MRCPs is deficient in individuals with PD (Cunnington et al., 1999; Dick et al., 1989; Jahanshahi et al., 1995; Praamstra et al., 2002). Thus, they were an appropriate electrophysiological marker to investigate the underlying mechanisms of GVS on motor function in PD as done in Study 3. The results of Study 1 revealed that there were no statistically significant differences between MRCPs obtained in the active GVS condition compared to the sham. The consistency of the graphical and statistical results across the active and sham stimulation conditions confirmed the successful removal of the GVS-related artifact. Additionally, the significant differences observed between electrodes Cz and C4 were consistent with previous reports of the contralateral movement-related activity progressing from pre-movement preparation to motor execution (Colebatch, 2007). This consistency with previous literature further indicated that the strategy employed to remove the GVS-related artifact did not influence the acquisition of MRCPs. Thus, Study 1 validated the employment of this novel strategy to remove the GVS-related artifact without compromising the identification of MRCPs. Study 1 also manipulated the GVS frequency, altering it from 3 Hz employed in the pilots to 0.01 Hz. This manipulation led to the reduction in the number of IC labels associated with the GVS-related artifact from 28 identified in the pilots down to 1 identified in Study 1.

Study 2 aimed to 1) assess the feasibility and logistics of implementing a foot movement task to the experimental paradigm outlined in Study 1 and 2) evaluate the effectiveness of the GVS artifact removal strategy at extracting a GVS-related component associated with a higher amplitude (0.30-0.40 mA) compared to that used in Study 1. The first aim was achieved with the successful acquisition of MRCPs from both finger and foot movements. This demonstrates the

multi-modal applicability of the methodological paradigm and EEG processing pipeline to obtain MRCPs from different limb movements. This is important because it implies the future potential of applying this methodology when studying motor function in PD using more ecologically valid tasks such as walking. Moreover, there were differences in distributions of activation across the electrode sites for finger and foot movements that remained consistent with previous reports (Böcker et al., 1994; Brunia & van de Bosch, 1984). Specifically, finger movements elicited larger activations in the contralateral hemisphere whereas foot movements were associated with larger activations in the ipsilateral hemisphere. The second aim of Study 2 was achieved with the result of no significant differences between the active and sham GVS conditions. Parallel to Study 1, this finding confirmed the effectiveness of the processing pipeline at extracting the GVS-related artifact, even when applying a GVS current of a higher magnitude than that employed in Study 1. However, this higher current intensity also produced supra-threshold cutaneous sensations for most of the participants in Study 2. Given the importance of blinding clinical participants to intervention conditions, the decision to reduce the GVS intensity in Study 3 was informed by this result. Nevertheless, knowing that the processing strategy was effective at removing GVS-related artifacts associated with higher stimulation intensities is valuable. Future clinical studies applying higher intensities may prove to be more therapeutic, despite being above sensory threshold.

The aims of Study 3 were 1) to observe the direct effects of GVS on MRCPs in PD and 2) assess the feasibility of applying the methodological design and EEG processing pipeline to a clinical population. The ultimate goal of this study was to provide a potential electrophysiological marker of change during GVS in PD which may explain the therapeutic effects of vestibular stimulation in PD observed previously. This study provided a preliminary understanding of the mechanisms of action underlying GVS in PD which may lead to further dose optimization with

the aim of maximizing benefits for patients. The findings for the individual analyses of the finger and foot movement data yielded no significant differences between active and sham GVS conditions. However, there was a main effect of condition that emerged only in the combined analysis of the finger and foot data which may suggest that this study was significantly affected by low power due to a small sample size. This effect was characterized by a significant increase in the negativity of the early BP at Cz that was associated with the active GVS condition compared to the sham. Given that the early BP is reported to be diminished in PD, it suggests a potential therapeutic effect of GVS on early movement preparation. One limitation of Study 3 that constrains the interpretation of this finding was that the sample size was not sufficiently large to produce this effect in the individual analyses of the finger and foot data. The successful acquisition of MRCPs following the application of the EEG processing pipeline further confirms the validity of the novel methodology and supports its applicability in clinical as well as neurologically healthy populations.

This body of work is the first to employ ICA to successfully identify, quantify and extract the GVS-related artifact from the EEG data. Previous strategies involving bandwidth filters, QR decomposition and regression independent vector analysis (q-IVA) have been reported to remove the GVS-related artifact from EEG data (Kim et al., 2013; Lee et al., 2018; Schmidt-Kassow et al., 2016; Wilkinson et al., 2012). Schmidt-Kassow et al. (2016) and Wilkinson et al. (2012) employed bandwidth filters to remove the GVS-related artifact from concurrent GVS-EEG data. However, their findings of the effects of GVS on the P300 and N170 were reported without providing a clear account of the artifact extraction method and its effect on the EEG data. The processing strategy described here allowed for the thorough investigation of the effect different cleaning techniques had on the EEG data. Indeed, the FFT plots conducted in the pilot revealed that the sole application of bandwidth filters was insufficient at completely removing the GVS artifact from the EEG data.

The additional employment of ICA as a decomposition technique in Study 1 was required to achieve 'clean' EEG data following the extraction of ICs associated with the GVS-related artifact. These ICs were identified by their characteristics of bipolar and temporally lateralized topographical distributions. As such, one advantage of the strategy developed in this thesis over those employed in previous studies (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012) is that it provides a replicable account of the quantifiable characteristics of the GVS-related artifact as has been previously done for other known artifactual sources (blinks, saccades, muscle activity and heart rate (Klug & Gramann, 2020). Another advantage of identifying the characteristics of the GVS-related artifact is the effective distinction that can be made between the signals of interest stemming from genuine brain activity and the artifactual signals introduced by the GVS stimulus. The processing strategy reported in this thesis also employed an accessible tool (ICA) that has been validated and extensively used in a broad range of research from stationary to dynamic paradigms and is available in a range of software (Brain Vision Analyser and EEGLAB) (Klug & Gramann, 2020). A few previous studies have provided step-by-step accounts of their artifact rejection techniques as well as providing characteristics of the stimulation artifacts (Lee et al., 2018; Lee et al., 2019). However, these present with limitations that were overcome in the current body of work.

First, previous studies either employed only one set of stimulation parameters or varied only the frequency of the AC GVS delivered (Lee et al., 2018; Lee et al., 2019). This thesis varied the GVS intensity applied (0.20-0.30 mA, 0.30-0.40 mA and 0.25-0.35 mA in Studies 1, 2 and 3, respectively) enabling the observation of how different stimulation parameters affect the ability of the processing strategy in effectively removing the GVS-related artifact. Only one other study has investigated the effects different GVS intensities (Kim et al., 2013). However, their findings may

not be applicable to the current body of work because of their employment of a random noise current for GVS. AC GVS refers to the application of a sinusoidal waveform whereas the frequency and amplitude of a noise waveform varies randomly (Dlugaiczyk et al., 2019). Second, the strategies employed in these previous studies only demonstrate that the GVS artifact can be removed from at-rest EEG data. The processing strategy developed in this thesis demonstrates not only that the GVS-related artifact can be successfully removed from continuous EEG data but also that it does not interfere with the acquisition of ERPs. The lack of significant differences between MRCPs during active and sham GVS conditions for both finger and foot movements confirmed this. An advantage of this is that it validates this strategy to be employed when observing the direct effects of GVS on functionally and clinically relevant electrophysiological markers, i.e., the BP in a PD population.

Another important finding from this body of work was the significant but small increase in the negativity of the early BP at Cz associated with the active GVS condition in Study 3. This is a clinically relevant finding because previous studies have reported the early BP to be diminished in PD populations (Cunnington et al., 1999; Dick et al., 1989; Jahanshahi et al., 1995; Praamstra et al., 2002). The early BP is usually reflective of early-phase and nonspecific activations in preparation for a voluntary movement (Shibasaki & Hallett, 2006; Colebatch, 2007). This is consistent with a cardinal symptom of PD: bradykinesia, defined as a slowness in the initiation of a voluntary movement (Davie, 2008; Jankovic, 2008). An increase in the activation of the early BP therefore suggests a therapeutic effect of GVS on the mechanisms related to early-stage readiness for voluntary movement. Many studies have reported significant improvements in motor function following vestibular stimulation (Lee et al., 2015; Khoshnam et al., 2018; Pan et al., 2008; Samoudi et al., 2015; Wilkinson et al., 2016; Wilkinson et al., 2019; Yamamoto et al., 2005).

Therefore, this body of work may be the first to provide an initial understanding of the mechanisms underlying the clinical benefits of vestibular stimulation in PD motor deficits observed previously.

Vestibular stimulation may modulate motor function via vestibular-basal ganglia connections (Stiles & Smith, 2015). This is of particular relevance to PD given the important implications of the basal ganglia in the motor dysfunction observed in the disease (Davie, 2008; Jankovic, 2008). Animal studies have revealed several potentials pathways between the vestibular system and the basal ganglia (Hitier et al., 2014; Horowits et al., 2005; Lai et al., 2000). The most widely researched of which suggests there are projections from the vestibular nucleus to the thalamus which in turn directly project to the dorsolateral putamen of the striatum (Lai et al., 2000). Other potential, indirect pathways to the striatum have been proposed via other structures such as the pedunculopontine tegmental nucleus (PPN) and hippocampus (Hitier et al., 2014; Horowits et al., 2005). Human imaging studies support these potential vestibular-basal ganglia connections with PET and fMRI studies showing increased activations in the putamen and caudate nucleus in response to either caloric or galvanic vestibular stimulation (Bottini et al., 1994; Della-Justina et al., 2015; Emri et al., 2003; Vitte et al., 1996). One recent study showed that GVS increased the connectivity of the PPN to other brain areas associated with somatosensory and motor function in PD (Cai et al., 2018), in which PPN connectivity is known to be reduced (Fling et al., 2014; Vercruysse et al., 2015). The basal ganglia are known to influence motor function through direct and indirect cortico-subcortical projections to the motor cortex (Herrero, Barcia & Navarro, 2002). These findings are consistent with the role of the vestibular system in motor functions such as balance, gait coordination, motor navigation and oculomotor stabilization of eye movements (Fitzpatrick & Day, 2004; Lacour & Borel, 1993; Clark, 1970). It is possible that vestibular stimulation may indirectly modulate activity in the motor cortex associated with movement

preparation via the connections the vestibular system shares with the basal ganglia. However, whilst these connections describe the pathways through which GVS may be influencing motor dysfunction in PD, they do not provide a functional explanation of its effects on neuronal activity.

One aim of this thesis was to investigate a putative electrophysiological mechanism for the effects of vestibular stimulation in PD using markers that were functionally and clinically relevant to PD (MRCPs). Most previous research on the effects of vestibular stimulation on PD have proposed stochastic resonance (SR) as an electrophysiological mechanism (Cai et al., 2018; Lee et al., 2015; Pal et al., 2009; Samoudi et al., 2005; Yamamoto et al., 2005). Stochastic resonance refers to the facilitation of responsiveness to weak subthreshold signals in a non-linear system such as the CNS via the introduction of an external random noise signal (McDonnell & Ward, 2011). Support for this putative mechanism comes from a concurrent GVS-EEG study showing that GVS modulates multiple EEG oscillations during rest in neurologically healthy individuals (Kim et al., 2013). This effect was attributed to the specific employment of a zero-mean, linearly detrended, noisy current with a 1/*f*-type power spectrum (pink noise), which may switch fixed oscillatory states to more dynamic ones, therefore making the brain more malleable to change (Buzsaki, 2006). However, widespread power spectra changes in various frequency bands have also been observed during DC GVS (Wilkinson et al., 2012), suggesting that SR may not be the only putative mechanism to explain the widespread changes in EEG oscillations produced by GVS.

Another putative mechanism that may better explain the results of Study 3 is neural entrainment, which refers to the synchronization of endogenous cortical oscillations to an externally applied sinusoidal current (Khatoun et al., 2019; Krause et al., 2019; Schutter, 2016). This is consistent with the employment of an alternating current in the studies of this thesis as applying AC has been shown to modulate cortical oscillations (Helfrich et al., 2014). A recent

study has also shown that vestibular stimulation using an alternating current normalizes the pathologically altered cortical coupling in M1, SMA and the premotor area (PMA) of theta, alpha and gamma frequency bands in PD participants (Lee et al., 2019). Thus, it is possible that vestibular stimulation may have a 'resetting' effect on brain oscillations, disrupting pathological rhythms (Smith, 2018). Relating this to the findings of Study 3, it is possible that the application of GVS at a frequency of 0.01 Hz entrained the slow-wave oscillations underlying the BP (Armstrong et al., 2018; Jo et al., 2013; Schmidt et al., 2016), thus producing an increase in the early BP amplitude. This finding taken together with the previous studies on the effects of GVS on brain oscillations is promising because it suggests a therapeutic effect on the abnormal cortical and subcortical oscillations previously reported in PD (Hammond et al., 2007; Heinrichs-Graham et al., 2014) with neural entrainment as the putative mechanism.

Neural entrainment has been proposed as the putative mechanism for other types of brain stimulation techniques such as tACS (Helfrich et al., 2014). This is relevant because tACS involves the application of external sinusoidal electrical currents - similar to the AC GVS employed here - via electrodes placed on the scalp above targeted brain regions (Antal & Paulus, 2013). Unlike vestibular stimulation, only two studies have demonstrated the potential clinical benefit of tACS in PD. One study showed significant reductions in tremor during tACS and a randomized cross-over trial demonstrated improvements of bradykinesia and mild cognitive impairment following tACS when accompanied by physical therapy (Brittain et al., 2013; Del Felice et al., 2019). EEG and MEG recordings of PD participants following tACS have showed attenuation of exaggerated beta band oscillations, suggesting tACS functions by modulating abnormal oscillations (Del Felice et al., 2019; Krause et al., 2014). It is likely that the clinical effects of tACS in PD have not been as robust as with vestibular stimulation because each technique harnesses a different neural

pathway. tACS involves applying an exogenous stimulus to a target brain area under the electrodes whereas GVS harnesses the endogenous, pre-existing, sensory network of the vestibular system (Black & Rogers, 2020). Although tACS may certainly affect the areas under the electrodes, it does not necessarily reflect endogenous neural patterns of those areas. Moreover, even neuromodulation techniques that directly target damaged brain areas, such as DBS of the subthalamic nucleus in PD (Brown et al., 2001; Levy et al., 2002; Wichmann & Dostrovsky, 2011), may not reflect the regional dynamics of those areas (Black & Rogers, 2020). This may hinder the ability of these neuromodulation techniques to produce long-term neuroplastic changes in oscillatory patterns. However, by using the vestibular system as the 'highway' to other brain areas, the modulatory signal sent by GVS can be transformed to match the naturally developed oscillatory patterns of these brain regions (Black & Rogers, 2020). These signals may be used to promote naturally developed oscillations that protect the brain from abnormal oscillations, through neuroplastic change (Black & Rogers, 2020). In this way, stimulating the vestibular system may be a more viable way of accessing and modulating damaged brain areas, than applying an external stimulus to the head or invasively inserting electrodes within damaged regions as other techniques have done (Antal & Paulus, 2013; Nitsche, Cohen & Wasserman, 2008; Wassermann, 1998).

It is perhaps surprising that a positive effect of GVS did not also translate to the measures of muscle activation (EMG). The results showed no differences between EMG amplitudes in the active or sham GVS conditions. However, measurement of EMG reflects the muscle output in the motor execution phase (MP) and the results of Study 3 suggests that the effects of GVS are specific to the early stages of movement preparation (early BP). Moreover, EMG measurement in this thesis was primarily employed as a marker of muscle activation onset to determine epochs for the MRCPs. Future research should measure behavioural outcomes specifically associated with

movement initiation to observe whether they parallel the GVS effects on the early BP. For example, simple RT tasks versus cued choice RT tasks that dissociate between motor preparation and execution may be suitable to measure the effects of GVS on movement initiation (Dick et al., 1984).

Limitations and Future Research

The main limitation affecting the studies in this thesis relate to a lack of power due to small sizes. The optimal sample size for all studies was calculated at $n = 12$ using a G*Power Calculation and this was generally treated as a minimum given that previous literature used sample sizes ranging between 10-23 participants (Kim et al., 2013; Lee et al., 2019; Schmidt-Kassow et al., 2016). However, several other factors influenced the recruitment of a minimum of 12 participants for each study. The eleven and nine participants recruited for studies 1 and 2 respectively were based on limited access to a student population. Thus, the effect of being under the minimum of $n = 12$ may have resulted in the lack of a significant difference between active and sham GVS which was contrary to what previous literature had demonstrated in healthy populations (Wilkinson et al., 2012; Schmidt-Kassow et al., 2016). Being underpowered was particularly problematic for study 3 as the significant positive effect of GVS on the early BP was only observed when the finger and foot data were combined to increase the number of data points. Importantly, this effect was not observed in the separate finger and foot analyses which suggests insufficient power to detect a significant difference between active and sham conditions. Nevertheless, the results of study 3 suggest that given a sufficiently large sample size, an effect may emerge separately in the finger and foot data. Studying a larger clinical sample may also enable distinctions in GVS effects on MRCPs between different PD sub-types. For example, PD patients with FOG have recently been shown to have MRCPs with higher amplitude and more variable latency than PD patients without FOG (Karimi, Niu, Almeida & Jiang, 2020). Future research could investigate how PD participants

with or without FOG may respond differently to GVS. Future applications of the novel methodology validated in Studies 1 and 2 should also evaluate its efficacy in larger sample sizes. This may permit differences between the active and sham GVS conditions to emerge in the neurologically healthy population as has previously been reported (Schmidt-Kassow et al., 2016; Wilkinson et al., 2012).

Another limitation relating to sample is the lack of a control group of neurologically healthy and age-matched older adults to compare to the PD participants. Recruitment of a control group for this study was prevented by the lockdown established in March 2020 to respond to the COVID-19 pandemic. Previous studies have reported the early BP to be reduced in PD populations, however, this was in comparison to the MRCPs obtained from age-matched control participants (Cunnington et al., 1999; Dick et al., 1989; Jahanshahi et al., 1995; Praamstra et al., 2002). Without a control group to compare baseline MRCPs to, it is uncertain whether the early BP of the PD participants in Study 3 is truly deficient. Therefore, it is unclear whether the effect GVS had on the early BP reflects a compensatory boost or 'normalisation' of early pre-movement preparation. Moreover, the inclusion of a control group within a similar age range as the PD participants would determine whether the GVS effect is age-related or PD-specific. Future studies should include an age-matched control group to clarify the nature of the effect of GVS on the early BP in PD.

The GVS protocol implemented in this thesis may have been insufficient to produce stronger effects on MRCPs. The amplitude range of 0.20 to 0.40 mA employed in this thesis may have been too small in terms of intensity. Future studies should apply the methodology used here to other sub-sensory amplitudes above 0.40 mA or supra-threshold amplitudes. For example, some studies have shown behavioural responses such as changes in perceptions of trajectory and EMG activation in response to GVS applied using >1 mA amplitudes (Britton et al., 1993; Fitzpatrick et

al., 1999). Indeed, in strictly clinical terms, it may not be important whether a stimulation treatment is perceptible as long as it is effective. Nevertheless, the decision to employ an imperceptible stimulus in this thesis was justified by the importance of a placebo in the theoretical investigation of the underlying mechanisms of a novel, potential therapy (Chambless & Hollon, 1998). Similarly, the GVS frequency of 0.01 Hz may have been too low to produce noticeable effects. The previous concurrent GVS-EEG study by Schmidt-Kassow et al. (2016) employed AC GVS at frequencies of 0.8 Hz and 1 Hz to observe their effects of auditory oddball task performance. Future applications of the methodology in this thesis should investigate whether higher frequencies affect ERPs with different underlying oscillatory frequencies to MRCPs. Additionally, the duration of the stimulation period in this thesis was limited to 10-15 minutes per participants. To understand the long-term effects of GVS on MRCPs, longer or repeated GVS sessions should be investigated as has been done previously in clinical studies (Wilkinson et al., 2014; Wilkinson et al., 2016; Wilkinson et al., 2019). Finally, the strongest clinical effects of vestibular stimulation on PD were observed when employing CVS (Wilkinson et al., 2016; Wilkinson et al., 2019). Future research should investigate the electrophysiological responses to CVS in the same way as was done in this body of work to determine whether there are differences between the two techniques in terms of their underlying frequency.

The clinical characteristics of the PD sample employed in Study 3 may have affected the extent to which participants were responsive to GVS. The PD sample showed a high heterogeneity in the severity of motor symptoms as measured by the motor examination of the MDS-UPDRS (see Table 4). There was also a high variability in the number of years since diagnosis across participants ranging from one to eleven years of living with PD. This may have led to variations in the MRCP response to GVS. Thus, future studies should address the issue of variable motor

abilities more directly, potentially by comparing PD participants based on the severity of their motor symptoms. This may be particularly useful in identifying best responders to vestibular treatment. The PD sample in Study 3 also scored relatively high on the MiniBEST assessment, suggesting all participants showed largely intact balance functions. 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.

Finally, the statistical logic of employing difference in mean amplitudes to determine the successful removal of the GVS-related noise by ICA can be problematic. ERP data that is contaminated by noise does not necessarily cause a significant difference in mean amplitudes, but noise may cause the variability to increase in the active GVS condition versus the sham GVS condition. The low samples size of the three studies also compounds this issue in the analyses as they may be too underpowered to detect significantly different means. Future studies should employ statistical analyses that assess the difference/equivalence of variability between GVS and non-GVS conditions as a stronger evaluation of whether ICA removes GVS-related noise. For example, Bayesian statistics could be employed to determine whether variance in the active GVS condition matched that in the sham GVS condition. Although a visual evaluation of the data pre- versus post-ICA was conducted for this thesis, future studies should aim to assess this change statistically to ascertain whether ICA reduces variability in the active GVS conditions.

Future research should apply the methodology developed in this thesis to more ecologically valid movement tasks. The simple finger extensions and ankle dorsiflexion tasks employed in this

thesis were justified by previous literature using similar, self-paced movement tasks and the clinical relevance to PD diagnosis (Goetz et al., 2008). This was sufficient in terms of validating the experimental design and the EEG processing strategy. However, more recent research has focused on the MRCPs derived from more complex movements such as grasping, reaching and lifting which are more prevalent in everyday life (Di Russo et al., 2017). These studies have revealed the presence of prominent BPs in the parietal lobe preceding these praxic actions (Bozzacchi et al., 2015; Wheaton, Shibasaki & Hallet, 2005). The involvement of the parietal lobe is perhaps related to the goal-oriented nature of these more complex actions (Wheaton, Yakota & Hallett, 2005). Utilizing these more complex, goal-oriented movements may be directly relevant to the difficulties individuals with PD face during activities of daily living (ADLs) such as eating, drinking, dressing etc. (Hariz & Forsgren, 2011). Moreover, given the effect of GVS on the early BP observed in Study 3, future research should also investigate the effects of GVS on MRCPs elicited by walking in PD with specific interest on gait initiation. Many previous studies confirm the vestibular contributions to locomotion (Bent et al., 2000; do Nascimento, Nielsen & Voigt, 2005; Fitzpatrick, et al., 1999), and one has even reported improvements in the gait of healthy participants and patients with bilateral vestibulopathy during vestibular stimulation (Iwasaki et al., 2018). To observe potential GVS effects on gait-related cortical activity would be invaluable to our understanding of the underlying mechanisms of vestibular stimulation in PD. It would provide further validation for the methodology developed in this thesis to apply it to locomotion in line with the growing field of mobile EEG (De Sanctis et al., 2014; Ehinger et al., 2014; Gramann et al., 2010). Certainly, the successful implementation of a foot movement task in Study 2 hint at the potential multi-modality of this approach and its application to more active movement tasks.

In summary, this thesis reported the development of a novel methodology to study the simultaneous effects of GVS during the recording of EEG. Specifically, the studies described here provide validation for using ICA to identify, quantify and effectively remove the GVS-related artifact without compromising the acquisition of MRCPs. This strategy was validated when employing finger and foot movement tasks to elicit MRCPs as well as for the application to a clinical population. Investigating what happens to the brain during GVS in this way can elucidate its mechanisms of action in producing the therapeutic benefits previously reported (Grabherr et al., 2015). Indeed, the results of Study 3 may indicate that GVS ameliorates PD by modulating motor processes related to voluntary movement preparation. The findings from this thesis may also prove applicable to other clinical conditions in which MRCPs are abnormal, such as dystonia and stroke. Dystonia has been associated with an attenuated BP whereas increases and decreases in the amplitudes of the BP and MP have been observed in stroke, depending on location and size of lesions (Ceballos-Baumann et al., 1995; Colebatch, 2007; Jankelowitz & Colebatch, 2005). Furthermore, future research could apply the processing strategy employed in this thesis to brain stimulation techniques other than GVS, such as tACS, to investigate whether the electrical artifacts associated with such techniques can also be successfully identified and removed. Finally, by investigating a potential mechanism of action during movements in PD, this thesis has progressed the application of vestibular stimulation for regulatory approval and widespread clinical adoption.

References

Albani, G., Sandrini, G., Kunig, G., Martin-Soelch, C., Mauro, A., Pignatti, R., ... & Leenders, K. L. (2003). Differences in the EMG pattern of leg muscle activation during locomotion in Parkinson's disease. *Functional neurology*, *18*(3), 165-178.

Antal, A., & Paulus, W. (2013). Transcranial alternating current stimulation (tACS). *Frontiers in human neuroscience*, *7*, 317.

Armstrong, S., Sale, M. V., & Cunnington, R. (2018). Neural oscillations and the initiation of voluntary movement. *Frontiers in psychology*, *9*, 2509.

Aviles-Olmos, I., Foltynie, T., Panicker, J., Cowie, D., Limousin, P., Hariz, M., ... & Zrinzo, L. (2011). Urinary incontinence following deep brain stimulation of the pedunculopontine nucleus. *Acta neurochirurgica*, *153*(12), 2357-2360.

Baek, J. H., Zheng, Y., Darlington, C. L., & Smith, P. F. (2010). Evidence that spatial memory deficits following bilateral vestibular deafferentation in rats are probably permanent. *Neurobiology of Learning and Memory*, *94*(3), 402-413.

Balaban, C. D., Jacob, R. G., & Furman, J. M. (2011). Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. *Expert review of neurotherapeutics*, *11*(3), 379-394.

Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clinical neurophysiology*, *123*(4), 644-657.

Been, G., Ngo, T. T., Miller, S. M., & Fitzgerald, P. B. (2007). The use of tDCS and CVS as methods of non-invasive brain stimulation. *Brain research reviews*, *56*(2), 346-361.

Benabid, A. L. (2003). Deep brain stimulation for Parkinson's disease. *Current opinion in neurobiology*, *13*(6), 696-706.

Bense, S., Stephan, T., Yousry, T. A., Brandt, T., & Dieterich, M. (2001). Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). *Journal of Neurophysiology*, *85*(2), 886-899.

Bent, L. R., Inglis, J. T., & McFadyen, B. J. (2004). When is vestibular information important during walking?. *Journal of neurophysiology*, *92*(3), 1269-1275.

Bent, L. R., McFadyen, B. J., Merkley, V. F., Kennedy, P. M., & Inglis, J. T. (2000). Magnitude effects of galvanic vestibular stimulation on the trajectory of human gait. *Neuroscience letters*, *279*(3), 157-160.

Best, C., Bense, S., & Dieterich, M. (2007). Vestibular dysfunction in major depression. *Neuroscience*, *3*(147), 865-866.

Best, C., Eckhardt-Henn, A., Tschan, R., & Dieterich, M. (2009). Psychiatric morbidity and comorbidity in different vestibular vertigo syndromes. *Journal of neurology*, *256*(1), 58-65.

Bi, L. L., Wang, J., Luo, Z. Y., Chen, S. P., Geng, F., Chen, Y. H., ... & Gao, T. M. (2013). Enhanced excitability in the infralimbic cortex produces anxiety-like behaviors. *Neuropharmacology*, *72*, 148-156.

Bigelow, R. T., & Agrawal, Y. (2015). Vestibular involvement in cognition: Visuospatial ability, attention, executive function, and memory. *Journal Of Vestibular Research: Equilibrium & Orientation*, *25*(2), 73-89.

Black, R. D., & Rogers, L. L. (2020). Sensory Neuromodulation. *Frontiers in Systems Neuroscience*, *14*, 12.

Black, R. D., Rogers, L. L., Ade, K. K., Nicoletto, H. A., Adkins, H. D., & Laskowitz, D. T. (2016). Non-invasive neuromodulation using time-varying caloric vestibular stimulation. *IEEE journal of translational engineering in health and medicine*, *4*, 1-10.

Bloem, B. R., Beckley, D. J., Van Dijk, J. G., Zwinderman, A. H., Remler, M. P., & Roos, R. A. (1996). Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *11*(5), 509-521.

Böcker, K. B., Brunia, C. H., & Cluitmans, P. J. (1994). A spatio-temporal dipole model of the readiness potential in humans. II. Foot movement. *Electroencephalography and clinical Neurophysiology*, *91*(4), 286-294.

Boschert, J., Hink, R. F., & Deecke, L. (1983). Finger movement versus toe movement-related potentials: further evidence for supplementary motor area (SMA) participation prior to voluntary action. *Experimental Brain Research*, *52*(1), 73-80.

Bottini, G., Sterzi, R., Paulesu, E., Vallar, G., Cappa, S. F., Erminio, F., ... & Frackowiak, R. S. (1994). Identification of the central vestibular projections in man: a positron emission tomography activation study. *Experimental brain research*, *99*(1), 164-169.

Bozzacchi, C., Spinelli, D., Pitzalis, S., Giusti, M. A., & Di Russo, F. (2015). I know what I will see: action-specific motor preparation activity in a passive observation task. *Social cognitive and affective neuroscience*, *10*(6), 783-789.

Brandt, T., Dieterich, M., & Strupp, M. (2005). *Vertigo and dizziness*. Springer-Verlag London Limited.

Brittain, J. S., Probert-Smith, P., Aziz, T. Z., & Brown, P. (2013). Tremor suppression by rhythmic transcranial current stimulation. *Current Biology*, *23*(5), 436-440.

Britton, T. C., Day, B. L., Brown, P., Rothwell, J. C., Thompson, P. D., & Marsden, C. D. (1993). Postural electromyographic responses in the arm and leg following galvanic vestibular stimulation in man. *Experimental brain research*, *94*(1), 143-151.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *Journal of Neuroscience*, *21*(3), 1033-1038.

Brunia, C. H. M., & Van den Bosch, W. E. J. (1984). Movement-related slow potentials. I. A contrast between finger and foot movements in right-handed subjects. *Electroencephalography and Clinical Neurophysiology*, *57*(6), 515-527.

Bucher, S. F., Dieterich, M., Wiesmann, M., Weiss, A., Zink, R., Yousry, T. A., & Brandt, T. (1998). Cerebral functional magnetic resonance imaging of vestibular, auditory, and nociceptive areas during galvanic stimulation. *Annals of Neurology*, *44*(1), 120-125. doi:10.1002/ana.410440118

Buzsaki, G. (2006). *Rhythms of the Brain*. Oxford University Press.

Cai, J., Lee, S., Ba, F., Garg, S., Kim, L. J., Liu, A., ... & McKeown, M. J. (2018). Galvanic vestibular stimulation (GVS) augments deficient pedunculopontine nucleus (PPN) connectivity in mild Parkinson's disease: fMRI effects of different stimuli. *Frontiers in neuroscience*, *12*, 101.

Cauquil, A. S., Faldon, M., Popov, K., Day, B. L., & Bronstein, A. M. (2003). Short-latency eye movements evoked by near-threshold galvanic vestibular stimulation. *Experimental brain research*, *148*(3), 414-418.

Cauquil, A. S., Gervet, M. F. T., & Ouaknine, M. (1998). Body response to binaural monopolar galvanic vestibular stimulation in humans. *Neuroscience letters*, *245*(1), 37-40.

Ceballos-Baumann, A. O., Passingham, R. E., Warner, T., Playford, E. D., Marsden, C. D., & Brooks, D. J. (1995). Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *37*(3), 363-372.

Chambless, D. L., & Hollon, S. D. (1998). Defining empirically supported therapies. *Journal of consulting and clinical psychology*, *66*(1), 7.

Chaudhuri, K. R., Martinez-Martin, P., Brown, R. G., Sethi, K., Stocchi, F., Odin, P., ... & Barone, P. (2007). The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Movement disorders*, *22*(13), 1901-1911.

Clark, B. (1970). The vestibular system. *Annual Review of Psychology, 21*(1), 273-306.

Coats, A. C. (1973). Effect of varying stimulus parameters on the galvanic body-sway response. *Annals of Otology, Rhinology & Laryngology*, *82*(1), 96-102.

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Academic press.

Colebatch, J. G. (2007). Bereitschaftspotential and movement-related potentials: origin, significance, and application in disorders of human movement. *Movement Disorders*, *22*(5), 601-610.

Cui, R. Q., & Deecke, L. (1999). High resolution DC-EEG analysis of the Bereitschaftspotential and post movement onset potentials accompanying uni-or bilateral voluntary finger movements. *Brain topography*, *11*(3), 233-249.

Cullen, K. E. (2012). The vestibular system: multimodal integration and encoding of self-motion for motor control. *Trends in neurosciences*, *35*(3), 185-196.

Cunnington, R., Iansek, R., & Bradshaw, J. L. (1999). Movement-related potentials in Parkinson's disease: External cues and attentional strategies. *Movement disorders: official journal of the Movement Disorder Society*, *14*(1), 63-68.

Cunnington, R., Iansek, R., Johnson, K. A., & Bradshaw, J. L. (1997). Movement-related potentials in Parkinson's disease. Motor imagery and movement preparation. *Brain: a journal of neurology*, *120*(8), 1339-1353.

Davie, C. A. (2008). A review of Parkinson's disease. *British medical bulletin*, *86*(1), 109-127.

Davis, N. J., Gold, E., Pascual-Leone, A., & Bracewell, R. M. (2013). Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *European Journal of Neuroscience*, *38*(7), 2973-2977.

Day, B. L., Severac Cauquil, A., Bartolomei, L., Pastor, M. A., & Lyon, I. N. (1997). Human body-segment tilts induced by galvanic stimulation: a vestibularly driven balance protection mechanism. *The Journal of physiology*, *500*(3), 661-672.

Deecke, L., Eisinger, H., & Kornhuber, H. H. (1980). Comparison of Bereitschaftspotential, pre-motion positivity and motor potential preceding voluntary flexion and extension movements in man. In *Progress in brain research* (Vol. 54, pp. 171-176). Elsevier.

Deecke, L., Grözinger, B., & Kornhuber, H. H. (1976). Voluntary finger movement in man: Cerebral potentials and theory. *Biological cybernetics*, *23*(2), 99-119.

Deecke, L., Scheid, P., & Kornhuber, H. H. (1969). Distribution of readiness potential, pre-motion positivity, and motor potential of the human cerebral cortex preceding voluntary finger movements. *Experimental brain research*, *7*(2), 158-168.

Decety, J. (1996). The neurophysiological basis of motor imagery. *Behavioural brain research*, *77*(1-2), 45-52.

de Jesus Guirro, R. R., de Oliveira Guirro, E. C., & de Sousa, N. T. A. (2015). Sensory and motor thresholds of transcutaneous electrical stimulation are influenced by gender and age. *PM&R*, *7*(1), 42-47.

Del Felice, A., Castiglia, L., Formaggio, E., Cattelan, M., Scarpa, B., Manganotti, P., ... & Masiero, S. (2019). Personalized transcranial alternating current stimulation (tACS) and physical therapy to treat motor and cognitive symptoms in Parkinson's disease: A randomized cross-over trial. *NeuroImage: Clinical*, *22*, 101768.

Della-Justina, H. M., Gamba, H. R., Lukasova, K., Nucci-da-Silva, M. P., Winkler, A. M., & Amaro, E. (2015). Interaction of brain areas of visual and vestibular simultaneous activity with fMRI. *Experimental brain research*, *233*(1), 237-252.

Delval, A., Defebvre, L., & Tard, C. (2017). Freezing during tapping tasks in patients with advanced Parkinson's disease and freezing of gait. *PloS one*, *12*(9), e0181973.

den Otter, A. R. (2005). Gait control after stroke: a neuromuscular approach to functional recovery.

Derost, P. P., Ouchchane, L., Morand, D., Ulla, M., Llorca, P. M., Barget, M., ... & Durif, F. (2007). Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population?. *Neurology*, *68*(17), 1345-1355.

De Sanctis, P., Butler, J. S., Malcolm, B. R., & Foxe, J. J. (2014). Recalibration of inhibitory control systems during walking-related dual-task interference: a mobile brain-body imaging (MOBI) study. *Neuroimage*, *94*, 55-64.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., ... & Gruber, D. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, *355*(9), 896-908.

Dick, J. P. R., Cowan, J. M. A., Day, B. L., Berardelli, A., Kachi, T., Rothwell, J. C., & Marsden, C. D. (1984). The corticomotoneurone connection is normal in Parkinson's disease. *Nature*, *310*(5976), 407-409.

Dick, J. P. R., Rothwell, J. C., Day, B. L., Cantello, R., Buruma, O., Gioux, M., ... & Marsden, C. D. (1989). The Bereitschaftspotential is abnormal in Parkinson's disease. *Brain*, *112*(1), 233-244.

Dietz, V., & Colombo, G. (1998). Influence of body load on the gait pattern in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *13*(2), 255-261.

Dietz, V., & Michel, J. (2008). Locomotion in Parkinson's disease: neuronal coupling of upper and lower limbs. *Brain*, *131*(12), 3421-3431.

Dilda, V., MacDougall, H. G., Curthoys, I. S., & Moore, S. T. (2012). Effects of galvanic vestibular stimulation on cognitive function. *Experimental Brain Research*, *216*(2), 275-285. doi:10.1007/s00221-011-2929-z

Di Russo, F., Berchicci, M., Bozzacchi, C., Perri, R. L., Pitzalis, S., & Spinelli, D. (2017). Beyond the “Bereitschaftspotential”: action preparation behind cognitive functions. *Neuroscience & Biobehavioral Reviews*, *78*, 57-81.

Dlugaiczyk, J., Gensberger, K. D., & Straka, H. (2019). Galvanic vestibular stimulation: from basic concepts to clinical applications. *Journal of neurophysiology*, *121*(6), 2237-2255.

do Nascimento, O. F., Nielsen, K. D., & Voigt, M. (2005). Influence of directional orientations during gait initiation and stepping on movement-related cortical potentials. *Behavioural brain research*, *161*(1), 141-154.

Eagger, S., Luxon, L. M., Davies, R. A., Coelho, A., & Ron, M. A. (1992). Psychiatric morbidity in patients with peripheral vestibular disorder: a clinical and neuro-otological study. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*(5), 383-387.

Egner, T., & Gruzelier, J. H. (2001). Learned self-regulation of EEG frequency components affects attention and event-related brain potentials in humans. *Neuroreport*, *12*(18), 4155-4159.

Ehinger, B. V., Fischer, P., Gert, A. L., Kaufhold, L., Weber, F., Pipa, G., & König, P. (2014). Kinesthetic and vestibular information modulate alpha activity during spatial navigation: a mobile EEG study. *Frontiers in human neuroscience*, *8*, 71.

Elble, R. J., Moody, C., Leffler, K., & Sinha, R. (1994). The initiation of normal walking. *Movement disorders*, *9*(2), 139-146.

Emri, M., Kisely, M., Lengyel, Z., Balkay, L., Márián, T., Mikó, L., ... & Tóth, A. (2003). Cortical projection of peripheral vestibular signaling. *Journal of neurophysiology*, *89*(5), 2639-2646.

Ezure, K., Cohen, M. S., & Wilson, V. J. (1983). Response of cat semicircular canal afferents to sinusoidal polarizing currents: implications for input-output properties of second-order neurons. *Journal of Neurophysiology*, *49*(3), 639-648.

Factor, S. A., Steenland, N. K., Higgins, D. S., Molho, E. S., Kay, D. M., Montimurro, J., ... & Payami, H. (2011). Postural instability/gait disturbance in Parkinson's disease has distinct subtypes: an exploratory analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(5), 564-568.

Fattapposta, F., Pierelli, F., Traversa, G., My, F., Mostarda, M., D'Alessio, C., ... & Amabile, G. (2000). Preprogramming and control activity of bimanual self-paced motor task in Parkinson's disease. *Clinical Neurophysiology*, *111*(5), 873-883.

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*, *39*(2), 175-191.

Fitzpatrick, R. C., & Day, B. L. (2004). Probing the human vestibular system with galvanic stimulation. *Journal of applied physiology*, *96*(6), 2301-2316.

Fitzpatrick, R. C., Wardman, D. L., & Taylor, J. L. (1999). Effects of galvanic vestibular stimulation during human walking. *The Journal of Physiology*, *517*(Pt 3), 931.

Fling, B. W., Cohen, R. G., Mancini, M., Carpenter, S. D., Fair, D. A., Nutt, J. G., & Horak, F. B. (2014). Functional reorganization of the locomotor network in Parkinson patients with freezing of gait. *PloS one*, *9*(6), e100291.

Franchignoni, F., Horak, F., Godi, M., Nardone, A., & Giordano, A. (2010). Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *Journal of rehabilitation medicine*, *42*(4), 323-331.

Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiological reviews*.

Gensberger, K. D., Kaufmann, A. K., Dietrich, H., Branoner, F., Banchi, R., Chagnaud, B. P., & Straka, H. (2016). Galvanic vestibular stimulation: cellular substrates and response patterns of neurons in the vestibulo-ocular network. *Journal of Neuroscience*, *36*(35), 9097-9110.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., ... & Dubois, B. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders: official journal of the Movement Disorder Society*, *23*(15), 2129-2170.

Goldberg, J. M., Smith, C. E., & Fernandez, C. (1984). Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *Journal of neurophysiology*, *51*(6), 1236-1256.

Grabherr, L., Macauda, G., & Lenggenhager, B. (2015). The moving history of vestibular stimulation as a therapeutic intervention. *Multisensory research*, *28*(5-6), 653-687.

Gramann, K., Gwin, J. T., Bigdely-Shamlo, N., Ferris, D. P., & Makeig, S. (2010). Visual evoked responses during standing and walking. *Frontiers in human neuroscience*, *4*, 202.

Grassi, S., & Pettorossi, V. E. (2001). Synaptic plasticity in the medial vestibular nuclei: role of glutamate receptors and retrograde messengers in rat brainstem slices. *Progress in neurobiology*, *64*(6), 527-553.

Gunzler, S. A., Pavel, M., Koudelka, C., Carlson, N. E., & Nutt, J. G. (2009). Foot-tapping rate as an objective outcome measure for Parkinson disease clinical trials. *Clinical neuropharmacology*, *32*(2), 97-102.

Hallpike, C. S., Harrison, M. S., & Slater, E. (1951). Abnormalities of the caloric test results in certain varieties of mental disorder. *Acta oto-laryngologica*, *39*(2-3), 151-159.

Hammond, C., Bergman, H., & Brown, P. (2007). Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends in neurosciences*, *30*(7), 357-364.

Hardie, R. J., Lees, A. J., & Stern, G. M. (1984). On-off fluctuations in Parkinson's disease: a clinical and neuropharmacological study. *Brain*, *107*(2), 487-506.

Hariz, M. (2017). My 25 stimulating years with DBS in Parkinson’s disease. *Journal of Parkinson's Disease*, *7*(s1), S33-S41.

Hariz, G. M., & Forsgren, L. (2011). Activities of daily living and quality of life in persons with newly diagnosed Parkinson's disease according to subtype of disease, and in comparison to healthy controls. *Acta Neurologica Scandinavica*, *123*(1), 20-27.

Heinrichs-Graham, E., Wilson, T. W., Santamaria, P. M., Heithoff, S. K., Torres-Russotto, D., Hutter-Saunders, J. A., ... & Gendelman, H. E. (2014). Neuromagnetic evidence of abnormal movement-related beta desynchronization in Parkinson's disease. *Cerebral cortex*, *24*(10), 2669-2678.

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Entrainment of brain oscillations by transcranial alternating current stimulation. *Current biology*, *24*(3), 333-339.

Hely, M. A., Morris, J. G., Reid, W. G., & Trafficante, R. (2005). Sydney multicenter study of Parkinson's disease: Non-L-dopa–responsive problems dominate at 15 years. *Movement disorders: official journal of the Movement Disorder Society*, *20*(2), 190-199.

Hermens, H. J., Freriks, B., Merletti, R., Stegeman, D., Blok, J., Rau, G., ... & Hägg, G. (1999). European recommendations for surface electromyography. *Roessingh research and development*, *8*(2), 13-54.

Herrero, M. T., Barcia, C., & Navarro, J. (2002). Functional anatomy of thalamus and basal ganglia. *Child's Nervous System*, *18*(8), 386-404.

Hitier, M., Besnard, S., & Smith, P. F. (2014). Vestibular pathways involved in cognition. *Frontiers in integrative neuroscience*, *8*, 59.

Hodges, P. W., & Bui, B. H. (1996). A comparison of computer-based methods for the determination of onset of muscle contraction using

electromyography. *Electroencephalography and clinical Neurophysiology*, *101*(6), 511-519.

Horak, F. B., Wrisley, D. M., & Frank, J. (2009). The balance evaluation systems test (BESTest) to differentiate balance deficits. *Physical therapy*, *89*(5), 484-498.

Horowitz, S. S., Blanchard, J., & Morin, L. P. (2005). Medial vestibular connections with the hypocretin (orexin) system. *Journal of Comparative Neurology*, *487*(2), 127-146.

Horváth, K., Aschermann, Z., Kovács, M., Makkos, A., Harmat, M., Janszky, J., ... & Kovács, N. (2017). Minimal clinically important differences for the experiences of daily living parts of movement disorder society–sponsored unified Parkinson's disease rating scale. *Movement Disorders*, *32*(5), 789-793.

Iwasaki, S., Fujimoto, C., Egami, N., Kinoshita, M., Togo, F., Yamamoto, Y., & Yamasoba, T. (2018). Noisy vestibular stimulation increases gait speed in normals and in bilateral vestibulopathy. *Brain stimulation*, *11*(4), 709-715.

Jacob, R. G., Møller, M. B., Turner, S. M., & Wall, C. (1985). Otoneurological examination in panic disorder and agoraphobia wih panic attacks: A pilot study. *The American journal of psychiatry*.

Jahanshahi, M., & Hallett, M. (Eds.). (2003). *The Bereitschaftspotential: Movement-related cortical potentials*. Springer Science & Business Media.

Jahanshahi, M., Jenkins, I. H., Brown, R. G., Marsden, C. D., Passingham, R. E., & Brooks, D. J. (1995). Self-initiated versus externally triggered movements: I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain*, *118*(4), 913-933.

Jankelowitz, S. K., & Colebatch, J. G. (2005). Movement related potentials in acutely induced weakness and stroke. *Experimental brain research*, *161*(1), 104-113.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of neurology, neurosurgery & psychiatry*, *79*(4), 368-376.

Jo, H. G., Hinterberger, T., Wittmann, M., Borghardt, T. L., & Schmidt, S. (2013). Spontaneous EEG fluctuations determine the readiness potential: is preconscious brain activation a preparation process to move?. *Experimental brain research*, *231*(4), 495-500.

Jung, T. P., Makeig, S., Westerfield, M., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2000). Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects. Clinical Neurophysiology, 111(10), 1745-1758.

Kalia, L. V., & Lang, A. E. (2016). Parkinson disease in 2015: evolving basic, pathological and clinical concepts in PD. *Nature reviews Neurology*, *12*(2), 65.

Karimi, F., Niu, J., Almeida, Q., & Jiang, N. (2020). Movement Related Cortical Potentials in Parkinson's Disease Patients with Freezing of Gait. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)* (pp. 2857-2860). IEEE.

Kataoka, H., Okada, Y., Kiriyama, T., Kita, Y., Nakamura, J., Morioka, S., ... & Ueno, S. (2016). Can postural instability respond to galvanic vestibular stimulation in patients with Parkinson's disease?. *Journal of movement disorders*, *9*(1), 40.

Khatoun, A., Asamoah, B., & Mc Laughlin, M. (2019). How does transcranial alternating current stimulation entrain single-neuron activity in the primate brain?. *Proceedings of the National Academy of Sciences*, *116*(45), 22438-22439.

Khoshnam, M., Häner, D., Kuatsjah, E., Zhang, X., & Menon, C. (2018). Effects of galvanic vestibular stimulation on upper and lower extremities motor symptoms in Parkinson's Disease. *Frontiers in Neuroscience*, *12*, 633.

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behavioural brain research*, *223*(2), 403-410.

Kim, D. J., Yogendrakumar, V., Chiang, J., Ty, E., Wang, Z. J., & McKeown, M. J. (2013). Noisy galvanic vestibular stimulation modulates the amplitude of EEG synchrony patterns. *PloS one*, *8*(7), e69055.

Kim, K. S., Minor, L. B., Della Santina, C. C., & Lasker, D. M. (2011). Variation in response dynamics of regular and irregular vestibular-nerve afferents during sinusoidal head rotations and currents in the chinchilla. *Experimental brain research*, *210*(3-4), 643-649.

King, L. A., Priest, K. C., Salarian, A., Pierce, D., & Horak, F. B. (2012). Comparing the Mini-BESTest with the Berg Balance Scale to evaluate balance disorders in Parkinson's disease. *Parkinson's Disease*, *2012*.

Klem, G. H. (1999). The ten-twenty electrode system of the international federation. the internanional federation of clinical nenrophysiology. *Electroencephalogr. Clin. Neurophysiol. Suppl.*, *52*, 3-6.

Klug, M., & Gramann, K. (2020). Identifying key factors for improving ICA-based decomposition of EEG data in mobile and stationary experiments. *bioRxiv*.

Ko, L. W., Chikara, R. K., Chen, P. Y., Jheng, Y. C., Wang, C. C., Yang, Y. C., ... & Kao, C. L. (2020). Noisy galvanic vestibular stimulation (Stochastic resonance) changes

electroencephalography activities and postural control in patients with bilateral vestibular hypofunction. *Brain Sciences*, *10*(10), 740.

Krause, M. R., Vieira, P. G., Csorba, B. A., Pilly, P. K., & Pack, C. C. (2019). Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. *Proceedings of the National Academy of Sciences*, *116*(12), 5747-5755.

Krause, V., Wach, C., Südmeyer, M., Ferrea, S., Schnitzler, A., & Pollok, B. (2014). Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease. *Frontiers in human neuroscience*, *7*, 928.

Lacour, M., & Borel, L. (1993). Vestibular control of posture and gait. *Archives Italiennes de Biologie*, *131*(2), 81-104.

Lai, H., Tsumori, T., Shiroyama, T., Yokota, S., Nakano, K., & Yasui, Y. (2000). Morphological evidence for a vestibulo-thalamo-striatal pathway via the parafascicular nucleus in the rat. *Brain research*, *872*(1-2), 208-214.

Lakens, D. (2021). Sample size justification.

Lang, W. (2003). Surface recordings of the Bereitschaftspotential in normals. In *The Bereitschaftspotential* (pp. 19-34). Springer, Boston, MA.

Lee, J. W. (2015). Effect of galvanic vestibular stimulation on movement-related cortical potential. *Journal of physical therapy science*, *27*(6), 2009-2011.

Lee, J. W., Lee, G. E., An, J. H., Yoon, S. W., Heo, M., & Kim, H. Y. (2014). Effects of galvanic vestibular stimulation on visual memory recall and EEG. *Journal of physical therapy science*, *26*(9), 1333-1336.

Lee, J. W., Park, W. S., & Yoon, S. W. (2016). Effects of galvanic vestibular stimulation on event related potentials. *Journal of Physical Therapy Science*, *28*(9), 2604-2607.

Lee, S., Kim, D. J., Svenkeson, D., Parras, G., Oishi, M. M. K., & McKeown, M. J. (2015). Multifaceted effects of noisy galvanic vestibular stimulation on manual tracking behavior in Parkinson's disease. *Frontiers in systems neuroscience*, *9*, 5.

Lee, S., Liu, A., Wang, Z. J., & McKeown, M. J. (2019). Abnormal phase coupling in Parkinson's disease and normalization effects of subthreshold vestibular stimulation. *Frontiers in human neuroscience*, *13*, 118.

Lee, S., McKeown, M. J., Wang, Z. J., & Chen, X. (2018). Removal of high-voltage brain stimulation artifacts from simultaneous EEG recordings. *IEEE Transactions on Biomedical Engineering*, *66*(1), 50-60.

Lenggenhager, B., Lopez, C., & Blanke, O. (2008). Influence of galvanic vestibular stimulation on egocentric and object-based mental transformations. *Experimental Brain Research*, *184*(2), 211-221.

Leijnse, J. N., Campbell-Kyureghyan, N. H., Spektor, D., & Quesada, P. M. (2008). Assessment of individual finger muscle activity in the extensor digitorum communis by surface EMG. *Journal of neurophysiology*, *100*(6), 3225-3235.

Levine, J., Toder, D., Geller, V., Kraus, M., Gauchman, T., Puterman, M., & Grisaru, N. (2012). Beneficial effects of caloric vestibular stimulation on denial of illness and manic delusions in schizoaffective disorder: a case report. *Brain Stimulation*, *5*(3), 267-273.

Levy, R., Ashby, P., Hutchison, W. D., Lang, A. E., Lozano, A. M., & Dostrovsky, J. O. (2002). Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain*, *125*(6), 1196-1209.

Li, C. T., Lu, C. F., Lin, H. C., Huang, Y. Z., Juan, C. H., Su, T. P., ... & Lin, W. C. (2017). Cortical inhibitory and excitatory function in drug-naive generalized anxiety disorder. *Brain stimulation*, *10*(3), 604-608.

Libet, B., Gleason, C. A., Wright, E. W., & Pearl, D. K. (1993). Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). In *Neurophysiology of consciousness* (pp. 249-268). Birkhäuser, Boston, MA.

Linden, D. E. (2005). The P300: where in the brain is it produced and what does it tell us?. *The Neuroscientist*, *11*(6), 563-576.

Lobel, E., Kleine, J. F., Bihan, D. L., Leroy-Willig, A., & Berthoz, A. (1998). Functional MRI of galvanic vestibular stimulation. *Journal of neurophysiology*, *80*(5), 2699-2709.

Lopez, C., & Blanke, O. (2011). The thalamocortical vestibular system in animals and humans. *Brain research reviews*, *67*(1-2), 119-146.

Luck, S. J. (2014). *An introduction to the event-related potential technique*. MIT press.

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, *125*(3), 624-639.

Markia, B., Kovács, Z. I., & Palkovits, M. (2008). Projections from the vestibular nuclei to the hypothalamic paraventricular nucleus: morphological evidence for the existence of a vestibular stress pathway in the rat brain. *Brain Structure and Function*, *213*(1-2), 239-245.

McDonnell, M. D., & Ward, L. M. (2011). The benefits of noise in neural systems: bridging theory and experiment. *Nature Reviews Neuroscience*, *12*(7), 415-425.

McIntyre, C. C., & Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of disease*, *38*(3), 329-337.

Metman, L. V., Del Dotto, P., LePoole, K., Konitsiotis, S., Fang, J., & Chase, T. N. (1999). Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Archives of neurology*, *56*(11), 1383-1386.

Metts, B. A., Kaufman, G. D., & Perachio, A. A. (2006). Polysynaptic inputs to vestibular efferent neurons as revealed by viral transneuronal tracing. *Experimental brain research*, *172*(2), 261-274.

Miles, J., & Shevlin, M. (2001). *Applying regression and correlation: A guide for students and researchers*. Sage.

Moon, S. Y., Lee, B. H., & Na, D. L. (2006). Therapeutic effects of caloric stimulation and optokinetic stimulation on hemispatial neglect. *Journal of Clinical Neurology*, *2*(1), 12-28.

Mota, I. A., & Lins, O. G. (2017). Bereitschaftspotential preceding spontaneous and voluntary eyelid blinks in normal individuals. *Clinical Neurophysiology*, *128*(1), 100-105.

Murakami, D. M., Erkman, L., Hermanson, O., Rosenfeld, M. G., & Fuller, C. A. (2002). Evidence for vestibular regulation of autonomic functions in a mouse genetic model. *Proceedings of the National Academy of Sciences*, *99*(26), 17078-17082.

Nagaratnam, N., Ip, J., & Bou-Haidar, P. (2005). The vestibular dysfunction and anxiety disorder interface: a descriptive study with special reference to the elderly. *Archives of gerontology and geriatrics*, *40*(3), 253-264.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

Neshige, R., Lüders, H., & Shibasaki, H. (1988). Recording of movement-related potentials from scalp and cortex in man. *Brain: a journal of neurology*, *111*, 719.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., ... & Pascual-Leone, A. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain stimulation*, *1*(3), 206-223.

Nutt, J. G., Woodward, W. R., & Anderson, J. L. (1985). The effect of carbidopa on the pharmacokinetics of intravenously administered levodopa: the mechanism of action in the treatment of parkinsonism. *Annals of neurology*, *18*(5), 537-543.

Okada, Y., Kita, Y., Nakamura, J., Kataoka, H., Kiriyama, T., Ueno, S., ... & Shomoto, K. (2015). Galvanic vestibular stimulation may improve anterior bending posture in Parkinson's disease. *Neuroreport*, *26*(7), 405-410.

Okun, M. S. (2012). Deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, *367*(16), 1529-1538.

Onton, J., & Makeig, S. (2011). ERP features and EEG dynamics: an ICA perspective. *Oxford handbook of event-related potential components.*

Pal, S., Rosengren, S. M., & Colebatch, J. G. (2009). Stochastic galvanic vestibular stimulation produces a small reduction in sway in Parkinson's disease. *Journal of Vestibular Research*, *19*(3, 4), 137-142.

Pan, W., Soma, R., Kwak, S., & Yamamoto, Y. (2008). Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. *Journal of neurology*, *255*(11), 1657-1661.

Parsons, T. D., Rogers, S. A., Braaten, A. J., Woods, S. P., & Tröster, A. I. (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *The Lancet Neurology*, *5*(7), 578-588.

Patil, A. L., Sood, S. K., GoyAl, V., & KochhAr, K. P. (2017). Cortical potentials prior to movement in Parkinson's disease. *Journal of clinical and diagnostic research: JCDR*, *11*(3), CC13.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, *60*(4), 389-443.

Pezzoli, G., & Zini, M. (2010). Levodopa in Parkinson's disease: from the past to the future. *Expert opinion on pharmacotherapy*, *11*(4), 627-635.

Pfurtscheller, G. (1997). EEG event-related desynchronization (ERD) and synchronization (ERS). *Electroencephalography and Clinical Neurophysiology*, *1*(103), 26.

Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American geriatrics Society*, *39*(2), 142-148.

Praamstra, P., Jahanshahi, M., & Rothwell, J. C. (2003). Surface recordings in patients with movement disorders and the impact of subcortical surgery. In *The Bereitschaftspotential* (pp. 131-153). Springer, Boston, MA.

Preuss, N., Hasler, G., & Mast, F. W. (2014). Caloric vestibular stimulation modulates affective control and mood. *Brain stimulation*, *7*(1), 133-140.

Price, C. J., & Friston, K. J. (2002). Functional imaging studies of neuropsychological patients: applications and limitations. *Neurocase*, *8*(5), 345-354.

Rajagopalan, A., Jinu, K. V., Sailesh, K. S., Mishra, S., Reddy, U. K., & Mukkadan, J. K. (2017). Understanding the links between vestibular and limbic systems regulating emotions. *Journal of natural science, biology, and medicine*, *8*(1), 11.

Ramachandran, V. S., McGeoch, P. D., & Williams, L. (2007). Can vestibular caloric stimulation be used to treat Dejerine–Roussy Syndrome?. *Medical hypotheses*, *69*(3), 486-488.

Rubens, A. B. (1985). Caloric stimulation and unilateral visual neglect. *Neurology*, *35*(7), 1019-1019.

Russell, N. A., Horii, A., Smith, P. F., Darlington, C. L., & Bilkey, D. K. (2006). Lesions of the vestibular system disrupt hippocampal theta rhythm in the rat. *Journal of neurophysiology*, *96*(1), 4-14.

Russmann, H., Ghika, J., Villemure, J. G., Robert, B., Bogousslavsky, J., Burkhard, P. R., & Vingerhoets, F. J. G. (2004). Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. *Neurology*, *63*(10), 1952-1954.

Samoudi, G., Jivegård, M., Mulavara, A. P., & Bergquist, F. (2015). Effects of stochastic vestibular galvanic stimulation and LDOPA on balance and motor symptoms in patients with Parkinson's disease. *Brain stimulation*, *8*(3), 474-480.

Scanlon, B. K., Levin, B. E., Nation, D. A., Katzen, H. L., Guevara-Salcedo, A., Singer, C., & Papapetropoulos, S. (2013). An accelerometry-based study of lower and upper limb tremor in Parkinson's disease. *Journal of Clinical Neuroscience*, *20*(6), 827-830.

Schmidt, S., Jo, H. G., Wittmann, M., & Hinterberger, T. (2016). 'Catching the waves'–slow cortical potentials as moderator of voluntary action. *Neuroscience & Biobehavioral Reviews*, *68*, 639-650.

Schmidt-Kassow, M., Wilkinson, D., Denby, E., & Ferguson, H. (2016). Synchronised vestibular signals increase the P300 event-related potential elicited by auditory oddballs. *Brain Research*, *1648*, 224-231.

Schrag, A., & Quinn, N. (2000). Dyskinesias and motor fluctuations in Parkinson's disease: A community-based study. *Brain*, *123*(11), 2297-2305.

Schutter, D. J. (2016). Cutaneous retinal activation and neural entrainment in transcranial alternating current stimulation: a systematic review. *Neuroimage*, *140*, 83-88.

Schwab, R. S. (1969). Projection technique for evaluating surgery in Parkinson's disease. In *Third symposium on Parkinson's disease* (pp. 152-157). E&S Livingstone.

Shibasaki, H., Barrett, G., Halliday, E., & Halliday, A. M. (1980). Components of the movement-related cortical potential and their scalp topography. *Electroencephalography and clinical neurophysiology*, *49*(3-4), 213-226.

Shibasaki, H., Barrett, G., Halliday, E., & Halliday, A. M. (1981). Cortical potentials associated with voluntary foot movement in man. *Electroencephalography and clinical neurophysiology*, *52*(6), 507-516.

Shibasaki, H., & Hallett, M. (2006). What is the Bereitschaftspotential?. *Clinical neurophysiology*, *117*(11), 2341-2356.

Shibasaki, H., & Rothwell, J. C. (1999). EMG-EEG correlation. The International Federation of Clinical Neurophysiology. *Electroencephalography and clinical neurophysiology. Supplement*, *52*, 269-274.

Smith, P. F. (1997). Vestibular-hippocampal interactions. *Hippocampus*, *7*(5), 465-471.

Smith, P. F. (2017). The vestibular system and cognition. *Current Opinion in Neurology, 30*(1), 84-89. doi:10.1097/WCO.0000000000000403

Smith, P. F. (2018). Vestibular functions and Parkinson's disease. *Frontiers in neurology*, *9*, 1085.

Smith, P. F., & Zheng, Y. (2013). From ear to uncertainty: Vestibular contributions to cognitive function. *Frontiers in Integrative Neuroscience*, *7*84. doi:10.3389/fnint.2013.00084

Staab, J. P. (2016). Functional and psychiatric vestibular disorders. In *Handbook of clinical neurology* (Vol. 137, pp. 341-351). Elsevier.

Stackman, R. W., Clark, A. S., & Taube, J. S. (2002). Hippocampal spatial representations require vestibular input. *Hippocampus*, *12*(3), 291-303.

Steffen, T., & Seney, M. (2008). Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified Parkinson disease rating scale in people with parkinsonism. *Physical therapy*, *88*(6), 733-746.

Stephan, T., Deutschländer, A., Nolte, A., Schneider, E., Wiesmann, M., Brandt, T., & Dieterich, M. (2005). Functional MRI of galvanic vestibular stimulation with alternating currents at different frequencies. *Neuroimage*, *26*(3), 721-732.

Stiles, L., & Smith, P. F. (2015). The vestibular–basal ganglia connection: Balancing motor control. *Brain research*, *1597*, 180-188.

Straka, H., & Dieringer, N. (2000). Convergence pattern of uncrossed excitatory and inhibitory semicircular canal-specific inputs onto second-order vestibular neurons of frogs. *Experimental brain research*, *135*(4), 462-473.

Taniguchi, S., Peper, F., & Shimokawa, T. (2018). Assessment of leg muscle activity using toe tapping in patients with Parkinson's disease: comparison of two types of toe tapping. *Journal of physical therapy science*, *30*(5), 689-693.

Thanvi, B., Lo, N., & Robinson, T. (2007). Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment. *Postgraduate medical journal*, *83*(980), 384-388.

Titova, N., Jenner, P., & Chaudhuri, K. R. (2017). The future of Parkinson's treatment–personalised and precision medicine. *European Neurological Review*, *12*(1), 15-16.

Toro, C., Deuschl, G., Thatcher, R., Sato, S., Kufta, C., & Hallett, M. (1994). Event-related desynchronization and movement-related cortical potentials on the ECoG and

EEG. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *93*(5), 380-389.

Tran, S., Shafiee, M., Jones, C. B., Garg, S., Lee, S., Pasman, E. P., ... & McKeown, M. J. (2018). Subthreshold stochastic vestibular stimulation induces complex multi-planar effects during standing in Parkinson's disease. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *11*(5), 1180-1182.

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. *Neuropsychologia*, *48*(10), 2789-2810.

Utz, K. S., Korluss, K., Schmidt, L., Rosenthal, A., Oppenländer, K., Keller, I., & Kerkhoff, G. (2011). Minor adverse effects of galvanic vestibular stimulation in persons with stroke and healthy individuals. *Brain Injury*, *25*(11), 1058-1069.

Vanzan, S., Wilkinson, D., Ferguson, H., Pullicino, P., & Sakel, M. (2017). Behavioural improvement in a minimally conscious state after caloric vestibular stimulation: evidence from two single case studies. *Clinical Rehabilitation*, *31*(4), 500-507.

Vercruysse, S., Leunissen, I., Vervoort, G., Vandenberghe, W., Swinnen, S., & Nieuwboer, A. (2015). Microstructural changes in white matter associated with freezing of gait in Parkinson's disease. *Movement Disorders*, *30*(4), 567-576.

Verleger, R. (2012). Alterations of ERP components in neurodegenerative diseases. In *The Oxford handbook of event-related potential components*.

Vitte, E., Derosier, C., Caritu, Y., Berthoz, A., Hasboun, D., & Soulie, D. (1996). Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study. *Experimental brain research*, *112*(3), 523-526.

Vitek, J. L. (2002). Mechanisms of deep brain stimulation: excitation or inhibition. *Movement disorders: official journal of the Movement Disorder Society*, *17*(S3), S69-S72.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(1), 1-16.

Wassermann, E. M., Greenberg, B. D., Nguyen, M. B., & Murphy, D. L. (2001). Motor cortex excitability correlates with an anxiety-related personality trait. *Biological psychiatry*, *50*(5), 377-382.

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J., ... & Pahwa, R. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *Jama*, *301*(1), 63-73.

Wheaton, L. A., Shibasaki, H., & Hallett, M. (2005). Temporal activation pattern of parietal and premotor areas related to praxis movements. *Clinical neurophysiology*, *116*(5), 1201-1212.

Wheaton, L. A., Yakota, S., & Hallett, M. (2005). Posterior parietal negativity preceding self-paced praxis movements. *Experimental brain research*, *163*(4), 535-539.

Wichmann, T., & Dostrovsky, J. O. (2011). Pathological basal ganglia activity in movement disorders. *Neuroscience*, *198*, 232-244.

Wilkinson, D. (2021). Caloric and galvanic vestibular stimulation for the treatment of Parkinson's disease: rationale and prospects. *Expert Review of Medical Devices*, (just-accepted).

Wilkinson, D., Ade, K. K., Rogers, L. L., Attix, D. K., Kuchibhatla, M., Slade, M. D., ... & Hoffer, M. E. (2017). Preventing episodic migraine with caloric vestibular stimulation: a randomized controlled trial. *Headache: The Journal of Head and Face Pain*, *57*(7), 1065-1087.

Wilkinson, D. T., Ferguson, H. J., & Worley, A. (2012). Galvanic vestibular stimulation modulates the electrophysiological response during face processing. *Visual Neuroscience*, *29*(4-5), 255-262.

Wilkinson, D., Ko, P., Kilduff, P., McGlinchey, R., & Milberg, W. (2005). Improvement of a face perception deficit via subsensory galvanic vestibular stimulation. *Journal of the International Neuropsychological Society-JINS*.

Wilkinson, D., Morris, R., Milberg, W., & Sakel, M. (2013). Caloric vestibular stimulation in aphasic syndrome. *Frontiers in integrative neuroscience*, *7*, 99.

Wilkinson, D., Nicholls, S., Pattenden, C., Kilduff, P., & Milberg, W. (2008). Galvanic vestibular stimulation speeds visual memory recall. *Experimental Brain Research*, *189*(2), 243-248. doi:10.1007/s00221-008-1463-0

Wilkinson, D., Podlewska, A., Banducci, S. E., Pellat-Higgins, T., Slade, M., Bodani, M., ... & Ade, K. K. (2019). Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's disease. *Parkinsonism & related disorders*, *65*, 261-266.

Wilkinson, D., Podlewska, A., & Sakel, M. (2016). A durable gain in motor and non-motor symptoms of Parkinson’s disease following repeated caloric vestibular stimulation: a single-case study. *NeuroRehabilitation*, *38*(2), 179-182.

Wilkinson, D., Zubko, O., Sakel, M., Coulton, S., Higgins, T., & Pullicino, P. (2014). Galvanic vestibular stimulation in hemi-spatial neglect. *Frontiers in integrative neuroscience*, *8*, 4.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., ... & Patel, S. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *The Lancet Neurology*, *9*(6), 581-591.

Winter, L., Wollmer, A., Laurens, J., Straumann, D., & Kruger, T. H. (2013). Cox's chair revisited: can spinning alter mood states?. *Frontiers in psychiatry*, *4*, 132.

Wojtecki, L., Timmermann, L., Jörgens, S., Südmeyer, M., Maarouf, M., Treuer, H., ... & Sturm, V. (2006). Frequency-dependent reciprocal modulation of verbal fluency and motor functions in subthalamic deep brain stimulation. *Archives of neurology*, *63*(9), 1273-1276.

Yamamoto, Y., Struzik, Z. R., Soma, R., Ohashi, K., & Kwak, S. (2005). Noisy vestibular stimulation improves autonomic and motor responsiveness in central neurodegenerative disorders. *Annals of neurology*, *58*(2), 175-181.

Zheng, N., Qi, L., Gao, L., & Guan, L. (2012). Generalized MMSD feature extraction using QR decomposition. In *2012 Visual Communications and Image Processing* (pp. 1-5). IEEE.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta psychiatrica scandinavica*, *67*(6), 361-370.

Zink, R., Bucher, S. F., Weiss, A., Brandt, T., & Dieterich, M. (1998). Effects of galvanic vestibular stimulation on otolithic and semicircular canal eye movements and perceived vertical. *Electroencephalography and clinical neurophysiology*, *107*(3), 200-205.

Appendix A

Perception of Stimulation Questionnaire

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*)?

Appendix B

3.4 FINGER TAPPING
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

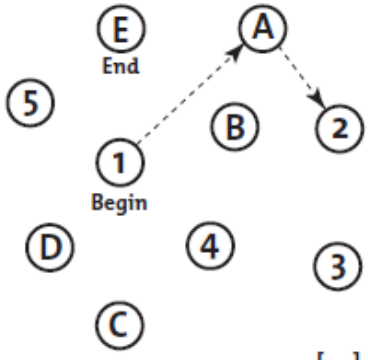
☐ L

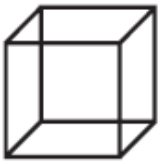
Appendix C

MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE — POINTS





Copy cube

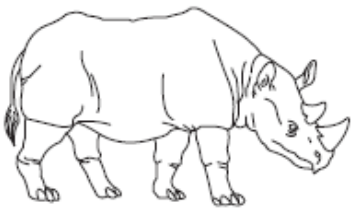
[ ] [ ]

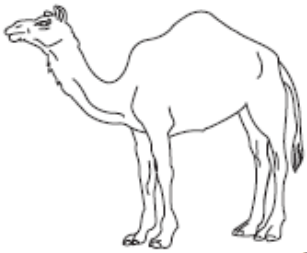
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING





[ ] [ ] [ ]

__/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

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Appendix D

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: ≤ 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].