Effects of Galvanic Vestibular Stimulation on EEG Correlates of Attention

A thesis submitted for the degree of Ph.D. in the Faculty of Social Sciences at the University of Kent

Rachael E. Morris

School of Psychology

University of Kent

October 2018

Abstract

Galvanic Vestibular Stimulation (GVS) is a non-invasive form of neural stimulation that involves applying weak, electric current over the mastoid processes. Brief periods of GVS have been shown to provide transient relief from symptoms of inattention in hemi-spatial neglect and extinction patients. In addition, GVS has been shown to have effects on spatial- and reward-based attention in healthy participants. Despite this growing body of evidence, the underlying mechanisms associated with GVS-induced changes remain largely unknown. Better understanding of the underlying mechanisms of GVS may help to generate more efficient brain stimulation protocols and to direct treatment to those most likely to respond.

Recently, studies have demonstrated that EEG may be a useful tool in investigating underlying changes with GVS. The current thesis therefore measured electrophysiological correlates known to be associated with attention in response to GVS. Chapters 2 and 3 investigated the impact of GVS on two ERP components, the N2pc and the P3, both shown to be associated with mechanisms involved in tasks often impaired in neglect patients. In these two chapters, GVS was shown to impact the N2pc relative to a sham condition. This may indicate that GVS impacted target detection and suppression of irrelevant distractors. In contrast, GVS did not impact the amplitude of the P3 relative to a sham group. Selective modulation of the N2pc, but not the P3 despite the same conditions, suggests a specific mechanism underlying GVS behavioural effects.

Based on literature demonstrating differing efficiency of GVS effects using different waveforms and stimulation intensities, Chapter 4 aimed to investigate maximally effective protocols of GVS on behavioural measures of accuracy and reaction time. This chapter also aimed to extend and resolve discrepancies in the behavioural findings of Chapters 2 and 3. Chapter 4, however, demonstrated no differences between the various conditions. This

indicated that GVS does not impact behavioural measures of accuracy and reaction time in the change-detection paradigm used.

It has been demonstrated behaviourally that GVS can induce lateral shifts of spatial attention. Furthermore, these shifts have been shown to be polarity specific. Chapter 5 investigated these effects using an electrophysiological measure of spatial distribution of attention, steady state visual evoked potentials (SSVEPs). In this chapter GVS was not found to have any effect on SSVEP amplitude either for left-anodal/right-cathodal or right-anodal/left-cathodal GVS. This may indicate that the previously demonstrated effects are task dependent, and/or that GVS does not influence covert attention. Overall, this work provides new insight into underlying electrophysiological mechanisms influenced by GVS. These findings are presented and discussed with relevance to the theoretical and practical implications.

This thesis is dedicated to the memory of Peter John Morris.

My inspiration and biggest supporter.

Acknowledgements

I would like to thank my supervisor Dr Joseph Brooks, not only for his expertise, guidance and knowledge, but also for his kind support and unwavering encouragement throughout my time at Kent. A big thank you also to Dr Markus Bindemann and Professor Heather Ferguson, for their guidance and insight. Also, for their kindness, encouragement and for making time for me. To Professor David Wilkinson, thank you for your guidance and role in enabling me to undertake this PhD. Thank you to the technical team, particularly Frank and John, for all of their expertise and support over the years. Finally, thank you to my family, friends and husband Ben, for their unconditional support, encouragement and patience.

Declaration

I declare that this thesis is my own work carried out under the normal terms of supervision.

……

Rachael Morris

Conference Presentations

The data from Chapters 2 and 3 have been presented at the following conferences:

Morris, R. E., Scrivener, C. L., Brooks, J. L. (2016). *Galvanic Vestibular Stimulation modulates the electrophysiological response during change detection.* Poster presented at the British Association for Cognitive Neuroscience Annual Scientific Meeting, Budapest, Hungary.

Morris, R., Scrivener, C., & Brooks, J.L. (2016). Electrophysiological correlates in healthy individuals of galvanic vestibular stimulation protocols used to treat hemi-spatial neglect. Poster presented at the Annual Meeting of the Vision Sciences Society, St Petersburg, USA.

Morris, R. E., Scrivener, C. L., Brooks, J. L. (2016). *Galvanic Vestibular Stimulation modulates the electrophysiological response during change detection.* Paper presented at the British Psychological Society funded seminar on the vestibular system.

Morris, R. E., Scrivener, C. L., Brooks, J. L. (2015). *Electrophysiological correlates in healthy individuals of galvanic vestibular stimulation protocols used to treat hemi-*

spatial neglect. Poster presented at the British Association for Cognitive Neuroscience Annual Scientific Meeting, Essex, UK.

Morris, R. E., Scrivener, C. L., Brooks, J. L. (2015). *Electrophysiological correlates in healthy individuals of galvanic vestibular stimulation protocols used to treat hemi-spatial neglect.* Poster presented at the joint meeting of the British and Dutch Neuropsychological Societies, London, UK.

Table of Contents

ABSTRACT 2

ACKNOWLEDGEMENTS 4

CHAPTER 1 General Introduction 9

1.1 INTRODUCTION 10

1.2 THE VESTIBULAR SYSTEM 13

1.2.1 Anatomy of the Vestibular System 13

1.2.2 Artificial Stimulation of the Vestibular System 15

1.3 GVS EFFECTS ON ATTENTION AND COGNITIVE PROCESSING 17

1.3.1 Hemi-spatial Neglect 17

1.3.2 Extinction 22

1.3.3 GVS in Healthy Subjects 23

1.4 POTENTIAL THEORIES AND MECHANISMS 24

1.5 EEG MEASURES OF ATTENTION AND COGNITIVE PROCESSING 28

1.5.1 N2pc 28

1.5.2 P3 30

1.5.3 SSVEP 34

1.6 THE STRUCTURE OF THE CURRENT THESIS 37

CHAPTER 2 Does Galvanic Vestibular Stimulation Modulate Electrophysiological Correlates of Attention? 39

2.1 INTRODUCTION 40

2.2 METHOD 45

2.3 RESULTS 51

2.4 DISCUSSION 65

CHAPTER 3 Does Galvanic Vestibular Stimulation Modulate Electrophysiological Correlates of Attention? An Improved Design. 72

3.1 INTRODUCTION 73

3.2 METHOD 76

3.3 RESULTS 81

3.4 DISCUSSION 104

CHAPTER 4 Do "Noisy" GVS Waveforms Alter Performance on a Change-Detection Task? 109

4.1 INTRODUCTION 110

4.2 METHOD 112

4.3 RESULTS 115

4.4 DISCUSSION 118

CHAPTER 5 The Effect of Galvanic Vestibular Stimulation on Steady-State Visual-Evoked Potentials. 123

5.1 INTRODUCTION 124

5.2 METHOD 128

5.3 RESULTS 132

5.4 DISCUSSION 135

CHAPTER 6 Summary, Conclusions and Future Directions. 141

REFERENCES 163

APPENDICES 184

Chapter 1:

General Introduction

1.1 Introduction

Galvanic Vestibular Stimulation (GVS) is a non-invasive form of neural stimulation that involves passing small amounts of electrical current between two electrodes placed over the mastoid processes (e.g., Coats, 1972; Dilda, Macdougall, Curthoys, & Moore, 2012; Utz, Dimova, Oppenländer, & Kerkhoff, 2010; Wilkinson, Zubko, & Sakel, 2009; Wilkinson et al., 2014). Relative to some other forms of brain stimulation, GVS is painless, inexpensive and simple to administer, making it seemingly well suited for use as a therapeutic tool (Utz et al., 2010). In particular, a growing body of evidence has documented the effects of GVS on spatial processing and attention. For instance, a number of studies have shown GVS to be effective in ameliorating symptoms of the attention disorder hemi-spatial neglect (e.g., Rorsman, Magnusson, & Johannson, 1999; Saj, Honore, & Rosseaux, 2006; Utz, Keller, Kardinal, & Kerkhoff, 2011; Wilkinson et al., 2014; Zubko et al., 2013). Moreover, a smaller number of studies have demonstrated effects of GVS on spatial- and reward-based attention in neurologically healthy participants (e.g., Blini, Tilikete, Farne, & Hadj-Bouziane, 2018; Ferrè, Longo, Fiori, & Haggard, 2013; Patel et al., 2015).

Despite the known therapeutic potential of GVS, the specific mechanisms that drive these behavioural changes remain unclear. Investigation into the underlying mechanisms of GVS is important, as a better understanding could help to refine brain stimulation protocols, such as directing treatment to those with deficits that are most likely to respond. In addition, an improved understanding of underlying neural and electrophysiological correlates of GVS might help to resolve some discrepancies that have previously arisen in the literature. For instance, in contrast to the majority of the literature, some studies have also found that GVS was not effective in ameliorating symptoms of hemi-spatial neglect (Ruet, Jokic, Denise, Leroy, & Azouvi, 2014; Volkening, Kerkhoff, & Keller., 2018). Additionally, other research has disputed which types of GVS set-ups are most effective at modulating spatial attention

(Nakamura, Kita, Kojima, Okada, & Shomoto, 2015; Oppenländer et al., 2015; Utz et al., 2011). Previous research has attributed many of these discrepancies to the differing pathologies of the patient samples, however this is speculation. Further investigation into more specific cognitive processes that are and are not improved by GVS could provide some insight into resolving such discrepancies.

Some insight into the effects of GVS on neural activity have been gained through the use of functional imaging techniques such as fMRI (e.g., Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Fink et al., 2003; Lobel, Kleine, Le Bihan, Leroy-Willig, & Berthoz, 1998; Stephan, Hufner, & Brandt, 2009). Responses to vestibular signals have been found across several cortical and subcortical areas, discussed in section 1.4. Although useful, the findings of fMRI investigations are limited in how they can reveal the mechanisms underlying GVS and its effect on cognitive processing. One reason for this is that few studies have incorporated a task into study design. Instead, the neural response to GVS has been recorded while participants lie inactive, thus preventing the ability to view associations between regions of activity and specific aspects of attention processing. In addition, fleeting and spontaneous changes in neural activity may have been masked on account of the limited temporal resolution of fMRI. In an attempt to address these limitations, a smaller number of studies have used electrophysiological recording to view real time changes in electrical activity (e.g., Kim et al., 2013; Lee et al., 2014; Lee, Park, & Yoon, 2016; Schmidt-Kassow, Wilkinson, Denby, & Ferguson, 2016; Wilkinson, Ferguson, & Worley, 2012). In particular, event related potentials (ERPs), a measure of voltage fluctuations time-locked to a stimulus, may provide an ideal tool for measuring underlying mechanisms of GVS, due to their sensitivity in isolating different attentional and other cognitive mechanisms (Lee et al., 2016).

EEG and ERP changes associated with GVS have thus far received limited attention in the literature, but may provide important clues as to the underlying mechanisms of GVS and

aid in refining stimulation protocols to maximise therapeutic and cognitive enhancement benefit. A wealth of ERP components are known to be associated with different aspects of cognitive processing. This thesis therefore aims to investigate changes in underlying electrophysiological correlates of attention during GVS. This chapter will first discuss the vestibular system and vestibular stimulation, before reviewing literature on attention and spatial-perception effects of GVS. Finally, specific electrophysiological measures are introduced that may provide suitable markers for understanding the underlying mechanisms of GVS.

1.2. The Vestibular System

1.2.1 Anatomy of the Vestibular System

The vestibular system, integrated with information from other sensory modalities, is crucial for spatial orientation and balance (Colclasure & Holt, 2004). In the science community, the vestibular system is increasingly becoming recognised as a “sixth sense”, alongside traditional descriptions of sight, audition, smell, touch and taste (Grabherr, Macauda, & Lenggenhager, 2015). Vestibular sensory information has perhaps often been overlooked due to the fact that unlike the traditional five senses, the vestibular system provides no overt or conscious sensation (Day & Fitzpatrick, 2005). Addtionally, while other senses can be stimulated in isolation, stimulation that activates the vestibular system also activates other sensors as well, even with eyes closed (Angelaki, Klier, & Snyder, 2009).

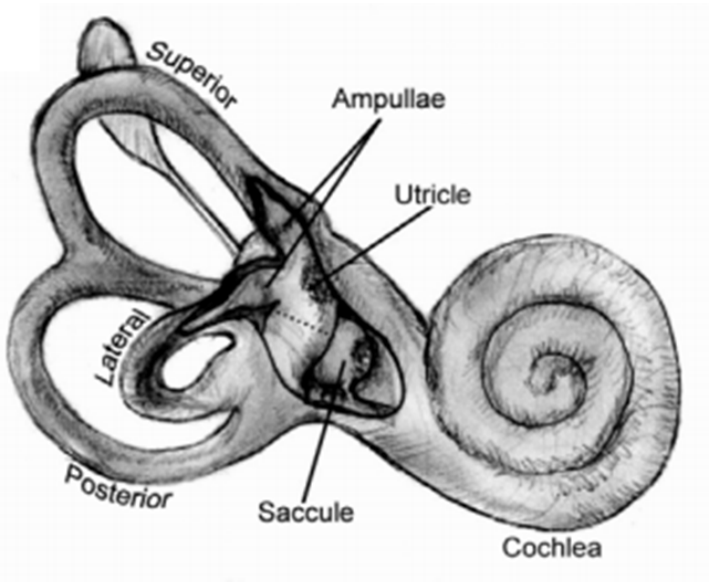

Figure 1.1. Representation of the basic anatomy of the peripheral vestibular system. Image from (Colclasure & Holt, 2004).

The basic anatomy of the peripheral vestibular system is depicted in Figure 1.1. Housed within dense bone in the inner ear, the vestibular system is comprised of two types of motion sensing organ; three tubular-shaped structures known as the semicircular canals, and two

sack-shaped structures known as the vestibule and the saccule (Colclasure & Holt, 2004). The three semicircular canals; superior, posterior and lateral, are positioned to record angular velocity, or rotational head movements, in each spatial plane (Angelaki & Cullen, 2008). Conversely, the two otoliths; the utricle and the saccule, sense linear acceleration, such as forwards and backwards or up and down head movements. The utricle is positioned to detect horizontal acceleration, while the saccule is positioned to detect vertical acceleration (Jamali, Sadeghi, & Cullen, 2008). The vestibular organs within each ear work together to measure head movements in all directions (Highstein & Holstein, 2012).

Small hair cells within the semicircular canals and otoliths transduce mechanical signals into electrical receptor potentials (Colclasure & Holt, 2004). The semicircular canals are filled with fluid known as endolympth, which flows in response to a head rotation, bending the small hair cells. Depending on the direction of movement, this either increases or decreases afferent activity. Similarly, when the head experiences a linear acceleration, the hair cells in the utricle and saccule become bent, transmitting sensory information to the afferent vestibular nerves and ultimately the central nervous system (Highstein & Holstein, 2012). As a phylogenetically ancient system, the vestibular system has developed a sophisticated network of connections and contributions to a number of neural and cognitive functions (Palla & Lenggenhager, 2014). For example, vestibular signals are crucial for control of the vestibulo-ocular reflex, which works to stabilise images on the retina during head movements (e.g., Angelaki, 2004; Angelaki & Hess, 2005; Angelaki et al., 2009). In addition, vestibular input has been shown to affect spatial attention and perception (e.g., Ferrè et al., 2013; Figliozzi, Guariglia, Silvetti, Siegler, & Doricchi, 2005; Patel et al., 2015), reward sensitivity (Blini et al., 2018) and memory (e.g., Smith, Geddes, Baek, Darlington, & Zheng, 2010).

1.2.2 Artificial Stimulation of the Vestibular System

Vestibular contribution to neural and cognitive function has been investigated through artificial stimulation of the vestibular nerves, for example, through motion devices and caloric and galvanic vestibular stimulation. The use of motion as therapeutic intervention has a long history, first documented by ancient Greek physicians as a cure for "madness" (Grabherr et al., 2015). Later, the observation of involuntary eye-movements following motion treatments, now termed nystagmus, fuelled investigation in the vestibular system (Wells, 1757-1817; Purkinje, 1820, as cited in Grabherr et al., 2015). More recently, better controlled motion devices such as rotation chairs, have been used to influence cognitive processes. For example, Figliozzi et al. (2005) demonstrated that rotating participants in a chair shifted covert attention toward the direction of the rotation. Since participants are most often positioned upright, rotation chairs usually activate the lateral semicircular canals. However, by positioning participants in the supine position, or by tilting the chair from the vertical axis, superior and posterior semicircular canals and the otoliths may also be activated (Palla & Lenggenhager, 2014). Though motion devices provide the closest to natural activation of the vestibular system, they cannot be precisely controlled and can cause unpleasant side effects, including disorientation and nystagmus (Palla & Lenggenhager, 2014).

Caloric Vestibular Stimulation (CVS) induces endolymphatic movement in the semicircular canals by applying warm or cool temperatures, usually via water or air, to the external ear canal (e.g., Wilkinson, Morris, Milberg, & Sakel, 2013). Like motion devices, CVS most strongly activates the lateral semicircular canals, but vertical semicircular canals may be activated also by altered positioning of the head (e.g., Palla & Lenggenhager, 2014). The effects of CVS on cognition have also been demonstrated in a number of studies, for example, to ameliorate attention deficits in patients with hemi-spatial neglect (e.g., Karnath &

Dieteric, 2006; Kerkhoff & Schenk, 2012; Moon, Lee, & Na, 2006; Rubens, 1985). While traditional methods of CVS involved irrigation of the external ear canal by injecting ice water, modern methods make use of a headset fixed with a metal probe that sits inside the ear, minimising unpleasant side effects including nausea and vertigo (e.g., Wilkinson et al., 2013).

The technique investigated in the current thesis is Galvanic Vestibular Stimulation (GVS). GVS is a well known technique of stimulating vestibular afferents by applying low intensity electrical current over the mastoid processes (Grabherr et al., 2015). Two electrodes are used, one anode and one cathode with different directional set-ups known to induce different patterns of neural activation (e.g., Fink et al., 2003). Left-anodal/right-cathodal stimulation inhibits the left and excites the right vestibular peripheral organs, decreasing the firing rate of the left vestibular nerve and increasing firing of the right (Fitzpatrick & Day, 2004). Right-anodal/left-cathodal, however, results in the opposite pattern of inhibition and excitation. Such stimulation mimicks a natural head movement towards the anode. Like other forms of vestibular stimulation, GVS has shown to influence various cognitive functions, with spatial attention and perception among them (e.g., Rorsman et al., 1999; Ferrè et al., 2013; Patel et al., 2015).

In terms of research, GVS has some methodological advantages over other forms of vestibular stimulation. For example, GVS can be elegantly controlled for timing and stimulation intensity, and different polarity set-ups can be used to investigate different hemispheric effects (Palla & Lenggenhager, 2014). Additionally, unlike motion devices, GVS can easily be used alongside neuroimaging methods such as fMRI and EEG, making it suitable for investigation of underlying mechanisms. Although similar effects have been demonstrated for CVS and GVS in hemi-spatial neglect (e.g., Kerkhoff & Schenk, 2012), one limitation of CVS from a research standpoint is the current lack of clarity on an appropriate

sham control (Ferrè, Day, Bottini, & Haggard, 2013). Electrical current with GVS on the other hand, can be applied at subsensory levels and therefore compared to a baseline where no stimulation is delivered (e.g., Wilkinson et al., 2014). Importantly, when thinking of use as a therapeutic tool, GVS may have some advantages over other forms of non-invasive neural stimulation. For example, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), work by applying stimulation to more selective brain areas of interest. Conversely, GVS activates a widespread vestibular network by applying stimulation over the mastoids (e.g., Fink et al., 2003). Since then application of GVS may be clearer for patients to administer themselves, it is ideally suited for repetitive, at-home administration.

1.3 GVS Effects on Attention and Cognitive Processing

1.3.1 Hemi-spatial neglect

Much of the evidence for the effects of GVS on attention comes from patients with sustained brain injury, in particular those with hemi-spatial neglect. Hemi-spatial neglect is a disabling attentional disorder most commonly caused by stroke to the right cerebral hemisphere (e.g., Parton, Malhotra, & Husain, 2004). The condition is clinically defined as an inability to attend to or explore stimuli presented on the contralesional side of space, despite intact sensory processing and visual acuity (e.g., Marotta, McKeeff, & Behrmann, 2003). Sufferers of neglect are therefore at frequent risk of collision and falls, significantly impacting on daily living, independence and employment opportunities (e.g., Czernuszenko & Czlonkowska, 2009). Additionally, neglect has been shown to associate with longer hospital stays (Wilkinson, Sakel, Camp, & Hammond, 2012), reduced capability in undertaking daily activities (e.g., Kalra, Perez, Gupta, & Witlink, 1997) and poor overall stroke rehabilitation outcome (e.g., Jehkonen, Loukosalo, & Kettunen, 2006; Katz, Hartman-

Maeir, Ring, & Soroker, 1999). Although estimates of prevalence are difficult in the absence of clear diagnositic criteria, reports suggest that the condition is surprisingly common, affecting around 43% of those with right hemisphere lesions and persisting to chronic stage in 17% of sufferers (e.g., Ringman, Saver, Woolson, Clarke, & Adams, 2004). Given the prevalance of the condition coupled with the severity, it is unsurprising that a number of potential treatments have been investigated, with GVS emerging in acclaim.

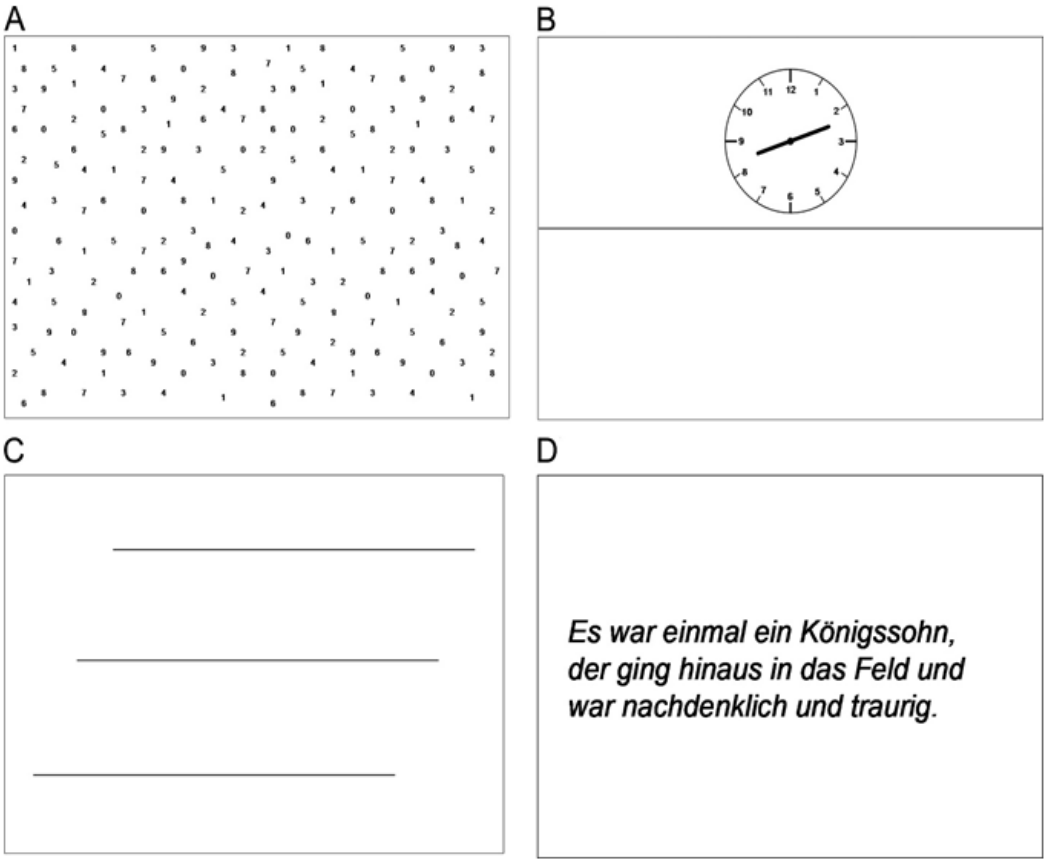

Figure 1.2. Example tests for inattention deficits. A: Cancellation task. B: Symmetrical figure copying. C: Line bisection. D: Text copying. Image from (Oppenländer et al., 2015).

Improvement of visual inattention symptoms with GVS is commonly measured using pencil and paper tasks such as those presented in Figure 1.2 (Oppenländer et al., 2015). Cancellation tasks require participants to cross through all examples of a given target (e.g., lines, stars or letters) in a busy display (Figure 1.2 A). This task provides a measure of egocentric spatial inattention, that is inattention to stimuli that fall on one side of the individual's body (Leyland, Godwin, & Benson, 2017). Rorsman et al. (1999) were the first to demonstrate that sub-sensory threshold GVS delivered online was able to induce transient recovery from neglect-related symptoms during a cancellation task. Importantly for rehabilitation purposes, more recent studies have furthered these findings by demonstrating that left-anodal/right-cathodal GVS is able to improve performance beyond the period of stimulation, remaining four weeks later (Wilkinson et al., 2014; Zubko et al., 2013). Example findings from Zubko et al. (2013) are pictured in Figure 1.3. Evidence for the effectiveness of both left-anodal/right cathodal and right-anodal/left-cathodal GVS in neglect is further strengthened by the demonstration that positive findings remain when compared to a sham group to control for placebo effects (Nakamura et al., 2015; Oppenländer et al., 2015).

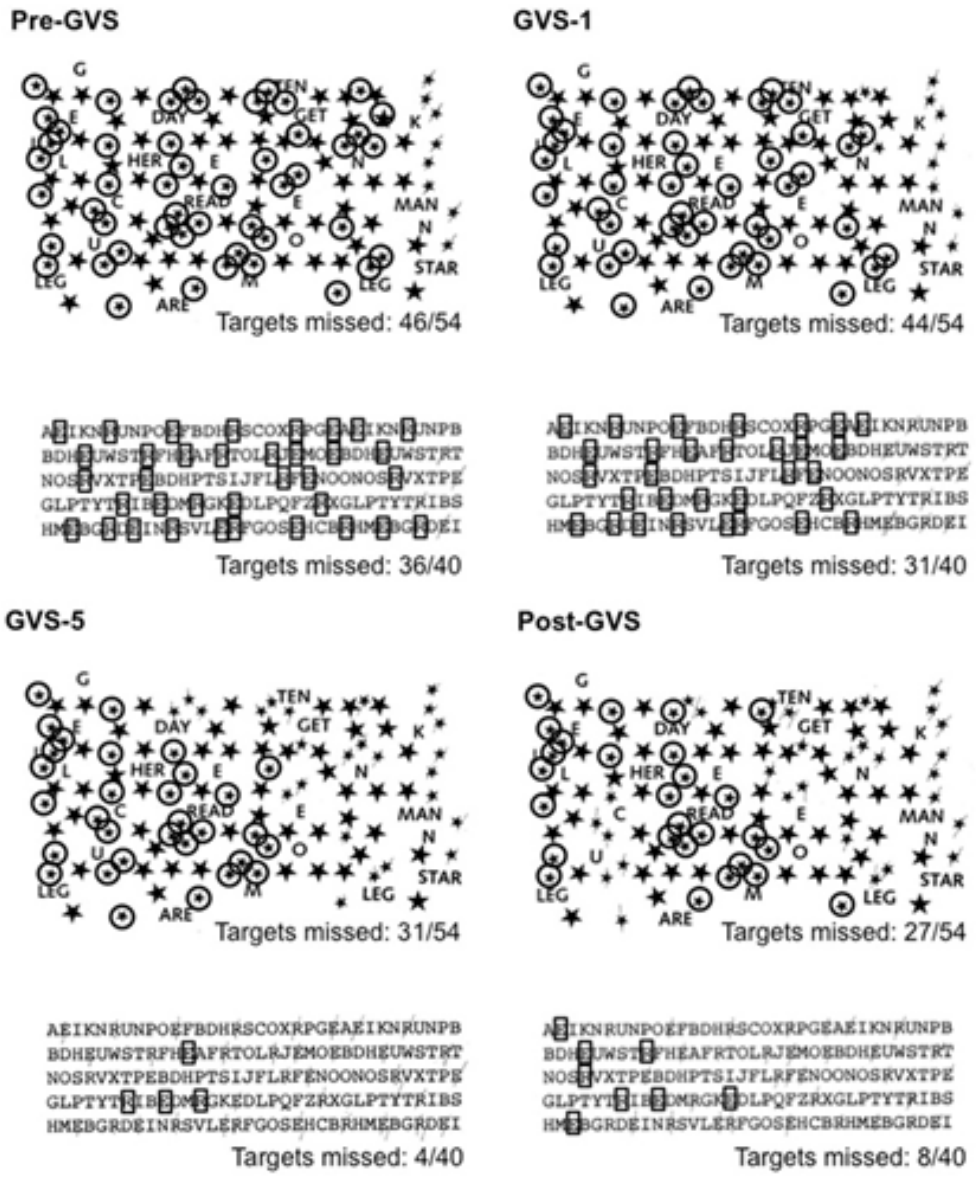

Figure 1.3. Example improvement on cancellation tasks demonstrated in Zubko et al. (2013). "Pre-GVS" shows baseline performance, "GVS-1" shows performance after one GVS session, "GVS-5" shows performance after five GVS sessions and "Post-GVS" shows performance three days later. Circled targets represent those that were missed by the participant.

In addition to cancellation, GVS has been shown to improve symptoms in hemi-spatial neglect in other tasks, including measures of allocentric (object-centred) attention,

such as symmetrical figure copying (Oppenländer et al., 2015; Wilkinson et al., 2014). Figure copying, shown in Figure 1.2B, measures object-centred inattention by comparing errors and ommissions for each hemifield when participants are asked to copy a simple drawing. A further task, line-bisection (see Figure 1.2C), measures both allocentric and egocentric inattention by requiring participants to mark where they believe to be the centre of a horizontal line. Line-bisection can be considered a measure of both allocentric and egocentric inattention since it relies on both the object as a spatial reference frame, but has also been demonstrated to be influenced by its lateral position on the page (e.g., Utz et al., 2011) and is correlated with scores on cancellation tasks (e.g., Reinhart, Wagner, Schulz, Keller, & Kerkhoff, 2013). Lasting improvement in the rightward shift in line-bisection judgements in neglect patients has been demonstrated with both left-anodal/right-cathodal and right-anodal/left-cathodal GVS (Oppenländer et al., 2015; Utz et al., 2011;Wilkinson et al., 2014). Finally, GVS has been shown to improve wider visuospatial deficits in neglect patients. For example, Saj et al. (2006) found that GVS was able to improve distorted verticality perception. Taken together, these findings demonstrate a growing body of evidence that GVS is a safe and effective method of modulating attention and perception.

Two studies however have also contradicted this literature, by failing to demonstrate an improvement with GVS on either line-bisection or cancellation tasks (Ruet et al., 2014; Volkening et al., 2018). Interpretation of the latter findings, with regard to the efficacy of GVS, is complicated since GVS was delivered alongside a standard visual scanning therapy. In addition to this, the author's of Volkening et al. (2018) speculate that high levels of individual variability between neglect patients, for example, encompassing different types and degree of deficit, different lesion sites and various times since injury and its impact on neural plasticity, may explain the lack of improvement in these studies.

Such variability between patient samples has been raised previously to speculate on why different studies have shown different GVS set-ups to be most beneficial. For example, Utz et al. (2011) directly compared the effects of left-anodal and right-anodal GVS on a line bisection task, finding that in keeping with the majority of previous literature, left-anodal was most beneficial. In contrast, Nakamura et al. (2015) found right-anodal, as compared to left-anodal, to be most beneficial in improving performance on a cancellation task. The authors propose this may be due to the fact that most participants in Utz et al. (2011) showed cortical injuries, while patients in their study mostly had sub-cortical injuries to the basal-ganglia, potentially altering the mechanism of effect. It is also important to note that these two studies used different tasks. In a recent study, Oppenländer et al. (2015) demonstrated that the efficacy of different polarity GVS set-ups was task dependent. For example, while left-anodal was most effective for cancellation and figure copying tasks, right-anodal was better for horizontal line bisection. These findings therefore highlight the need for greater clarification on the underlying functions that can be modulated with GVS.

1.3.2 Extinction

A condition related to hemi-spatial neglect is extinction. Extinction is clinically defined as the inability to report stimuli on the contralesional side of space, when it is presented simultaneously with stimuli on the ipsilesional side (e.g., Brozzoli, Demattè, Pavanic, Frassinetti, & Farnè, 2006). Like neglect, this occurs despite intact sensory processing and is therefore attributed to impaired spatial representation and attention (e.g., Barrett, Edmondson-Jones, & Hall, 2010). A smaller number of studies have investigated the effect of GVS on symptoms of extinction. For example, Kerkhoff et al. (2011) and Schmidt et al. (2013) demonstrated that both left-anodal/right-cathodal and right-anodal/left-cathodal GVS induced lasting improvement in symptoms of somatosensory extinction. Although not

visual as is the focus of this thesis, these studies provide further evidence for the impact of GVS on spatial attention and perception.

1.3.3 GVS in Healthy Subjects

Perhaps better clues as to the mechanisms underlying GVS can come from neurologically healthy participants, since without the differing effects of lesion site, plasticity and time since injury, these should provide a more homogenous sample. GVS effects on various cognitive and perceptual processes in healthy participants have been documented in previous literature. Similarly to the studies on neglect and extinction patients, GVS has been shown to affect spatial attention and perception. Moreover, these effects have been shown to be polarity specific. For example, Ferrè et al. (2013) demonstrated that while left-anodal/right-cathodal GVS shifted spatial attention to the left in a line-bisection judgement, right-anodal/left-cathodal stimulation shifted spatial attention to the right. Similar findings come from Patel et al. (2015), who stood participants blind-folded on a sled which moved either to the left or right. The results showed that during left-anodal/right-cathodal GVS, participants significantly over-estimated movements towards the left and under-estimated movements towards the right. However, no differences in spatial movement judgements were detected during right-anodal/left-cathodal stimulation. Like Ferrè et al. (2013), these findings indicate that left-anodal GVS at least, may shift spatial-attention towards the anode.

In a manner similar to neglect patients, GVS has also been shown to affect non-lateral spatial judgements in healthy participants. For example, Mars, Popov, and Vercher (2001) demonstrated that GVS influenced subjective vertical judgements, with judgements more shifted in the direction towards the anode. These findings were replicated by Volkening et al. (2014), with both studies finding effects in both visual and somatosensory modalities, thus complementing the evidence from hemi-spatial neglect patients. More broadly, Blini et al.

(2018) investigated the effect of GVS on reward-based attention in a Posner-style cuing-task, finding that GVS reduced sensitivity to reward. This study however, in contrast to previous studies (e.g., Bucker & Theeuwes, 2014), failed to demonstrate a link between reward and attentional capture and therefore this finding may more likely indicate vestibular links with affective and emotional processing (e.g., Preuss, Hasler, & Mast, 2014a; Preuss, Mast, & Hasler, 2014b), rather than attention *per se*.

In other areas, GVS has been shown to modulate broader cognitive functions. For example, Ferrè, Day, Bottini, & Haggard, (2013) demonstrated that application of left-anodal GVS increased sensitivity to somatosensory stimulation, relative to right-anodal GVS and a sham condition. GVS has also been linked with memory. For example, Lee et al., (2014) demonstrated that GVS reduced error rates in recall of visual stimuli. Similarly, Wilkinson, Nicholls, Pattenden, Kilduff & Milberg, (2008) found GVS to speed visual memory recall. While the primary focus of the current thesis is the effects of GVS on attention, the findings in wider cognitive functions provide further questions on the neural and cognitive mechanisms underlying GVS effects.

1.4 Potential Theories and Mechanisms

The behavioural effects of GVS on cognitive processes as summarised above indicate that vestibular contributions extend beyond simply balance and stability (Bigelow & Agrawal, 2015). Indeed, neuroimaging has demonstrated that vestibular input extends to a number of cortical and subcortical regions, both directly and indirectly (e.g., Bense et al., 2001; Fink et al., 2003; Lobel et al., 1998; Stephan et al., 2009). Unlike other sensory modalities, vestibular stimulation does not project to any primary cortical area. Instead, networks of activations including anterior and posterior parts of the insula, the temporoparietal junction and the inferior parietal lobule, along with the somatosensory and

primary- and pre- motor cortices have been detected (e.g., Bense et al., 2001). These regions may be broadly analogous with the parietoinsular vestibular cortex (PIVC) identified in non-human primates, that has been suggested as a core vestibular cortex (Lopez, Blanke, & Mast, 2012). Subcortically, vestibular input has also been shown to project to a number of regions, including the thalamus, cerebellum and the basal-ganglia (e.g., Bense et al., 2001).

Although imaging of vestibular connections helps provide some information of the underlying mechanisms of GVS, these studies are limited in the extent to which they can inform us of how and what functional role GVS might play in influencing cognition. One reason for this is that many GVS/imaging studies record activity while participants lie inactive, rather than engaging in a cognitive task. An exception to this is Fink et al. (2003), who recorded fMRI while applying GVS to neurologically healthy participants as they completed a variation of the line-bisection task. Since movement is prohibited in the fMRI scanner, participants completed the landmark task, in which lines are already bisected and participants are required to judge which are done so centrally. Although behaviourally GVS did not alter line-bisection judgement as it did in Ferrè et al. (2013), a significant interaction between areas stimulated by GVS and involved in task completion occurred only in the right posterior parietal and ventral premotor cortex. This finding may therefore suggest that activation of these areas with GVS underlies the modulation of allocentric spatial judgements in both healthy (Ferrè et al., 2013) and hemi-spatial neglect participants (Oppenländer et al., 2015; Utz et al., 2011; Wilkinson et al., 2014).

Fink et al's. (2003) study may also shed light on the polarity specific findings of GVS. Fink et al. (2003) demonstrated that while left-anodal/right-cathodal GVS activated vestibular projections predominantly in the right hemisphere, right-anodal/left-cathodal GVS bilaterally activated both hemispheres. Previously, it was discussed that Ferrè et al. (2013) and Patel et al. (2015) found leftward shifts of spatial-attention with left-anodal GVS, and

either rightward shifts (Ferrè et al., 2013) or no effect (Patel et al., 2015) with right-anodal GVS. Taken together, these findings may suggest that underlying lateral shifts of spatial-attention with GVS, is an induced over-activation of spatial-attention networks in the hemisphere opposite to the anode, resulting in contralateral attention bias (Ferrè et al., 2013). Such an explanation is in keeping with findings that lesions to the parietal lobe in either hemisphere causes attention deficits to the contralateral visual field, with the strongest impact occurring with right hemispheric damage (Làdavas, Del Pesce, & Provinciali, 1989).

Although these studies are important in informing theories of potential mechanisms underlying GVS, such findings do not explain non-lateral effects, such as on general figure copying (Wilkinson, Zubko, DeGutis, Milberg, & Potter, 2010) or face processing (Wilkinson, Ko, Kilduff, McGlinchey, & Milberg, 2005). Nor do they explain why different polarity set-ups have been demonstrated to impact different attention tasks differently (e.g., Oppenländer et al., 2015). In addition, vestibular stimulation has been demonstrated to improve representational neglect, in which participants neglect one side of space when asked to describe images from memory (e.g., Geminiani & Bottini, 1992; Rode & Perenin, 1994). One possible explanation for the effects of vestibular stimulation across different cognitive functions is that they are the product of increased general arousal (Schiff and Pulvar, 1999). This seems unlikely however, given the well documented polarity-specific effects of GVS, suggesting a more selective phenomenon (e.g., Fink et al., 2013; Oppenländer et al., 2015). An alternate explanation is that vestibular stimulation might project to specific, but wide-spread, neural areas involved in various cognitive functions (Ferrè et al., 2013; Smith et al., 2010). In patients, Schiff and Pulvar, (1999) demonstrated transient improvement in a range of cognitive deficits in an acute stroke patient, using vestibular stimulation. This lead to speculation that vestibular stimulation may engage a gating mechanism of cortico-cortico processing in thalamic nuclei, which enables reintegration of specific, injured cortical areas.

As yet, whether the effects of vestibular stimulation across different cognitive functions are due to the same or different underlying mechanisms remains unclear (Oppenländer et al., 2015.)

Another approach to studying underlying changes with GVS has been to measure EEG in response to stimulation (e.g., Kim et al., 2013; Lee et al., 2014; Lee et al., 2016; Schmidt-Kassow et al., 2016; Wilkinson et al., 2012). Unlike fMRI, EEG has very good temporal resolution and is therefore ideally suited for measuring fleeting and spontaneous changes in neural activity associated with GVS. Kim et al. (2013) was among the first to monitor EEG in response to GVS, demonstrating that stimulation modulated synchronisation of neural oscillations across theta, alpha, beta and gamma frequency bands. Although the authors relate these findings to neural oscilatory patterns in Parkinsons patients (e.g., Mallet et al., 2008), a condition shown previously to be improved with GVS (e.g., Yamamoto, Struzik, Soma, Ohashi, & Kwak, 2005), this study was conducted on healthy participants and without a task. Such studies therefore prevent more specific inferences to be drawn on the functional role of GVS in cognitive processes.

More broadly, Wilkinson et al. (2012) demonstrated that GVS increased the amplitude of the ERP component N170, known to be associated with face processing. Likewise, increases in the amplitudes of other ERP components have been found with GVS. For example, Schmidt-Kassow et al. (2016) showed that the amplitude of the P3, an ERP component that occurs in response to improbable stimuli, was increased with GVS in an auditory odd-ball paradigm. Lee et al. (2016) also used an odd-ball paradigm but with visual stimuli, where participants were asked to view matched pictures and words (e.g., rose - smell), with mismatched pairs constituting the odd-ball (e.g., sit - saxophone). In this paradigm, Lee et al. (2016) also found an increase in the amplitude of the P3 as well as the N1, an early component evoked in response to visual stimuli. Although these studies do not

allow much speculation on mechanisms underlying attention improvement in hemi-spatial neglect patients, they do demonstrate that EEG is a suitable tool for investigating underlying changes with GVS on attention tasks. In particular, ERPs known to be associated with specific cognitive processes, may provide an ideal measure for investigating a clearer functional role of GVS.

1.5 EEG Measures of Attention and Cognitive Processing

In the following thesis, the impact of GVS was investigated on two ERP components, the N2pc and the P3, along with one measure of neural oscillations, steady-state visual-evoked potentials (SSVEPs). These two main components were chosen based on their associaton with tasks known to be affected by hemi-spatial neglect that have shown to be improved with GVS previously. Some additional EEG measures are discussed where relevant throughout.

1.5.1 N2pc

The N2pc is an ERP component used widely in the visuospatial attention literature. It is assumed to reflect attentional selection of targets in multi-stimulus displays (e.g., Eimer, 1996; Kiss, Van Velzen, & Eimer, 2008; Li, Liu, & Hu, 2017; Luck & Ford, 1998; Mazza, Turatto, & Caramazza, 2009; Mazza, Turatto, Umiltà, & Eimer, 2007; Woodman & Luck, 1999; Woodman & Luck, 2003). The N2pc occurs in visual search and other similar tasks in response to a target presented amongst irrelevant competing distractors, for example, a coloured shape amongst white shapes (see Figure 1.4). “N2” refers to the fact that the N2pc is a negative voltage deflection that occurs at post-stimulus latencies of around 200-350 ms (Kiss et al., 2008). “Pc” relates to the component occurring maximally over posterior electrode sites, in the hemisphere contralateral to the attended target (Brisson & Jolic, 2007). That is, if a target is presented to the left visual field, signal at the contralateral (right)

posterior electrodes will be more negative than the ipsilateral (left) posterior electrodes. N2pc refers to the difference between the ipsilateral and contralateral responses. This is depicted in Figure 1.4.

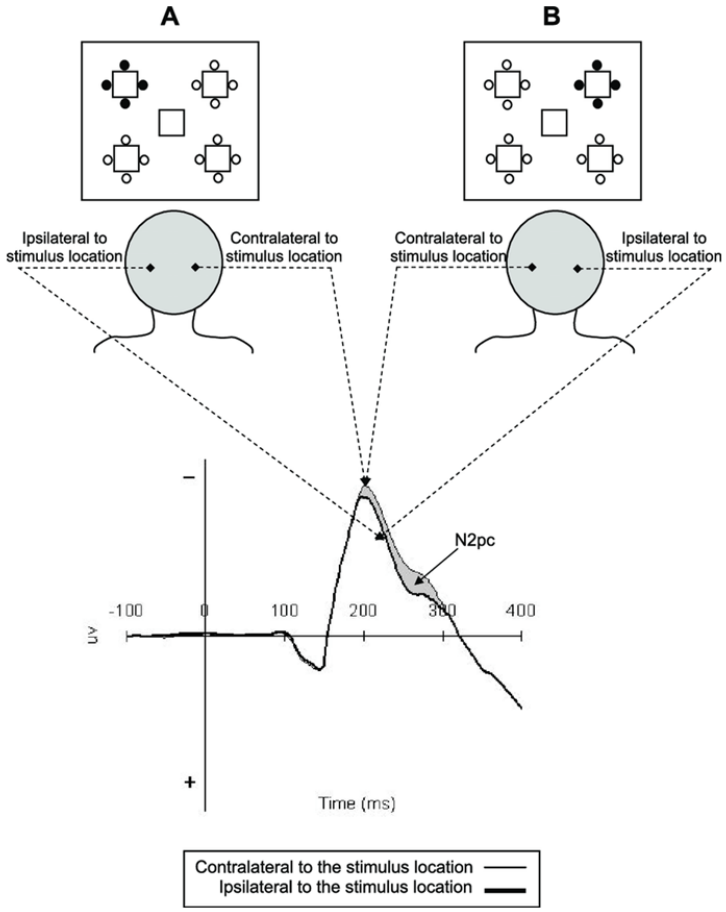

Figure 1.4. Typical timeframe of the N2pc. Diagram A indicates a target (filled in circles) presented to the left visual field. Diagram B indicates a target presented to the right visual field. Image from Lien, Ruthruff, Goodin, and Remington (2008).

The N2pc is of particular interest to studying the underlying mechanisms of GVS since impaired visual search is a hallmark of hemi-spatial neglect (e.g., Fellrath, Blanche-Durbec, Schnider, Jacquemoud, & Ptak, 2012). Typical neglect paper and pencil tasks such as cancellation tasks require the ability to identify targets amongst distractors. In addition, as a lateralised ERP component, the N2pc occurs only in response to targets presented in the left or right visual field and not on the vertical meridian (e.g., Hickey, McDonald, & Theeuwes,

2006) and therefore serves as a marker for spatial deployment of attention. Though it is known that the N2pc occurs in response to target detection among distractors, it is currently unclear whether the specific mechanism reflects the suppression of irrelevant distractor information or enhancement of target-relevant information.

On the one hand, findings that N2pc is absent when no distractors are present (e.g., Luck & Hillyard, 1994), that N2pc amplitude is increased with the addition of more distractors (e.g., Luck, Girelli, McDermott, & Ford, 1997), and that non-targets can elicit an N2pc if a distractor is present that is very similar to the target, have been interpretted as a reflection of the suppression of irrelevant distractors. On the other hand, findings that the N2pc occurs for targets when there is only one distractor present has led others to believe that the ERP component reflects a mechanism sensitive to task-relevant information (e.g., Eimer, 1996; Brisson & Jolic, 2007). In support of this, Hickey et al. (2006) demonstrated that both a target and single distractor in a display elicited an N2pc, but that the more salient, task-irrelavant distractor attracted attention first. These findings therefore indicate that rather than a suppression of distractors, the N2pc reflects a top-down mechanism relating to task-relevant features. An impact of GVS on the amplitude of the N2pc may therefore reflect improved top-down processes in detecting task relevant information or better suppression of irrelevant distractors.

1.5.2 P3

A second ERP component of interest is the P3, first named by Sutton, Braren, Zubin, and John (1965) on account of its positive voltage deflection which peaked at around 300 ms. Since then, it has been acknowledged that the time window of the P3 is much broader, appearing anywhere between 290 and 900 ms (see, e.g., Patel & Azzam, 2005; Polich, 2007). In short, the P3 occurs when a change or update is required in the mental represenation of a

stimulus, for example, in odd-ball and change-detection paradigms (Donchin & Coles, 1988; Polich, 1993; Zhou & Thomas, 2015). Due to the broad time window, it is widely accepted that the P3 can be broken into two sub-components that are distinguishable in latency and topography. The P3a peaks slightly earlier and is maximal over frontal electrode sites (e.g., Jeon & Polich, 2001; Polich, 1988; Polich, 2007). The P3a occurs in response to distinctive, improbable stimuli, regardless of whether the stimulus is relevant to the task (e.g., Katayama & Polich, 1998; Polich 2007). The P3a has therefore been taken to reflect involuntary attention shifts to deviant stimuli (Kok, 2001). In contrast, the P3b peaks at later latencies than the P3a and is mostly concentrated over central and parietal electrodes (e.g., Polich, 1988; Polich, 2007). The P3b is most often interpreted as reflecting updating context or working memory, and it is generally agreed that it occurs later due to it appearing after evaluation of stimuli (e.g., Kok, 2001). Typical timeframe and topography of the P3 are presented in Figure 1.5.

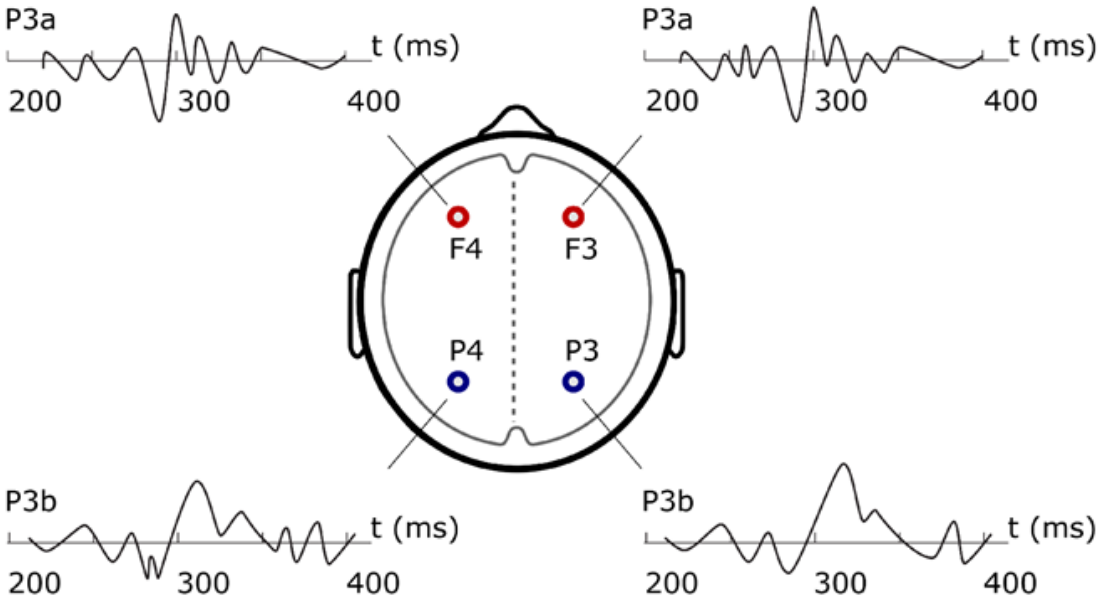

Figure 1.5. Example timeframe and topography of the P3. Top: P3a occurs earlier and over frontal electrode sites. Bottom: P3b occurs later and over central and parietal electrode sites. Image from Monajemi, Jarchi, Ong, and Sanei (2017).

The P3 is of interest in investigating underlying changes with GVS because it has shown to be suppressed in patients with hemispatial neglect (Saevarsson, Kristjánsson, Bach, & Heinrich, 2012). In addition, P3 amplitude has been shown to be increased relative to the amount of attentional resources that are focussed on the target (e.g., Becker & Shapiro, 1980; Wickens, Kramer, Vanasse, & Donchin, 1983). Habituation of the P3 with practice has also been demonstrated, suggesting that less attention is required as the task becomes automated (e.g., Jodo & Inoue, 1990; Polich, 1989). Taken together, these findings demonstrate a clear relationship between the allocation of attentional resources and the P3 (Polich & Kok, 1995). Importantly, the P3 is of interest because it has been shown to be affected by GVS previously. For example, Lee et al. (2016) demonstrated that pulses of GVS impacted P3

amplitude and latency in a visual odd-ball paradigm. Additionally, Schmidt-Kassow et al. (2016) demonstrated that P3 amplitude to auditory odd-ball stimuli was increased when paired with alternating GVS current delivered at the same frequency as the tones being played. Finally, given the links between P3 and working memory, the component is of interest to the current study as GVS has previously been shown to improve accuracy (Lee et al., 2014) and speed (Wilkinson et al., 2012) of visual memory recall, along with improving spatial memory in rats (e.g., Adel Ghahraman et al., 2016). The effect of GVS on the P3, however, has yet to be tested in a task similar to those used with neglect patients.

In this thesis, P3 was elicited during a change detection paradigm, which requires participants to detect a change between two briefly presented stimulus displays. It has been demonstrated previously that P3 amplitudes are greater for detected changes versus undetected changes, which has been interpreted by many to reflect the required update in stimulus representation between the two displays (e.g., Koivisto & Revonsuo, 2003; Kranczioch, Debener, & Engel, 2003; O'Connell, Dockree, & Kelly, 2012; Twomey, Murphy, Kelly, & O'Connell, 2015). However, some previous studies have compared P3 amplitude in unseen trials to trials in which no change occurred, finding a more positive P3 in the latter (Eimer & Mazza, 2005). Based on this finding, it has been concluded that it is unlikely that P3 reflects change detection *per se*. Instead, Eimer and Mazza (2005) asked participants to rate their confidence in their change detection decisions, finding a positive association between confidence reports and P3 amplitude. In support of the interpretation that P3 in change-detection is a reflection of confidence, Bergmann, Schubert, and Hagemann, (2016) demonstrated that the difference in amplitude between detected and undetected changes only occurred in young and not older participants, suggesting against the P3 as a reflection of change detection. Instead, these findings may reflect a decline in confidence with age, though confidence was not explicitly tested in this study. Salti, Bar-Haim, and

Lamy, (2012) have disputed such an assertion, however, by demonstrating the difference in P3 amplitude between detected and undetected changes remains even when confidence is controlled for. Given the unresolved nature of this question at present, an impact on the P3 with GVS in change-detection may reflect an improvement in updating of stimulus representations, or an improvement in confidence in task judgements.

1.5.3 SSVEP

The final electrophysiological measure used in this thesis is that of steady-state visual-evoked potentials (SSVEPs). An SSVEP is a neural oscillatory response triggered by flickering visual stimuli at a constant frequency (e.g., İşcan & Nikulin, 2018). When visual stimuli are flickered, the brain generates neural activity at the same frequency and multiples (harmonics) of this frequency. Fourier transform analysis then allows measurement of the amplitude of the SSVEP (see Figure 1.6). This therefore allows for a measure of neural responses that can be unambiguously associated with a specific external stimulus (Norcia, Appelbaum, Ales, Cottereau, & Rossion, 2015). Example stimuli used to elicit SSVEPs are pictured in Figure 1.7.

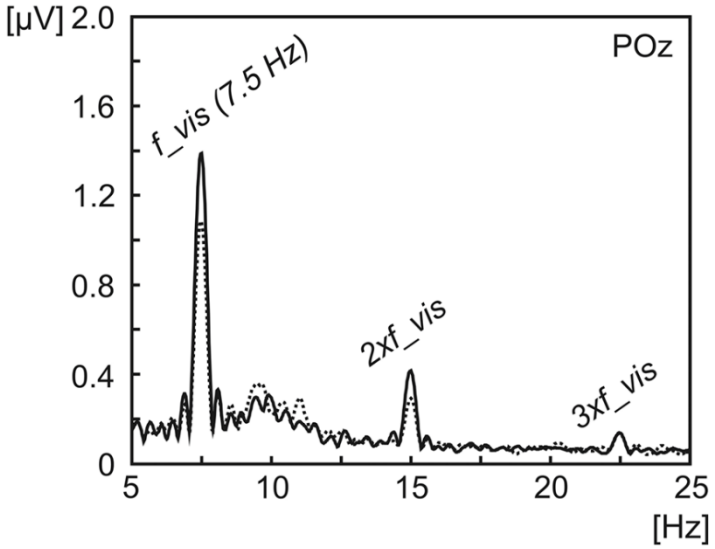

Figure 1.6. Example fourier transform analysis for stimuli flickered at a frequency of 7.5 Hz. Image from Saupe, Schröger, Andersen, and Müller (2009).

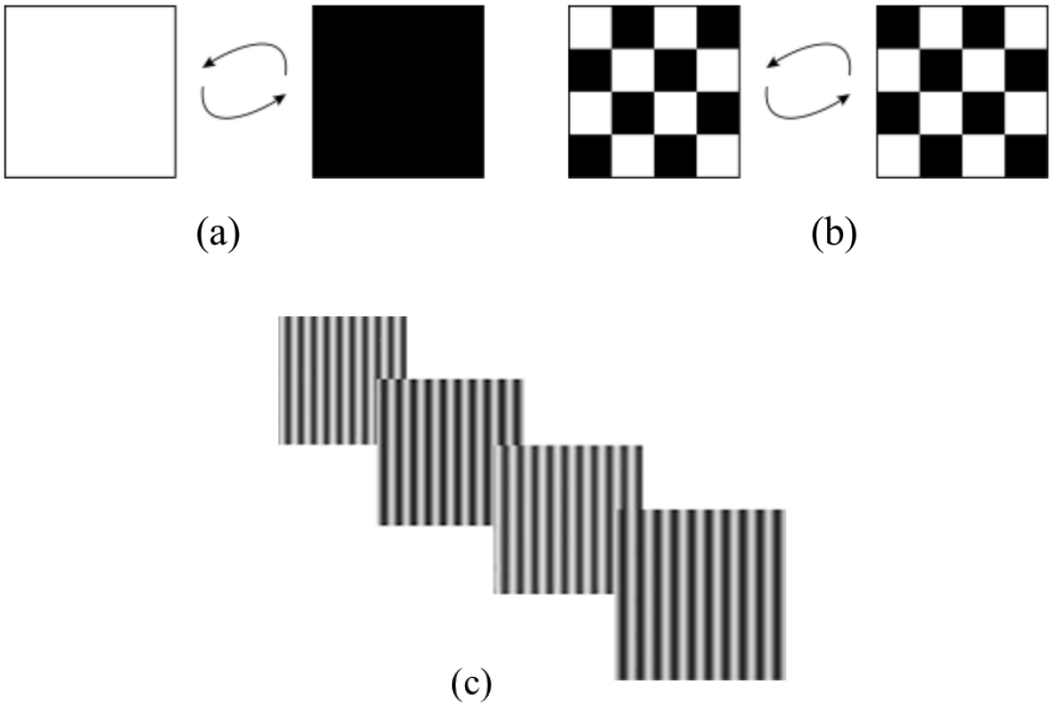

Figure 1.7. Example stimuli used to elicit an SSVEP. A and B from Zerafa, Camilleri, Falzon, and Camilleri (2013) and C from Ales and Norcia (2009).

SSVEPs are used widely in the literature on spatially selective attention (Xie, et al., 2016). Previous literature has demonstrated that the amplitude of the SSVEP is increased when attention is focussed towards the flickering display rather than away from it (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Toffanin et al., 2009). This has led to a technique known as "frequency tagging", which involves simultaneously presenting multiple flickering stimuli at different frequencies and measuring the amplitude of the SSVEP at each frequency as an indicator of selective attention. For example, Morgan et al. (1996) asked participants to respond when they saw the number "5" embedded in a rapid stream of letters. Participants were asked to attend to one of two streams presented simultaneously, whilst ignoring the other. Both streams were presented over the top of a background that was flickered at two different frequencies (see Figure 1.7). The results showed that the amplitude of the SSVEP frequency behind the attended stream was higher than the ignored stream, despite the background not being relevant to the task. Such findings therefore indicate that SSVEPs can be used to measure spatially selective allocation of attention.

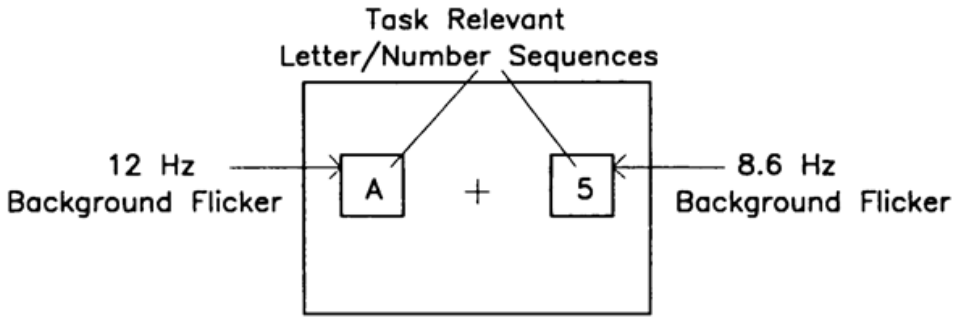

Figure 1.7. Example of "frequency tagging" stimuli used in Morgan et al. (1996).

SSVEPs are of interest to measuring the underlying changes with GVS since it has been shown previously that vestibular stimulation induces lateral shifts of attention. For

example, GVS has shown to ameliorate left inattention in hemi-spatial neglect participants (e.g., Rorsman et al., 1999; Wilkinson et al., 2014.) Polarity-specific effects of spatial attention and perception have also been demonstrated in healthy participants (e.g., Ferrè et al., 2013; Patel et al., 2015). Frequency tagging using SSVEPs may therefore provide an ideal marker for capturing lateral changes in attention with GVS, since any change should be reflected in an increase in amplitude at the relevant frequency.

1.6 The Structure of the Current Thesis

GVS has been shown to improve attention deficits in patients with hemi-spatial negect and extinction (e.g., Kerkhoff et al., 2011; Rormans et al., 1999). The stimulation has also been shown to have effects on attention and spatial perception in healthy participants, amongst other cognitive functions (e.g., Blini et al., 2018; Ferrè et al., 2013; Patel et al., 2015). Despite this, the mechanisms underlying behavioural changes remain unclear. This thesis therefore aims to investigate underlying changes with GVS using electrophysiological measures.

Chapter 2 investigated the effect of GVS on two ERP components, the N2pc and the P3. An increase in N2pc amplitude with GVS may indicate an improvement in detection of target relevant information or better suppression of irrelevant distractors. This component was chosen because of its association to tasks known to be impaired in hemi-spatial neglect participants, such as cancellation tasks, and its widespread use in the attention literature. An increase in P3 amplitude during GVS may indicate an improvement in updating stimulus representations. Thus, this component was chosen in addition since it has been shown to be affected by GVS previously, and is known to be supressed in hemi-spatial neglect patients.

Chapter 3 aimed to replicate and extend the findings of Chapter 2 by making improvements to the original paradigm. In particular, additional sham control conditions were

included to rule out the effects of placebo and the possibility of sensory artifacts of GVS acting as a cue to alert attention. Chapter 4 investigated the effects of higher intensity stimulation and different waveforms of GVS on behavioural improvement. Measures of accuracy using *d'* in Chapters 2 to 4 were calculated as the z-score of the percentage of false alarms subtracted from the z-score of the percentage of hits.

Through Chapters 2 to 4, a change-detection paradigm was used where participants were asked to detect changes between two briefly presented displays of coloured rectangles. This paradigm was chosen as visually similar to and requiring many of the same mechanisms as paper and pencil tasks used with hemi-spatial neglect patients, such as cancellation tasks. While visual search and feature "pop-out" tasks are commonly used to elicit the N2pc, these tasks were too simple for the neurologically healthy participants in this thesis and would have caused ceiling effects, preventing improvement with GVS. More complicated search tasks, such as conjunction searches, present problems with time-locking ERPs to stimulus detection due to inconsistent search patterns across participants and trials. Moreover, it has been suggested that the lack of awareness for visual stimuli in neglect patients is comparable to the lack of awareness in healthy participants in change blindness (Pisella & Mattingley, 2004). Therefore, a change-detection paradigm was used, as this has previously been shown to elicit N2pc and P3 (e.g., Tseng et al., 2012).

Finally, Chapter 5 investigated lateral shifts in attention using SSVEPs. Any changes in spatially selective attention with GVS should be captured by changes in SSVEP amplitude. Although GVS findings in hemi-spatial neglect acted as a motivation for this thesis, the studies here all use neurologically healthy participants. As relatively early studies into the area, testing healthy participants initially allows for a more homogenous sample where electrophysiological changes with GVS can be clearly seen without the confounds of differing pathologies and cognitive abilities.

Chapter 2

Does galvanic vestibular stimulation modulate electrophysiological correlates of attention?

Introduction

Galvanic Vestibular Stimulation (GVS) peripherally stimulates the vestibular nerves by applying small amounts of electrical current over the mastoid processes (e.g., Coats, 1972; Dilda, Macdougall, Curthoys, & Moore, 2012). A growing body of evidence has documented the therapeutic potential of GVS in ameliorating symptoms of a number of cognitive disorders, most prevalently in the attention disorders of hemi-spatial neglect and visual extinction (e.g., Oppenländer et al., 2015; Rorsman, Magnusson, & Johansson, 1999; Schmidt et al., 2013; Zubko, Wilkinson, Langston, & Sakel, 2013; Wilkinson et al., 2014). These studies have demonstrated that even brief periods of stimulation with GVS can provide lasting relief from the attentional bias demonstrated in line bisection and cancellation tasks. In addition, similar findings of GVS induced effects on spatial- and reward-based attention have been demonstrated in healthy participants (e.g., Blini, Tilikete, Farne, & Hadj-Bouziane, 2018; Ferrè, Longo, Fiori, & Haggard, 2013; Patel et al., 2015). Despite these effects, little is known of the mechanisms that underlie the behavioural change. This chapter seeks to address this by investigating the effect of GVS on two ERP components that are important for selective attention, the N2pc and the P3.

Some understanding of the mechanisms underlying GVS have been provided by functional neuroimaging (e.g., Bense, Stephan, Yousry, Brandt & Dieterich, 2001; Lopez, Blanke, & Mast, 2012; Stephan et al., 2005). For example, fMRI investigation has demonstrated an interaction between GVS and mechanisms that underlie visuospatial attention tasks in the right posterior parietal and ventral pre-motor cortex (Fink et al., 2003). In addition, some studies have measured electrophysiological effects of GVS (e.g., Jeong-Woo, Gi-Eun, Ji-Hyang, & Se-Won, 2014; Kim et al., 2013; Lee, Park, & Yoon, 2016; Schmidt-Kassow, Wilkinson, Denby, & Ferguson, 2016; Wilkinson, Ferguson, & Worley, 2012). For example, Kim et al. (2013) monitored neural oscillations in response to GVS,

finding that it was able to induce rhythmic changes and improve neural oscillations known to be maladaptive in patients with Parkinsons. Based on the findings that oscillations were transiently affected immediately following GVS, coupled with demonstrated dose-dependent effects on power, the authors speculated that GVS directly altered firing in projections of the vestibular nerve, and the consequent cortical connections. While these findings demonstrate EEG to be a suitable tool for measuring underlying mechanisms of GVS, to date, little research has looked into the effects on attention-related ERP components while participants are actively engaged in an attention task.

One attention-related ERP component is the N2pc, thought to reflect the spatial deployment of attention and be associated with target detection amongst distractors in visual search (e.g., Eimer, 1996; Tseng et al., 2012; Woodman, Arita, & Luck, 2009). The N2pc is of particular interest in this context, since it is thought to measure mechanisms that are required for completing standard hemi-spatial neglect paper and pencil tasks such as line bisection and cancellation tasks (e.g., Rorsman et al., 1999). The N2pc presents as a negative deflection, appearing in the N2 component time range, typically around 250 ms following stimulus onset. The “pc” refers to the fact that the negativity is seen in posterior electrodes, contralateral to the presented target (e.g., Luck & Hillyard, 1994; Woodman et al., 2009). Given that impairments in visual search and target detection are known to be improved by GVS (e.g., Wilkinson et al., 2014; Zubko et al., 2013), the N2pc provides a plausible attentional marker to view the electrophysiological response underlying these changes in behaviour. An increase in N2pc amplitude following GVS may therefore indicate improved allocation of attention during target detection among distractors.

A second ERP component of interest is the P3. The P3 is a postive voltage deflection that peaks anywhere in a broad time window of approximately 250-900 ms post stimulus, most maximally along midline central and parietal electrodes (e.g., Patel & Azzam, 2005;

Polich, 2007). Although disputed, the P3 is most often interpreted as an indicator of updating context or working memory, appearing in paradigms that require recognition of a change, such as odd-ball and change detection tasks (e.g., Donchin & Coles, 1988; Zhou & Thomas, 2015). The P3 is of interest in investigating the underlying mechanisms of GVS-induced attention changes, since a number of studies have demonstrated that it is modulated by attention (for a review, see e.g., Becker & Shapiro, 1980; Polich & Kok, 1995). In addition, the P3 has been shown to be suppressed in patients with hemi-spatial neglect (Saevarsson, Kristjánsson, Bach, & Heinrich, 2012). In the context of change detection, it has been suggested that greater P3 amplitudes for detected versus undetected changes may reflect updating of stimulus representations (e.g., Koivisto & Revonsuo, 2003; Kranczioch, Debener, & Engel, 2003; O'Connell, Dockree, & Kelly, 2012; Twomey, Murphy, Kelly, & O'Connell, 2015). Others have linked this finding to decision confidence (Bergmann, Schubert, & Hagemann, 2016; Eimer & Mazza, 2005), though this is disputed (Salti, Bar-Haim, & Lamy, 2012). An increase in P3 amplitude with GVS may therefore indicate an improvement in context or working memory updating, or in judgement confidence.

Modulation of the N2pc component has previously been shown using a related form of neural stimulation, transcranial direct current stimulation (tDCS). tDCS involves modulating cortical excitability by applying weak, direct current to a selected area of the scalp (Utz, Dimova, Oppenländer, & Kerkhoff, 2010). In one study, Tseng et al. (2012) applied exitatory tDCS over the right posterior parietal cortex (rPPC) of healthy participants, finding that this improved performance on a change detection task and increased N2pc amplitude in low performing individuals. Similarly, a small number of studies have demonstrated that tDCS is able to increase P3 amplitude, but this has yet to be applied to change detection (e.g., Izzidien, Ramaraju, Roula, & McCarthy, 2016.) Unlike tDCS however, GVS does not rely on placing electrodes over specific brain regions of interest (Utz

et al., 2010.) Instead, GVS activates a widespread vestibular network, reaching different cortical areas by placing electrodes over the mastoids (e.g., Bense et al., 2001; Lopez et al., 2012; Stephan et al., 2005). Returning to the context of neglect rehabilitation, this may be an advantage of GVS, as patients' functional anatomy is often affected by the presence of a lesion (Bolognini, Pascual-Leone, & Fregni, 2009).

With these findings in mind, the current study assessed the ability of GVS to alter the attention-related ERP components N2pc and P3 in healthy individuals. In a similar design to that used in Tseng et al. (2012), a change detection task was used. Such tasks are employed to measure change blindness, which refers to the phenomenon that large changes in a visual scene can be missed when the change occurs simultaneously with a brief distraction (e.g., Schankin, Hagemann, & Wascher, 2009; Simons & Levin, 1997). The main benefit of such a task is that performance is typically poor, and therefore of sufficient difficulty to avoid ceiling effects common in healthy participants. This is important because GVS may be most likely to have effects on performance and physiology when performance is poor or near threshold (e.g., Tseng et al., 2012). Moreover, it has been suggested that the lack of awareness for visual stimuli in neglect patients is comparable to the lack of awareness in healthy participants in change blindness (Pisella & Mattingley, 2004). In both scenarios, obvious visual stimuli are detected by early visual processes, yet the individual remains unaware of a large subset of this information. Therefore, a further benefit of this task is that it may allow for better comparison between GVS effects in the current study with healthy participants to those from previous patient studies.

Previous research has shown that even a few minutes of GVS can induce changes in attention (e.g., Zubko et al., 2013; Wilkinson et al., 2014). As yet, however, the maximally effective protocol is unclear. To date, the maximum stimulation period shown to be safe in one sitting is 30 minutes. Therefore, this stimulation period was chosen to allow for sufficient

trials to measure the effects of GVS, whilst minimising the risk of adverse side effects (Wilkinson, Zubko, & Sakel, 2009). Testing was separated into six, five minute blocks in an effort to prevent participant fatigue and reduce effects of sensory habituation to the stimulation (Balter, et al., 2004). Sub-sensory stimulation was used in a within-participants design to allow comparison with a sham session in which no stimulation was given, to rule out any effects associated with placebo or sensory artifacts of GVS.

Based on previous findings that the N2pc is associated with target detection among distractors (Eimer, 1996; Tseng et al., 2012), it was hypothesised that in the basic paradigm using sham stimulation, N2pc would be larger for targets (i.e., the one changed element between two sequential displays) that were detected as compared to those that were undetected. Likewise, it was expected that previous findings of greater P3 amplitudes for detected versus undetected targets would be replicated in the sham condition (e.g., Eimer & Mazza, 2005; Koivisto & Revonsuo, 2003).

Based on the notion that GVS may improve target detection among distractors, suppression of irrelevant distractors and context updating (Lee et al., 2016; Zubko et al., 2013; Wilkinson et al., 2014; Schmidt-Kassow et al., 2016) it was hypothesised that relative to sham stimulation, GVS would increase the amplitude of the N2pc and the P3. In particular, it was predicted that GVS would have its effect primarily on trials in which observers fail to detect changes to the stimulus displays, as these instances allow room for enhancement of target detection, distractor suppression and engagement of working memory processes. This means that GVS would increase the electrophysiological markers in undetected trials and bring them closer to that observed on detected trials. The N2pc and P3 for seen targets will likely be unaffected by GVS because they will presumably have reached a near-ceiling amplitude.

In order to observe the predicted electrophysiological effect on undetected-target trials, it is critical that detection performance does not change due to GVS. If performance were to change (i.e., GVS caused previously undetected trials to become detected), then this would mean that it would be unlikely to see any effect on undetected trial N2pc and P3 due to the affected trials jumping into the detected category. Any physiological effect would then be subsumed within the detected category which should already have higher amplitude N2pc and P3. Since the primary goal was to observe physiological changes on undetected trials due to GVS, stimulation intensity was kept low with the goal of preserving electrophysiological effects and no associated behavioural changes.

Method

Participants

Seventeen participants were recruited from the University of Kent in return for payment. Two participants were removed from the analysis; one for not completing the study protocol and one for excessively noisy data which, when analysed, N2pc values fell well outside of 2.5 standard deviations from the mean. The remaining sample included five males and ten females, all right handed, with a mean age of 23.7 years (*SD* = 2.8). Participants were screened prior to study enrolment for suitability to receive GVS to ensure that they had no history of vestibular disease or epilepsy. In addition, participants were screened for colour vision deficiency using Ishihara's Tests for Colour-Blindness (Ishihara, 1994). No participants were excluded on the basis of colour vision deficiency, defined as scores of less than 17 (Ishihara, 1994). All participants gave informed consent and the procedures were approved by the University of Kent Psychology Ethics Committee.

Stimuli and Apparatus

Stimuli consisted of displays of rectangles presented in seven easily discriminated colours (red, blue, violet, green, yellow, black and white[1]), which were selected randomly for each trial. Rectangles were sized at 1.81° wide and 2.11° high and were presented on a grey background. A minimum of 4.02° vertical and 6.53° horizontal distance was kept between all rectangles and their distance from fixation ranged from 18.92° horizontally and 11.52° vertically. An invisible 6 x 6 grid was created with visible rectangles for each trial selected randomly. The number of rectangles presented in each display ranged from 6 to 14 and was determined by an individual difficulty titration procedure prior to the main experiment, described below. An equal number of rectangles were presented on the left and on the right side of the screen. On average 4.07 (*SD* = 1.06) rectangles were presented on each side. Stimuli were presented on a 1920 x 1080 BenQXL2420T monitor with a 100Hz refresh rate. The experimental protocol was controlled by PsychoPy (Peirce, 2007).

Procedure

Following GVS and EEG electrode set-up, participants were positioned using a chin rest 57 cm from the screen. A standard change detection task was used in which two identical displays of coloured rectangles, S1 (presented for 200 ms) and S2 (presented for 2200 ms) were displayed, separated by a 900 ms blank screen (see Figure 2.1.) In 75% of trials, one of the rectangles changed colour (target present trials). 50% of the changes were targets presented at a random location on the right side of the screen and 50% were on the left side, ordered randomly. Participants were required to report whether or not they saw a change occur via two-alternative forced-choice keyboard response. To help prevent eye movements, a centrally-located fixation marker was presented for 1000 ms prior to the start of each trial and participants were asked to remain focussed on this area and use peripheral vision to

[1] RGB values and CIE colour space coordinates are given in Appendix A.

detect target changes. The fixation cross of the next trial began upon participant response, or if no response was given, 2200 ms after the onset of S2.

Participants first completed a block of 30 practice trials to ensure understanding of the task. To avoid ceiling effects in performance and make the task sufficiently difficult to elicit a sufficient number of target undetected trials, task difficulty was then adjusted to the individual using a 1-up 2-down staircase procedure as described in Levitt (1970). Thus, two additional distractor rectangles, one on the left and one on the right, were added with each two concurrent correct answers, while one distractor pair was removed with each one incorrect answer. This continued until the number of distractor rectangles had reversed 12 times, with the goal of convergence on a level of performance at approximately 71% correct. The final staircase threshold was decided by taking an average of reversal values. An additional distractor pair was then added with the goal of reducing accuracy to between 60% and 70%. The staircase was only performed during the first session and the number of rectangles presented was the same on both days.

Participants then completed six experimental blocks totalling 426 trials. These comprised of 320 change trials (160 left target and 160 right target) and 106 trials in which no change occurred. Participants completed this protocol twice, once receiving active GVS and once receiving sham stimulation, the order of which was counterbalanced between participants. GVS and sham sessions were administered on separate days, one week apart.

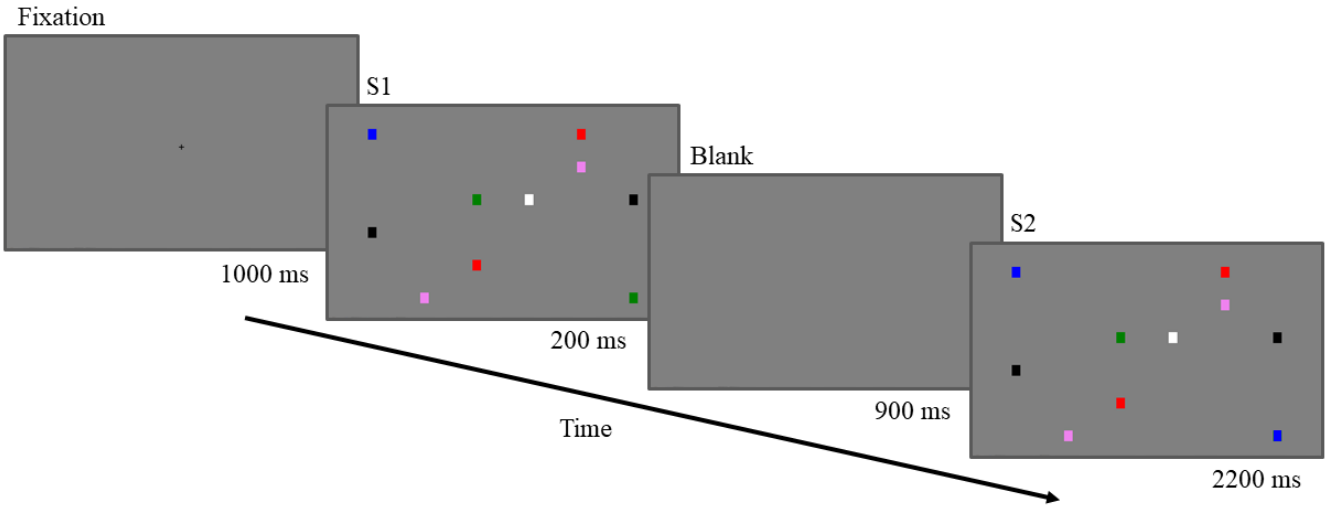

Figure 3.1. Timeline of stimuli presented during a change trial. The target in this example is located in the lower right and changes from green in S1 to blue in S2.

GVS Protocol

To prepare participants for GVS, the skin behind their ears was gently cleansed using an alcohol swab and conductive gel. Carbon-rubber, auto-adhesive electrodes were then placed over the mastoids and connected to a Magstim Eldith Transcranial DC Stimulator Plus^{TM} device. In line with recent GVS studies, bilateral, bipolar stimulation, comprised of left anodal (positive) and right cathodal (negative) was applied (e.g., Wilkinson et al., 2014; Zubko et al., 2013). To allow for the maximum intensity of stimulation to be given whilst minimising sensory artifacts, individual sub-sensory GVS threshholds were determined using a stepwise procedure similar to that described in Schmidt-Kassow et al. (2016). This involved applying .5 mA of stimulation for 15 seconds, with a 60 second fade-in period, and moving up or down in .025 mA increments until participants reported that they no longer felt sensation. At this point, a five minute break was given. After this, the stimulation intensity was tested again to ensure participants reported no sensation. GVS threshholds ranged from

.275 to .450 mA with a mean intensity of .347 mA. Stimulation was turned on at the start of the experimental blocks. During the sham condition, GVS set-up followed the same procedure, the experimenter feigned turning on the stimulation, but electrodes were not switched on during the task. To test if stimulation was sub-sensory, participants were informed following participation that they had only received active stimulation on one of the testing days. They were then required to make a forced-choice decision as to which of the two days this was.

Electrophysiological Recording and Analysis

EEG activity was recorded using Brain Products BrainAmp DC system using active Ag/AgCl electrodes in a standard 64 electrode arrangement (International 10/10 System). FT9 and FT10 were removed and placed at the side of each eye to record horizontal electro-oculogram (EOG). All electrodes were referenced online to FCz, with AFz as the ground. Offline, EEG data was re-referenced to an average reference. Unlike previous research in this area, offline referencing to the mastoids was not possible due to the GVS electrode placement. EEG electrodes overlying the GVS electrodes were removed and not included in the average reference. These were TP7, TP8, TP9, TP10, P7 and P8. During recording, electrodes were sampled at 1000 Hz and impedences kept below 10kΩ. A 250Hz low pass filter was applied at recording to prevent aliasing of higher frequencies.

ERP data analysis was conducted using Brain Vision Analyzer 2.1, and concentrated on trials in which a change target had occurred, therefore trials in which no change target was present were discarded. A bandpass filter was applied at 0.05-70 Hz and a notch filter at 50Hz. EEG activity containing blinks and horizontal eye movements was corrected using a semi-automatic ocular ICA correction. Semi-automatic artifact rejection was run to identify non-ocular artifacts of EEG activity exceeding 75 μV. Artifact rejection coupled with

accuracy (seen or unseen) resulted in greater segment numbers for left sided targets, $F(1, 14) = 72.16$, $p < .001$, $\eta_p^2 = .84$, and an interaction between target side and target detection such that more left targets were seen and more right targets were unseen, $F(1, 14) = 16.84$, $p = .001$, $\eta_p^2 = .55$. There were no other significant differences in segment numbers between other conditions, all Fs < .83 and all ps > .379. Data was segmented into 900 ms epochs from -100 to 800 ms, with zero set at the onset of S2, then baseline-corrected to a 100 ms pre-stimulus interval.

Table 2.1. Segment numbers for each condition.

Condition	Mean Segment Numbers
Sham Left Seen	81.27
Sham Right Seen	65.53
Sham Left Unseen	62.67
Sham Right Unseen	72.53
GVS Left Seen	82.33
GVS Right Seen	67.93
GVS Left Unseen	66.07
GVS Right Unseen	76.27

N2pc. Signal from electrodes PO7 and PO8 was averaged separately for each participant over a time range of 250 to 320 ms (Tseng et al., 2012). ERP waveforms were combined over electrode hemisphere, preserving the target location relative to the electrode location (ipsilateral and contralateral).

P3. Signal from electrodes P3, Pz, P4, C3, Cz, C4, F3, Fz and F4 was averaged separately for each participant, over a time window of 500-700 ms (Eimer & Mazza, 2005).

Results

Electrophysiological Data

N2pc. To test the hypothesis that GVS would affect the N2pc amplitude, data for target-present trials only were analysed using a 2x2x2x2 ANOVA. This included effect of stimulation type (GVS or sham), target detection (target seen or target unseen), target side (left or right) and ipsi/contra (ipsilateral or contralateral). Mean N2pc amplitudes for each condition are presented in Figure 2.2. The full ERP waveforms are presented in Figure 2.3, showing N2pc response to change targets separately for stimulation and target detection conditions. Topography maps are presented in Figure 2.4. As expected, N2pc was significantly larger when targets were seen versus unseen as demonstrated by an ipsi/contra by target detection interaction, $F(1, 14) = 6.01$, $p = .028$, $\eta_p^2 = .30$. There was also a main effect of target detection, $F(1, 14) = 9.48$, $p = .008$, $\eta_p^2 = .40$. Paired-samples *t*-tests comparing ipsi/contra (ipsilateral and contralateral) demonstrated that while seen targets elicited a clear N2pc, $t(14) = 2.33$, $p = .035$ $d = .17$, unseen targets, as expected, did not, $t(14) = .715$, $p = .486$, $d = .07$. This is in line with previous literature demonstrating a significant N2pc only for targets that are seen (e.g., Eimer & Mazza, 2005).

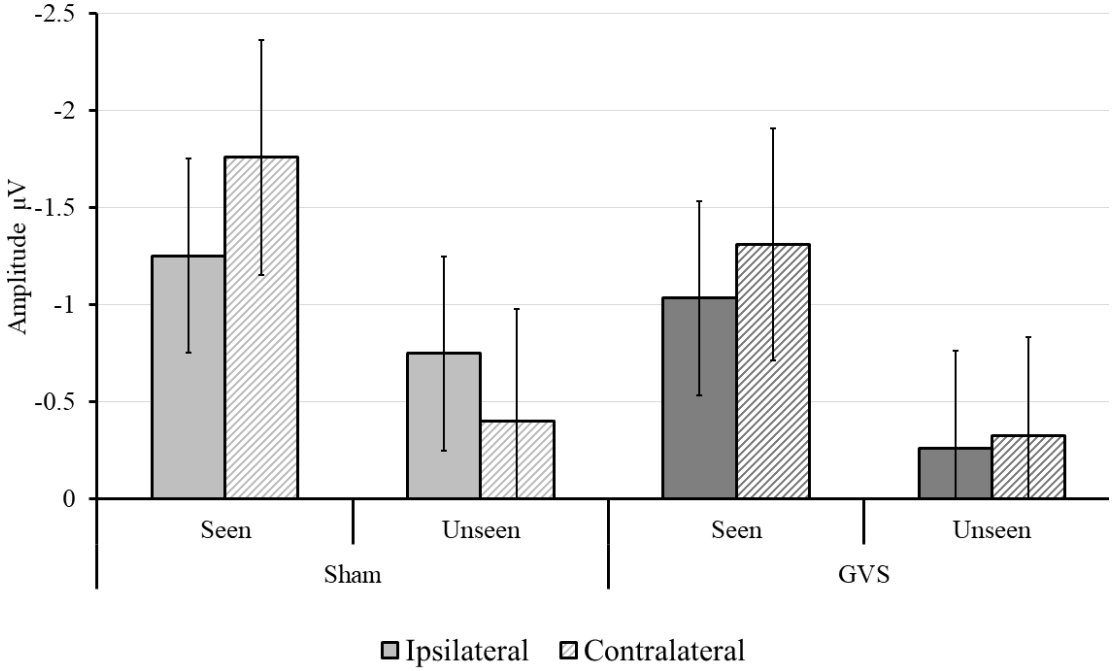

Figure 2.2. Mean amplitude (250-320ms), plotted as a function of stimulation, target detection and electrode. Error bars indicate standard errors

.

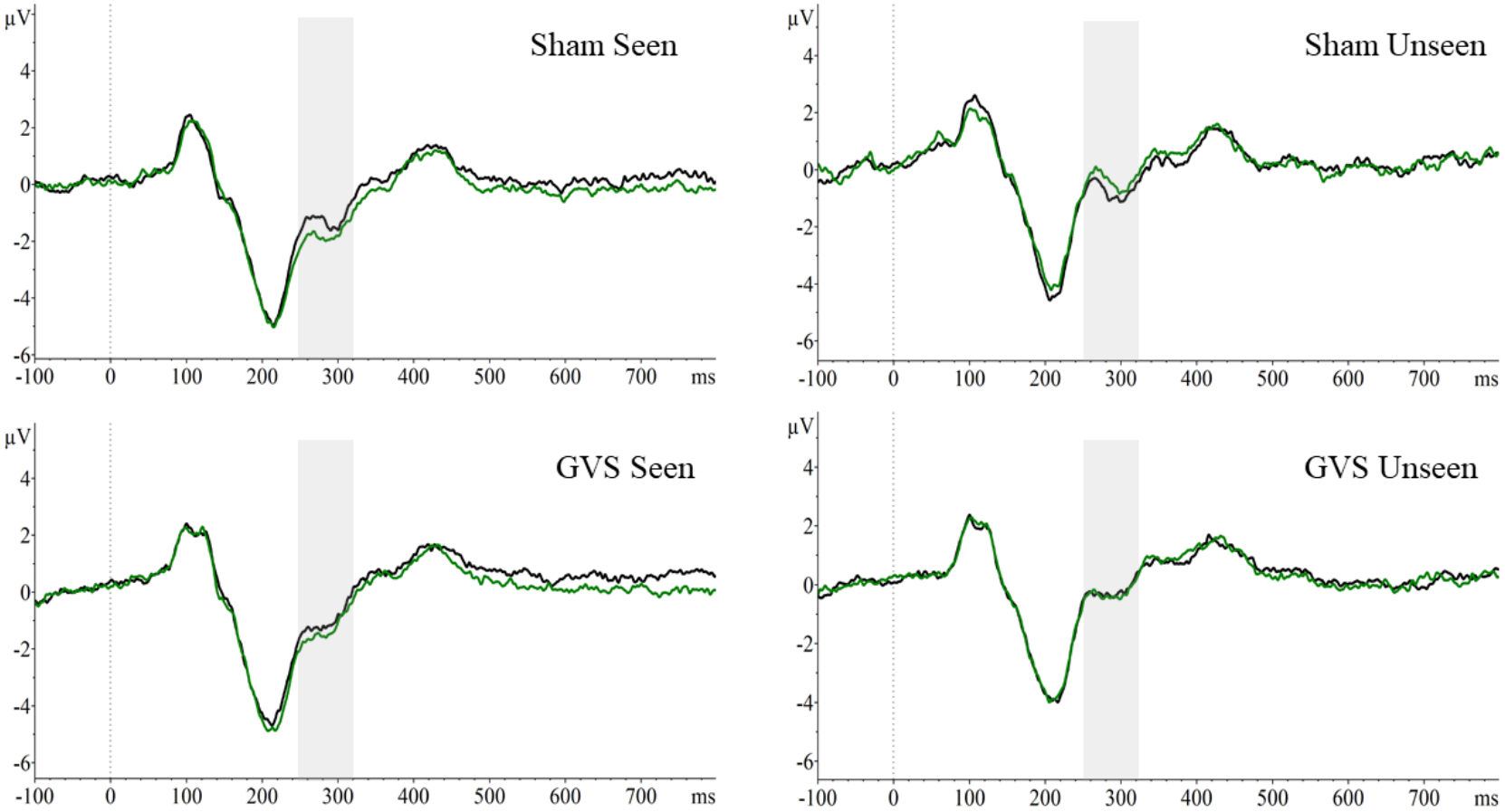

Figure 2.3. Grand averaged ERPs elicited from lateral posterior electrodes (PO7/PO8), with N2pc time window (250-320ms) shaded in grey. Waveforms depict response to seen targets (left), unseen targets (right), and during sham stimulation (top) and during GVS (bottom). Significant N2pcs were elicited only when targets were seen.

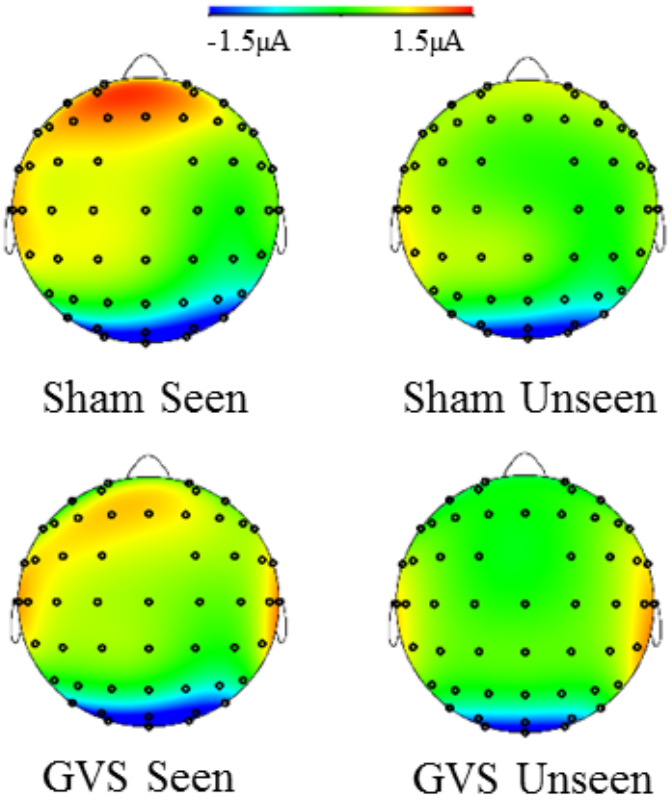

Figure 2.4. Topography maps within the N2pc time window (250-320 ms). Maps depict response to seen targets (left), unseen targets (right), and during sham stimulation (top) and during GVS (bottom).

In partial support of the hypothesis that GVS would affect N2pc amplitude, the interaction between stimulation, target detection and ipsi/contra was approaching significance, $F(1, 14) = 3.90$, $p = .068$, $\eta_p^2 = .22$. Although this effect was marginal, as a predicted effect it was investigated further. Difference scores were computed by calculating the mean differences between ipsilateral and contralateral amplitudes. This data is presented in Figure 2.5. Paired-samples *t*-tests on these difference scores (with alpha corrected at .05 / 4 = .013 for multiple comparisons) first compared amplitude for seen and unseen trials separately for GVS and sham. As expected, it was found that N2pc was larger when targets

were seen versus unseen during sham stimulation, $t(14) = 3.02$, $p < .013$, $d = 1.21$. In contrast, this difference was removed during GVS, $t(14) = .82$, $p = .424$, $d = .25$. Next, GVS and sham amplitudes were compared separately for seen and unseen targets. No difference was found between GVS and sham either for seen targets, $t(14) = 1.20$, $p = .252$, $d = .32$, or unseen targets, $t(14) = 1.84$, $p = .087$, $d = .48$. No other comparisons were significant; all $Fs < .2.19$, all $ps > .161$.

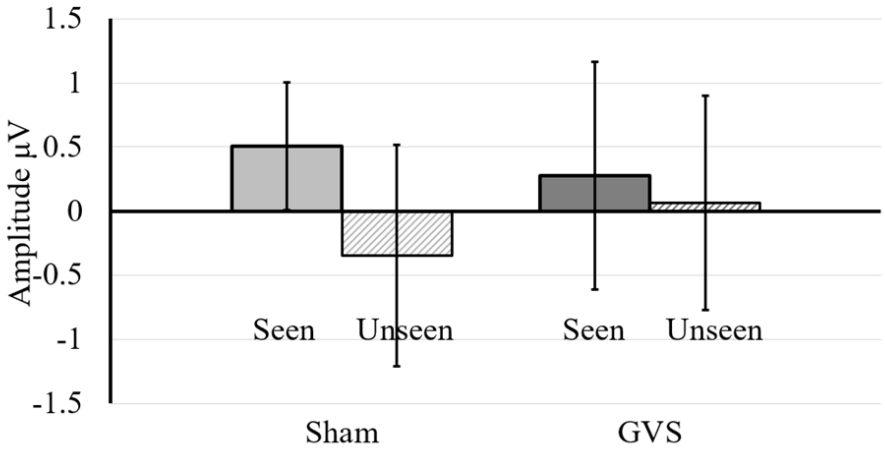

Figure 2.5 Mean N2pc amplitude difference between ipsilateral and contralateral sides, plotted as a function of stimulation type and target detection. Error bars indicate standard errors.

P3. Full ERP waveforms for each condition are presented in Figures 2.6 and 2.7. Mean P3 amplitude, extracted in a time window of 500-700 ms (Eimer & Mazza, 2005), is presented in Figure 2.8. A five-way ANOVA was conducted comparing P3 amplitude between stimulation (GVS or sham), electrode (frontal, central or parietal), electrode laterality (left, midline or right), target detection (seen or unseen) and target side (left or right). As predicted, based on previous findings (Eimer & Mazza, 2005), P3 amplitude was

higher when targets were seen versus unseen, $F(1, 14) = 10.81$, $p = .005$, $\eta_p^2 = .44$. There was also a main effect of electrode, $F(1, 14) = 8.21$, $p = .002$, $\eta_p^2 = .37$, with P3 amplitude maximal over parietal electrodes ($M = 1.88\mu V$), followed by central electrodes ($M = 1.24\mu V$), then frontal electrodes ($M = -1.05\mu V$). Amplitude at frontal electrodes was less positive than at central, $t(14) = 3.60$, $p < .003$, $d = .93$, and parietal electrodes, $t(14) = 2.88$, $p < .012$, $d = .74$, but there was no difference between amplitude at central and parietal electrodes, $t(14) = 1.18$, $p < .256$, $d = .36$. There was also a main effect of target side, $F(1, 14) = 10.33$, $p = .006$, $\eta_p^2 = .43$, with P3 amplitude larger for right-sided targets ($M = .76\mu V$) than left-sided targets ($M = .62\mu V$). There were no other significant main effects, all $Fs < 2.11$, all $ps > .140$.

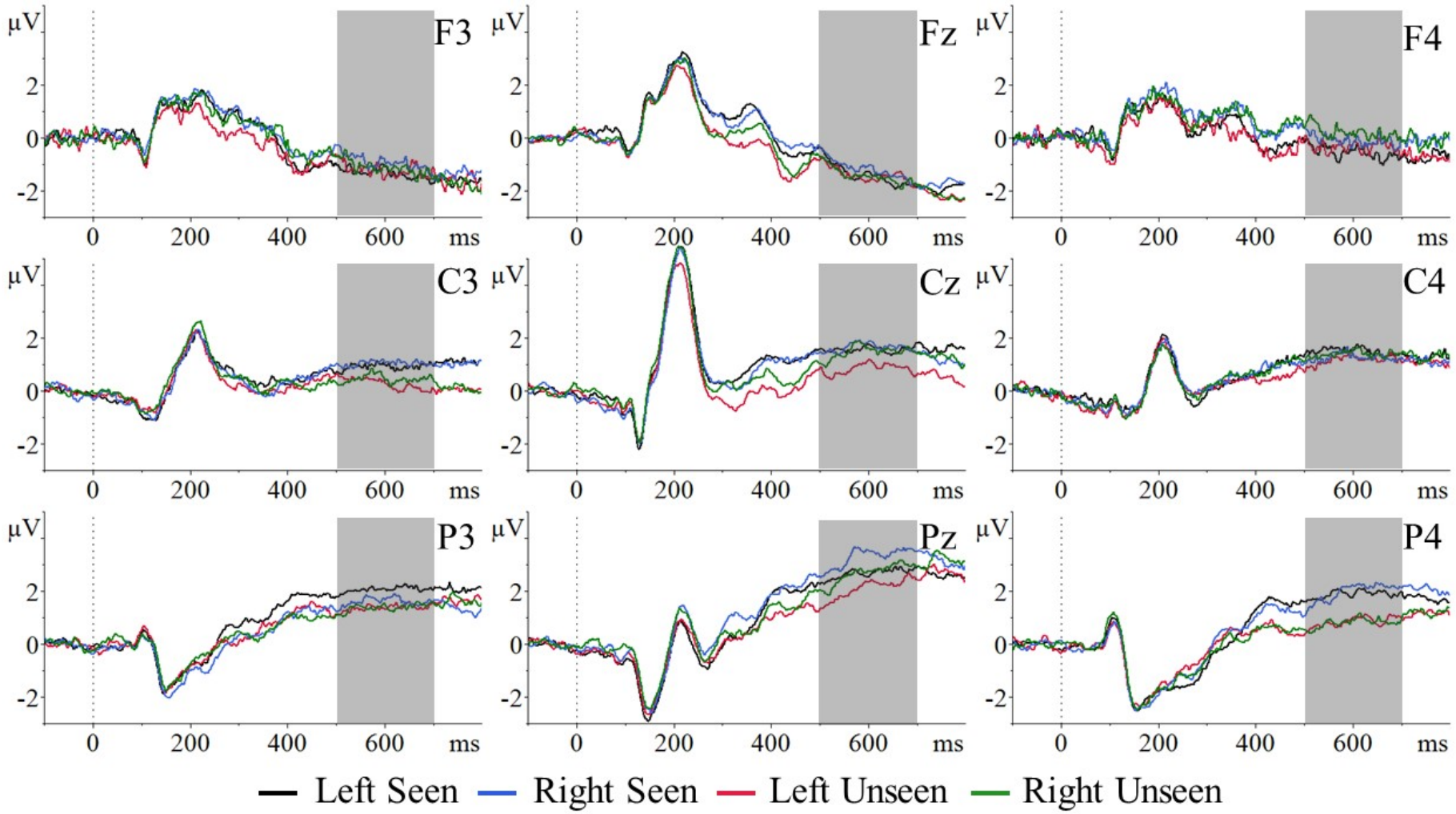

Figure 2.6. Grand average ERPs elicited for each condition during sham stimulation, with the P3 time window (500-700 ms) shaded in grey.

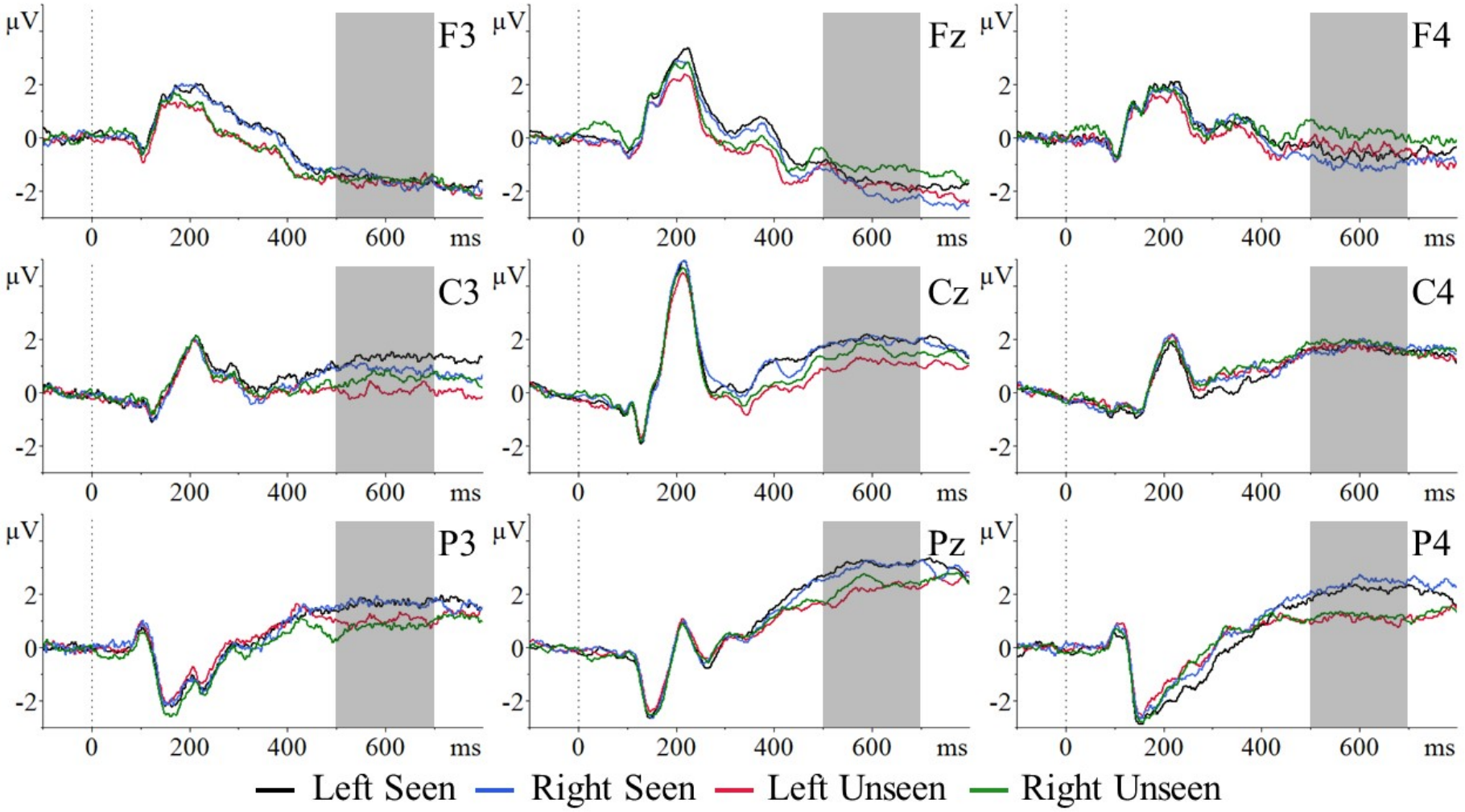

Figure 2.7. Grand average ERPs elicited for each condition during GVS stimulation, with the P3 time window (500-700 ms) shaded in grey.

Figure 2.8. Mean P3 amplitudes plotted as a function of stimulation, target side and target detection. Error bars indicate standard errors.

A marginally significant interaction was found between target side and target detection, $F(1, 14) = 4.60$, $p = .050$, $\eta_p^2 = .247$, presented in Figure 2.9. Paired-samples *t*-tests (with alpha corrected at .05 / 4 = .013 for multiple comparisons) compared left and right targets separately for seen and unseen trials, demonstrating that P3 was higher for right targets than left targets when unseen, $t(14) = 3.18$, $p < .013$, $d = .39$, whereas there was no difference between left and right when targets were seen, $t(14) = .31$, $p = .760$, $d = .03$. In addition, comparisons between seen and unseen trials separately for right and left targets demonstrated that P3 amplitude was higher for seen versus unseen targets only when they appeared on the left, $t(14) = 4.28$, $p < .013$, $d = .70$. There was no difference between seen and unseen when the targets appeared on the right $t(14) = 1.75$, $p = .103$, $d = .33$. Taken together, these findings demonstrate that P3 amplitude was only impacted by target side when the target was not seen.

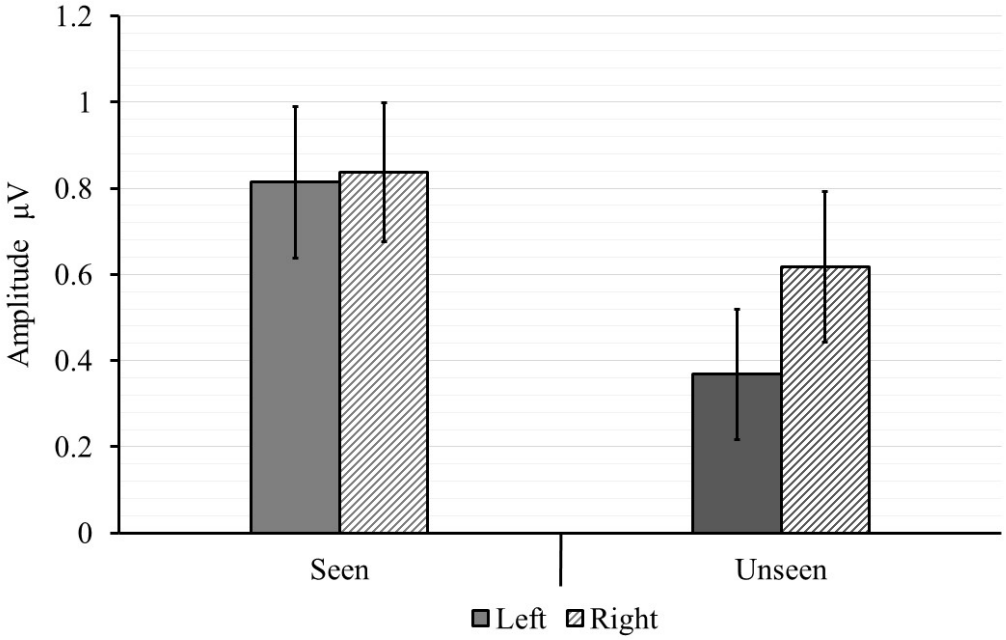

Figure 2.9. Mean P3 amplitude plotted as a function of target side and target detection. Error bars indicate standard error.

A further three interactions confirmed that P3 topography in the current study was consistent with that expected from previous literature (e.g., Patel & Azzam, 2005). Topography maps are presented in Figure 2.10. An electrode by target detection interaction, $F(1, 14) = 4.64$, $p = .018$, $\eta_p^2 = .25$, electrode by laterality interaction, $F(1, 14) = 11.78$, $p < .001$, $\eta_p^2 = .46$, and an electrode by laterality by target detection interaction, $F(1, 14) = 4.60$, $p = .003$, $\eta_p^2 = .25$, demonstrated that condition effects on P3 amplitude were maximal at Pz. To investigate these effects, three ANOVAs were conducted comparing target detection and laterality separately for frontal, central and parietal electrodes. These demonstrated that as expected, P3 amplitude was larger when targets were seen at parietal, $F(1, 14) = 15.00$, $p = .002$, $\eta_p^2 = .52$, and central electrode sites, $F(1, 14) = 8.17$, $p = .013$, $\eta_p^2 = .37$, but not frontal electrode sites, $F(1, 14) = 1.12$, $p = .307$, $\eta_p^2 = .07$. All electrodes sites showed a main effect of laterality, with P3 most positive at the midline parietal electrode sites ($M = 2.66$), $F(1, 14)$

= 6.12, p = .006, η_p^2 = .30, and over the right hemisphere in central (M = 1.51) and frontal electrodes (M = -.318), $F(1, 14) = 5.65$, p = .009, η_p^2 = .29 and $F(1, 14) = 4.98$, p = .014, η_p^2 = .26, respectively. At central electrode sites, P3 was most positive at the midline for seen targets, but most positive in the right hemisphere for unseen targets, as demonstrated by an electrode laterality by target detection interaction, $F(1, 14) = 8.05$, p = .002, η_p^2 = .37. This interaction was not significant at parietal electrodes, $F(1, 14) = 1.43$, p = .256, η_p^2 = .09, or frontal electrodes, $F(1, 14) = 3.31$, p = .051, η_p^2 = .19. No other interactions were significant, all $Fs < 2.20$, all $ps > .081$.

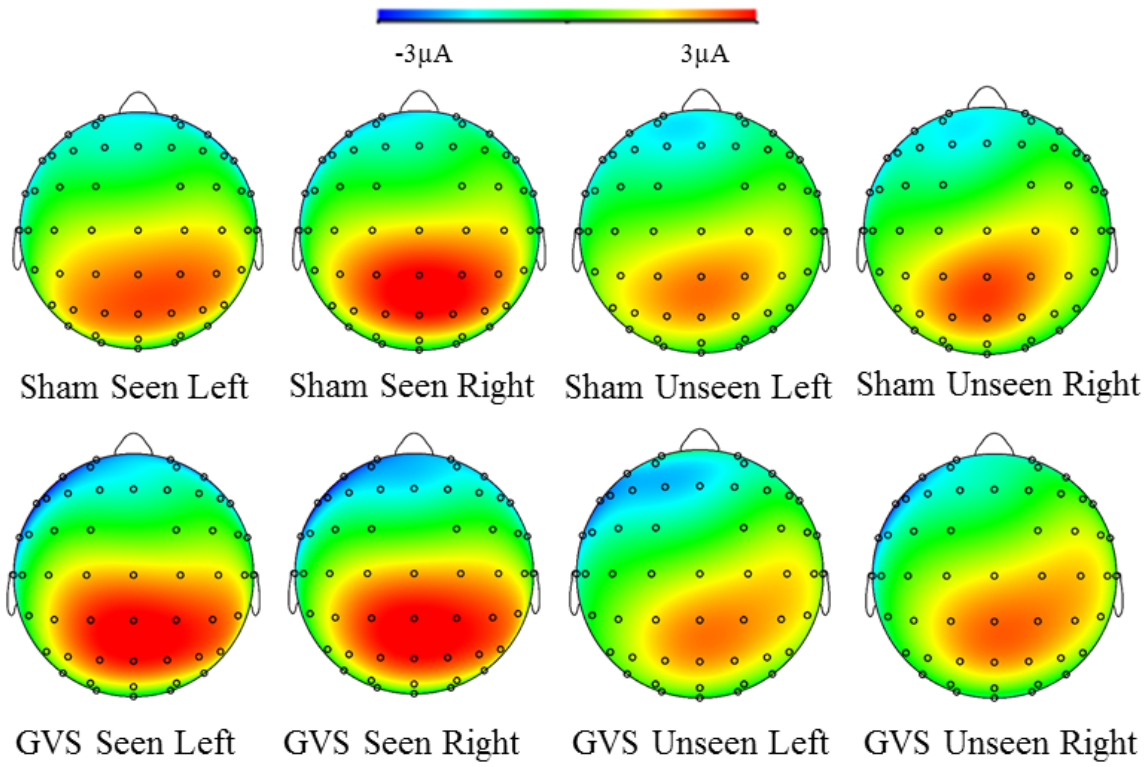

Figure 2.10. Topography maps for each condition within the P3 time window (500-700 ms).

Behavioural Data

Due to a computer error, one participant's behavioural data was unavailable for analysis. The following behavioural data is therefore from the remaining 14 participants.

Overall accuracy was low, with an accuracy of 50% in the sham condition and 49% in the GVS condition. This was lower than the 60% to 70% accuracy aimed for using the individual titration procedure (Levitt, 1970).

d'. Average *d'* scores were computed separately for GVS and sham conditions. These were analysed using a 2x2 ANOVA comparing stimulation (GVS or sham) and target side (left or right). Mean *d'* scores for each condition are depicted in Figure 2.11. Overall, average *d'* scores were 1.00 for GVS (*SD* = .50) and .92 for sham (*SD* = .46). In line with previous literature showing a natural leftward bias in young, healthy participants (Iyilikci, Becker, Gunturkun, & Amado, 2010; Verleger et al., 2010), a main effect of target side was found, $F(1, 13) = 13.70$, $p = .003$, $\eta_p^2 = .51$, with mean *d'* to left targets at 1.06, compared to .86 for right targets. As expected, due to the difficulty of the task and the low stimulation intensity, there were no significant effects of stimulation, all *Fs* < .68, all *ps* > .425.

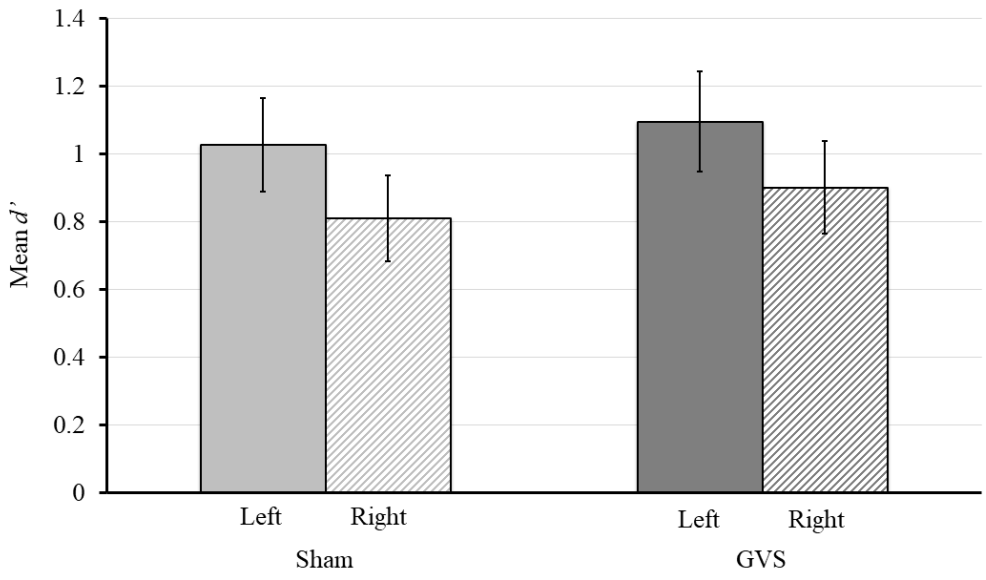

Figure 2.11. Mean d' scores plotted as a function of target side and stimulation type. Error bars indicate standard error.

Reaction Time. Mean reaction times were calculated for target present trials only. These are presented in Figure 2.12. Reaction times were analysed in a 2x2x2 ANOVA comparing stimulation type (GVS or sham), target detection (seen or unseen), and target side (left or right). Similar to the *d*' results, participants were quicker to respond to targets in the left visual field (*M* = .85 s), than in the right visual field (*M* = .87 s), $F(1,13) = 13.59$, $p = .003$, $\eta_p^2 = .51$. This is consistent with previous findings of a natural left visual field advantage in healthy participants (e.g., Iyilikci et al., 2010; Verleger et al., 2010).

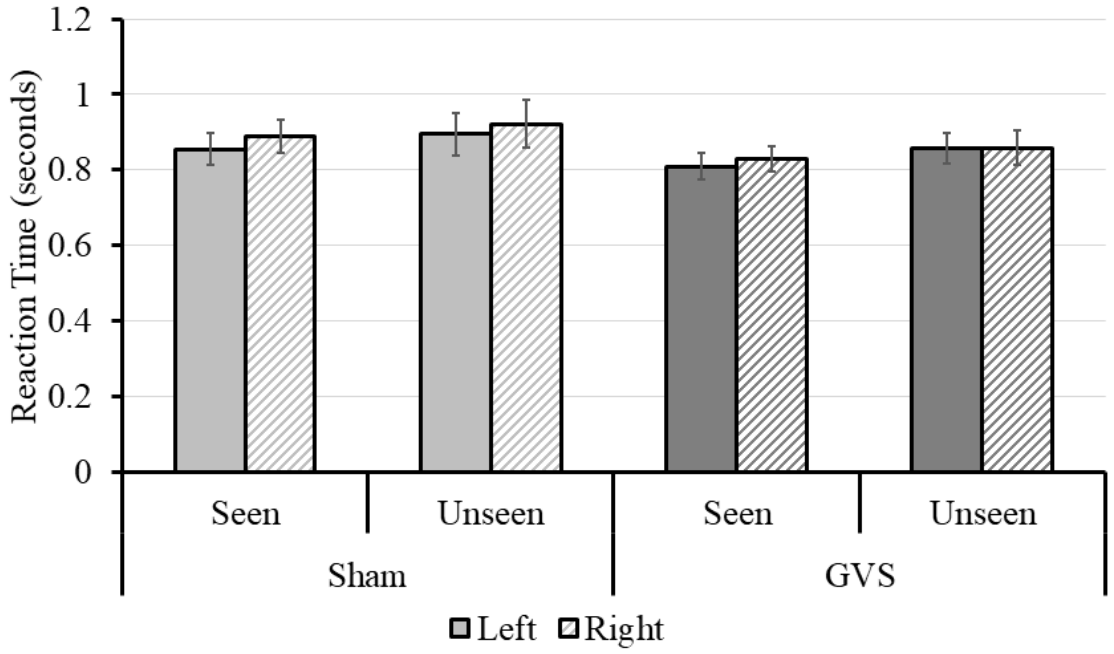

Figure 2.12. Mean reaction times plotted as a function of target detection, target side and stimulation type. Error bars indicate standard error.

Unexpectedly, there was a marginally significant interation between stimulation and target side, $F(1,13) = 4.55$, $p = .052$, $\eta_p^2 = .26$. To investigate this, paired-samples *t*-tests (with alpha corrected at 0.05 / 4 = .013 for multiple comparisons) demonstrated that during sham stimulation, participants were quicker to repond when the targets appeared in the left

visual field compared to the right visual field, $t(13) = 4.92$, $p < .001$, $d = .17$. However, this left-side advantage disappeared during GVS, $t(13) = 1.40$, $p = .184$, $d = .07$. Paired-samples *t*-tests also compared GVS and sham stimulation separately for left and right targets, finding no differences, $t(13) = .85$, $p = .412$, $d = .24$ and $t(13) = 1.29$, $p = .218$, $d = .37$, respectively. Mean reaction times collapsed over target detection are presented in Figure 2.13.

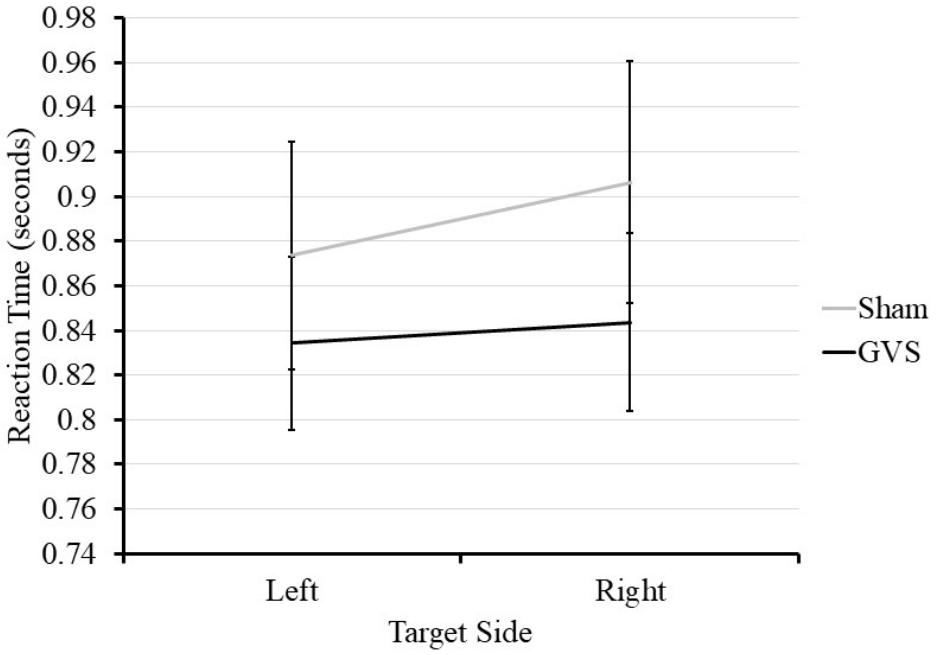

Figure 2.13. Mean reaction times collapsed over target detection.

No other comparisons were significant, all $Fs < 2.78$, $ps > .119$. GVS was well tolerated by all participants, with only minor tingling, itching or heat reported as side effects during the GVS titration procedure. Following testing, all participants reported that they were unable to detect which of the two days they had received active GVS versus sham stimulation. However, 94% of participants were able to correctly identify the day in a forced-choice decision.

Discussion

Galvanic Vestibular Stimulation (GVS) has been shown to affect attention processes, benefitting both healthy participants and sufferers of the attentional disorder hemispatial neglect (e.g., Blini et al., 2018; Ferrè et al., 2013; Patel et al., 2015; Wilkinson et al., 2014; Zubko et al., 2013). Despite this, the underlying mechanisms remain unclear. The goal of this chapter was to investigate the underlying electrophysiological response to GVS during an attention task. Previous research on the brain mechanisms affected by GVS has largely been done without a concurrent task, which makes it difficult to know how GVS modifies the mechanisms involved in a specific task. Here, a change-detection task was conducted while simultaneously delivering GVS and measuring EEG. Based on findings that GVS is able to induce changes in visiospatial attention and improvement in tasks that require target detection among distractors (e.g., Wilkinson et al., 2014; Zubko et al., 2013), it was predicted that relative to a sham condition, GVS would impact the amplitude of the attention-related ERP components N2pc and P3.

The paradigm used in the current study replicated many previously demonstrated electrophysiological correlates of change detection tasks. As in previous literature, N2pc occurred at lateral posterior electrodes and was found to be larger for seen targets than unseen (e.g., Eimer & Mazza, 2005; Tseng et al., 2012). This supports the notion that the N2pc components elicited in this study reflect target detection among distractors. Similarly, P3 amplitude was more positive for seen versus unseen targets, in line with previous literature (e.g., Koivisto & Revonsuo, 2003; O'Connell et al., 2012; Salti et al., 2012). It has been suggested that the P3 in change detection may reflect updating stimulus representations (e.g., Koivisto & Revonsuo, 2003; Kranczioch et al., 2003; Twomey et al., 2015). The finding that P3 was more positive for seen versus unseen targets is therefore in keeping with this interpretation, since detection of a change must be accompanied by a comparison of both

displays of the stimuli. Also in keeping with this interpretation, the topography of the P3 seen in the current study demonstrates a late posterior component in line with the P3b, which, as opposed to the earlier more anterior P3a, has been associated with context updating (e.g., Polich & Criado, 2006). Collectively, these findings indicate that the paradigm employed in this study reliably elicits N2pc and P3 components (even when a non-standard average reference was used due to GVS pad placement), which was an important goal of this first chapter.

Despite these findings, robust effects of GVS were not detected. However, there was marginal support that GVS impacted N2pc amplitude relative to sham stimulation, hinting at a trend in the data. Although not significant, this effect was explored due to the strong *a priori* predictions from previous literature (Tseng et al., 2012). It was originally predicted that effects would occur primarily in targets that were unseen. The rationale for this was the assumption that when targets were seen, N2pc would be at a near ceiling amplitude. Findings to support that GVS primary affected unseen trials to more closely resemble seen trials were mixed. Firstly, N2pc was significantly larger for seen versus unseen trials during sham stimulation, but this difference was removed during GVS. This supports that GVS did indeed impact N2pc, so that unseen and seen targets responses more closely resembled one another. On the other hand, although numerically it is suggested that underlying this effect is an increase in unseen N2pc amplitude, the difference between sham unseen and GVS unseen was not supported statistically.

An increase in N2pc amplitude has previously been shown using a related form of non-invasive neural stimulation (i.e., with tDCS) (Tseng et al., 2012). In contrast to the predictions of the current study, Tseng et al. (2012), found that following application of tDCS to the right posterior parietal cortex, N2pc amplitude increased for target-seen trials but not for target-unseen. There are several differences between Tseng et al, (2012) and the current

study however. Firstly, Tseng et al. (2012) found that the increase in N2pc for seen targets was only present in participants with poor task performance. Theoretically, this is in keeping with the assumption that N2pc may have a ceiling amplitude for seen targets, such that those with the worst task performance were the only ones able to improve. Due to the limited sample, median split into high and low performing participants was not possible in the current study. It was decided for efficiency reasons to have all participants perform poorly rather than split the sample based on performance.

A second possible explanation may relate to the accuracy improvement that Tseng et al. (2012) observed. In this case, some target trials that would have been unseen without stimulation would now be seen with stimulation. These are the very trials that would be expected to have increased in N2pc amplitude due to the stimulation. However, instead of now being categorised as unseen they have shifted categories to 'be seen'. Thus, any increase in N2pc amplitude associated with stimulation would be observed in the seen condition rather than the unseen condition due to trials jumping from across these conditions as a consequence of stimulation-induced behavioural improvement. This rationale suggests that the behavioural improvement found following tDCS in Tseng et al. (2012) may have masked any N2pc changes for the unseen targets and moved it to the seen condition. It was for this reason that it was decided to keep task difficulty high, and stimulation low, to avoid behavioural improvement in the current study, so as to isolate whether GVS had a specific improvement on the unseen trials. In this context, support that GVS impacted amplitude of N2pc mainly for unseen trials only is mixed.

A further hint of an impact of stimulation was seen through a behavioural effect, reflecting a marginal interaction between target side and stimulation for reaction time. Although this effect was non-significant, it was explored due to being very close to significance (p = .052) and due to strong predictions of target side effects of GVS (e.g.,

Wilkinson et al., 2014; Zubko et al., 2013). This effect was such that during sham, participants were significantly quicker to respond to targets presented in the left visual field than the right visual field, in line with a natural leftward bias in healthy participants (e.g., Iyilikci et al., 2010; Verleger et al., 2010). This bias was removed during GVS however, with participants equally quick to respond to targets in either visual field. This appears in contrast to previous findings that rather than suppressing, left-anodal GVS increased the leftward attentional bias in healthy participants and neglect patients in a line-bisection task (Ferrè et al., 2013; Patel et al., 2015; Utz, Keller, Kardinal, & Kerkhoff, 2011). Aside from the obvious additional complexity of the task used in the current study, a key difference between these studies and the current data are that much higher intensity stimulation was used (1mA and 1.5mA as compared with an average of .35mA respectively). It has previously been suggested that the leftward bias induced by higher intensity GVS could be due to overexitation of the right hemisphere, causing imbalance either between or within hemispheres (Ferrè et al., 2013). Therefore it is possible that, as predicted, the low levels of stimulation used in the current study were insufficient to induce this imbalance. The current data however may suggest that low levels of GVS might disrupt mechanisms that contribute to leftward attentional bias.

No effect of stimulation was found on the amplitude of the P3. P3 has been shown to be suppressed in attention disorder hemi-spatial neglect (Saevarsson et al., 2012). In addition, there is previous evidence that P3 amplitude is modulated by GVS in response to auditory (Schmidt-Kassow et al., 2016) and visual stimuli (Lee et al., 2016), which supports the idea that the vestibular system is involved in attention. One possible explanation for the null effect here might be the timing of the P3 in the current data. P3 was extracted from a time window of 500-700 ms (Eimer & Mazza, 2005), which is fairly late in the broad time window that P3 has been known to appear (Patel & Azzam, 2005). Therefore, it might be that P3 in the

current data is reflecting later, post-perceptual mechanisms than those previously shown to be effected by GVS. Another possible explanation might be that with performance at chance, accuracy may have been too low to be affected by the stimulation. In particular, some studies have linked more positive P3 amplitudes with response confidence (Eimer & Mazza, 2005). Since accuracy was around chance even during GVS, it is likely that participant confidence in their responses was low.

A final finding was that despite efforts to ensure participants felt no sensation of GVS, an overwhelming majority were able to detect when they were receiving active versus sham stimulation in a forced-choice decision, despite reporting feeling no sensation. Great care was taken to ensure stimulation was sub-sensory, including using titration protocols previously described to determine individual sensory thresholds (e.g., Schmidt-Kassow et al., 2016). Following participation, subjects continued to report no sensation of the GVS and were unaware that they had received active stimulation on only one of the testing days. In previous studies, this has been taken as evidence of sub-sensory stimulation. In the current study, asking participants to make a forced-choice decision highlighted that this is possibly not the case. This finding has implications for future GVS studies, as well as other types of stimulation, that participant self-report is insufficient to ensure stimulation is sub-sensory.

There are some limitations of the current chapter that may explain some of the non-significant findings. Firstly, accuracy in the current study was very low, which may have prevented sufficient increases in the N2pc and P3 amplitudes to reach significance. Task difficulty was set by adjusting the number of distractors on screen. This was determined by an up-down-staircase procedure, as described by Levitt, (1970). An additional distractor pair was then added with the aim of producing between 60-70% accuracy, to prevent ceiling effects and allow for improvement with GVS. In hindsight, the additional distractor pair reduced control over accuracy, resulting in chance performance. Chapter 3 therefore

addresses this limitation, by making improvements to the staircase procedure. A second potential explanation for the non-significant results is the low intensity stimulation used. Low intensity stimulation was used to ensure that the sensation was subsensory. Previous studies have demonstrated that low level stimulation (< .5 mA) does not elicit objective measures of vestibular response, such as postural sway or eye movements (e.g., Fitzpatrick & Day, 2004; Kim et al., 2013). Despite this, behavioural and EEG changes in response to GVS have been detected at these low intensities (e.g., Kim et al., 2013; Wilkinson et al., 2012). Given these findings, it is therefore unlikely that the non-significant effects were due to low levels of stimulation.

A final potential explanation for non-significant findings is the fact that only left-anodal GVS was used in the current study, which was compared to a sham control group. Some previous literature has demonstrated that the main effects of GVS arise from comparisons of left-anodal and right-anodal stimulation groups, rather than as compared to a sham group (e.g., Ferrè et al., 2013). The comparison of left-anodal GVS versus sham stimulation was chosen for the current study, to replicate protocols used in earlier hemi-spatial neglect patient studies (e.g., Wilkinson et al., 2014; Zubko et al., 2013). Given that the current study used healthy participants however, it is possible that smaller effect sizes in a healthy population prevented significant results when compared only to a sham group (Oppenländer et al., 2015). The comparison of effects of different polarity GVS therefore forms an interesting question, which is investigated further in Chapter 5.

In summary, the data presented demonstrate a change detection paradigm that reliably elicits N2pc and P3 components and can be used in conjuction with Galvanic Vestibular Stimulation. Trends in the data hint that application of GVS might impact N2pc amplitude, removing the difference in response to seen versus unseen trials. In addition, there is tentative evidence that GVS may reduce the leftward attentional bias in reaction time often seen in

healthy participants during visuospatial tasks (e.g., Iyilikci et al., 2010; Verleger et al., 2010). Importantly, the current data has metholodological implications for stimulation studies, providing evidence that protocols that have previously been used to ensure sub-sensory stimulation might not be sufficient.

With these findings in mind, Chapter 3 seeks to improve on the paradigm used here, to investigate whether the GVS effects on N2pc and reaction time can be replicated and extended, and to see whether P3 effects can also be demonstrated. To address the issue that stimulation might not be sub-sensory, a between-participants design was used. To further rule out the possibility that sensing electrical stimulation in general might explain effects, a second sham stimulation condition was also included that placed electrodes on the neck rather than over the mastoids. This meant that there were now three stimulation conditions; left anodal GVS and no stimulation sham as in Chapter 2, and a neck-sham condition that would provide any sensation similar to active GVS, but unlike GVS would not stimulate the vestibular nerves. Finally, to address the issue that larger effects might have been prevented by at-chance performance in the current study, stimuli size was increased to be more in line with those used by Tseng et al. (2012) in an effort to improve overall accuracy. Additionally, improvements were made to the titration procedure used for selecting the number of distractors, also in an effort to improve accuracy.

Chapter 3:

Does galvanic vestibular stimulation modulate electrophysiological correlates of attention? An improved design

Introduction

Chapter 2 investigated the response to (GVS) on two well-known electrophysiological correlates of change detection; the N2pc and the P3. Although significant effects of GVS were not detected on these ERP components, a marginal interaction between stimulation and target detection (p = .068) hinted at the possibility that GVS may impact N2pc amplitude. One possible explanation for this is that GVS improves spatial focus of attention and target detection among distractors, underlying previous findings of improvement on cancellation tasks in attention-impaired participants (e.g., Wilkinson et al., 2014; Zubko et al., 2013). This might be such that N2pc amplitude in response to seen and unseen targets became more similar to one another. Chapter 2 also hinted at an effect of GVS and target side on reaction time, such that while participants were significantly quicker to respond to targets in the left visual field during sham stimulation, in-line with previous findings of a left visual field advantage in healthy participants (e.g., Iyilikci, Becker, Gunturkun, & Amado, 2010; Verleger, Moller, Kuniecki, Smigasiewicz, Groppa, & Siebrier, 2010), participants were equally quick to respond to both left and right visual field targets during GVS. Again however, these effects were not significant and only hint at a trend (p = .052). The current chapter therefore seeks to improve on the paradigm used in Chapter 2, to investigate whether the trends demonstrated can be replicated and extended.

One issue that arose in Chapter 2 was the finding that almost all participants could correctly identify when they received active versus sham stimulation, despite using previously described protocols for determining sub-sensory levels of stimulation (e.g., Schmidt-Kassow, Wilkinson, Denby, & Ferguson, 2016). Where previous studies have taken participant reports of no sensation as evidence for sub-sensory stimulation, Chapter 2 demonstrated that despite reporting no sensation, most participants were able to identify when they were receiving active versus sham stimulation when required to make a forced

choice. This finding has important methodological implications for non-invasive neural stimulation studies, since the placebo effect has been documented in invasive forms of brain stimulation (e.g., Mercado et al., 2006). Based on this finding, the current chapter utilised a between-participants design, with participants receiving only either active or sham stimulation to reduce the possibility that any effects are attributable to placebo.

The design was further enhanced by including an additional sham condition, which further controlled for the effects of placebo. In line with previous GVS literature, Chapter 2 compared left-anodal GVS with a sham condition, in which electrodes were set up in the same way but the stimulation was not switched on during the task (e.g., Wilkinson et al., 2014; Zubko et al., 2013). The current chapter, in addition to the conditions used in Chapter 2, included a third stimulation condition where active left-anodal stimulation was applied, but electrodes were placed on the sides of the neck rather than over the mastoids (e.g., Ferrè, Day, Bottini, & Haggard, 2013; Pavlidou, Ferrè, & Lopez, 2017; Török et al., 2017). This means that participants in the neck sham condition would feel any of the sensory artifacts, such as faint tingling or heat, in the same way that participants in the GVS condition do, but since the electrode placement is away from the mastoids, this should not elicit vestibular effects in the same way as GVS.

The purposes served by this neck sham condition are three-fold. Firstly, if observed effects are attributable to placebo rather than the stimulation of vestibular afferents, by mimicking any sensory effects or general feeling of unusual stimulation occuring, the neck sham condition should produce findings that mirror the GVS condition (Ferrè et al., 2013). Secondly, use of the neck sham allows us to investigate the possibility that sensory artifacts of GVS might act as a cue and alert attention to one side of the body. In Chapter 2, a marginally significant interaction (p = .052) demonstrated that while participants were significantly quicker to respond to targets on the left of the screen in sham, this difference

between target side was removed with GVS. One possible explanation for this is that GVS disrupts mechanisms that contribute to natural, leftward attention bias. Another explanation however is that sensory artifacts of the GVS acted as a cue that alerted attention to the right side of the body, where sensory artifacts are most likely to be felt underneath the cathodal electrode (Ferrè et al., 2013), thus nullifying the natural target side difference. If the latter explanation is correct, then the effect on reaction time should also occur in the neck sham condition. Finally, use of the neck sham allows us to rule out the possibility that GVS simply causes changes in general arousal (Ferrè et al., 2013). Together, inclusion of the neck sham condition allows greater dissociation between general artifacts and effects of electrical stimulation, and helps point to a specific vestibular mechanism.

A final issue that arose in Chapter 2 was very poor performance scores, with accuracy on average of 50%, indicative of high task difficulty. Individual titration procedures, as described in Levitt (1970), were used to set the difficulty by adjusting the number of distractors that appeared on screen during a change detection task. A 1-up 2-down staircase procedure was used with the aim of calculating how many distractors were required to reach an accuracy of 71%. An additional distractor pair was then added, with the goal of achieving between 60% and 70% accuracy. This was to allow for improvement with GVS by preventing floor and ceiling effects. In hindsight, the addition of a further distractor pair following the staircase procedure impeded control over this equating of task difficulty across participants. It is possible that with task difficulty high enough to result in chance performance, that not all trials reported as seen truly reflect target detection and as such, this may have masked changes with GVS in the N2pc and P3 amplitudes. To address these issues, and with the aim of increasing performance scores, the current chapter used the same individual staircase procedure, but did not add the additional distractor pair for the experimental blocks, with the goal of achieving accuracy of 71%. Additionally, the number

of reversals was increased to improve staircase accuracy. Finally, stimuli were adjusted to be more in line with those used in Tseng et al's. (2012) study that demonstrated increased N2pc amplitude with tDCS, by increasing the size of the rectangles so that they are more easily detected.

With these issues addressed, the current study aimed to investigate the ability of GVS to alter the ERP components N2pc and P3. As in Chapter 2, a change detection task was used similar to that described in Tseng et al. (2012). Sub-sensory, left-anodal GVS was compared with a sham condition in which no stimulation occurred, and a sham condition in which left-anodal stimulation was applied to the neck, approximately five centimetres below the usual placement of the GVS electrodes. Left-anodal stimulation was used to be in keeping with previous patient studies (Wilkinson et al., 2014; Zubko et al., 2013). Based on the findings of Chapter 2 and previous literature, it was hypothesised that both N2pc and P3 amplitudes would be larger for targets that were detected versus undetected. Additionally, based on the notion that GVS might improve target detection among distractors, suppression of irrelevant distractors and context updating, it was hypothesised that GVS would impact the amplitude of the N2pc and the P3 relative to both sham stimulation conditions. Finally, based on findings from Chapter 2, it was hypothesised that GVS and target side would impact reaction time, such that while a clear advantage for left visual field targets would occur in the two sham conditions, this would be removed with GVS.

Method

Participants

Sixty participants were recruited from the University of Kent in exchange for course credit. Four participants were excluded for scoring below the cut-off of 17 on the Ishihara Test for Colour-Blindness (Ishihara, 1994). A further three participants were removed due to

incomplete data, and one due to hairstyle causing excessively noisy data. A technical fault prevented the analysis of a further four participants. The final sample consisted of 42 females and 6 males, all right handed, with a mean age of 20.5 years, SD = 5.1. Participants were screened for GVS suitability to ensure no history of vestibular disease or epilepsy. Participants gave informed consent and the study was approved by the University of Kent Psychology Ethics Committee.

Stimuli and Apparatus

As in Chapter 2, a standard change detection task was used where stimuli consisted of displays of rectangles, coloured randomly in red, blue, violent, green, yellow, black and white, (see figure 3.1). Rectangles were larger than that used in Chapter 2, sized at 2.2° high and 2.01° wide. Rectangles were positioned in an invisible 6 x 6 grid with visible rectangles selected randomly for each trial. There was a minimum of 3.01° horizontal and 1.01° vertical distance kept between all rectangles. The distance from fixation ranged from 11.92° horizontally and 6.43° vertically. As in Chapter 2, the number of rectangles was decided by an individual titration procedure, described below, to equate task difficulty across participants. The number of rectangles used ranged between 4 and 12, with an average of 7.29, *SD* = 2.14. An equal number of rectangles were presented on the left and right side of the screen. Stimuli were presented on a 1920x1080 BenQXL2420T monitor with a 100Hz refresh rate. The experimental protocol was controlled by PsychoPy (Peirce, 2007).

Procedure

First, GVS and EEG electrodes were set up as described below. Participants were then seated and positioned in a chin rest 57 cm from the screen. Aside from the changes to stimuli size, the task was identical to that used in Chapter 2. Two displays of coloured rectangles

were presented, separated by a short blank display (see Figure 3.1). The first display (S1) was presented for 200 ms, followed by a blank display of 900 ms, followed by a second display of coloured rectangles (S2) for 2200 ms, or until a response was made. On 75% of trials, one of the rectangles changed colour between S1 and S2 (target present trials). Participants were asked to report whether or not they saw a change occur. As in Chapter 2, 50% of change targets were presented on the left and 50% presented on the right side of the screen, ordered randomly. Participants were instructed to keep focus on the centre of the screen, where a fixation marker appeared for 1000 ms prior to the start of the trial.

Participants completed 30 practice trials, followed by the 1-up 2-down staircase procedure as described in Chapter 2 and in Levitt (1970). The goal of the staircase procedure was to predict the number of rectangles required to achieve 71% accuracy. In this procedure, the numbers of rectangles were adjusted until they reversed 20 times, then an average was taken. This was increased from the 12 reversals used in Chapter 2, in an effort to improve staircase accuracy. Differently to Chapter 2, no additional rectangle pair was added for the experimental blocks, also to improve staircase accuracy. Participants then completed a further practice, followed by six experimental blocks totalling 426 trials: 320 change trials (160 left target and 160 right target), and 106 trials in which no change occurred. Differently to Chapter 2, the current study used a between-participants design and therefore participants only took part in one of three stimulation conditions, receiving either active GVS (n = 15), sham (n = 17) or neck sham stimulation (n = 16).

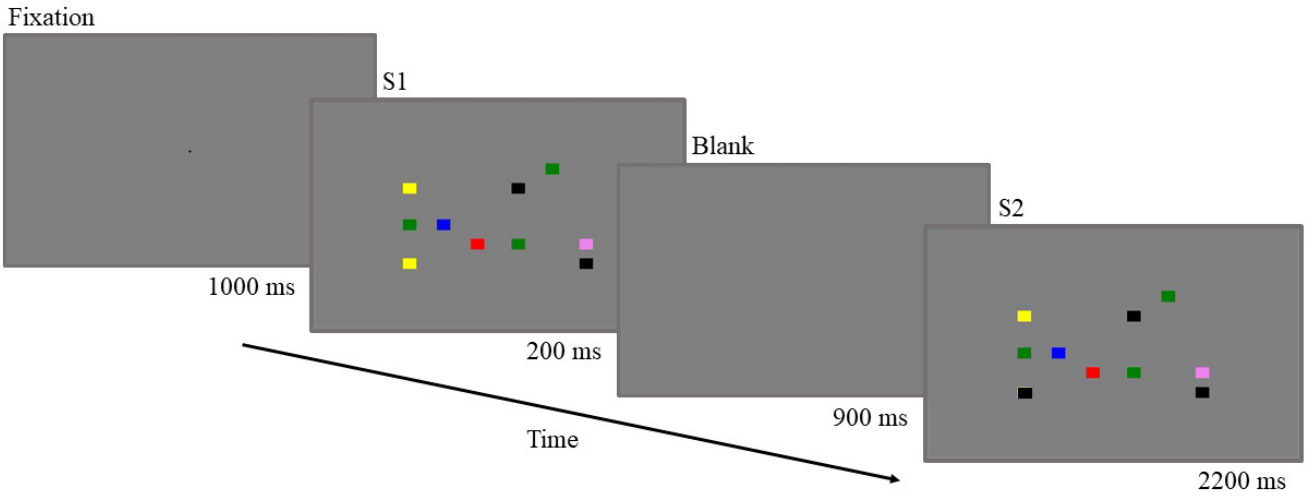

Figure 3.1. Timeline of stimuli presented during a change trial. The target in this example is located in the lower left and changes from yellow in S1 to black in S2.

GVS Protocol

The skin behind the ears was cleansed using an alcohol swab and conductive gel and then carbon-rubber, auto adhesive electrodes were placed either over the mastoids, for GVS and sham conditions, or on the sides of the neck, for the neck sham condition. Electrodes were connected to Magstim Eldith Transcranial DC Stimulator Plus™ device. As in Chapter 2 and in line with recent GVS studies (e.g., Wilkinson et al., 2014; Zubko et al., 2013) left anodal/right cathodal bilateral, bipolar stimulation was used. Differently to Chapter 2, no individual titration procedure was used and all participants in the GVS and neck sham conditions received .4mA of stimulation. .4mA was chosen as this has been described in previous literature as sub-sensory (e.g., Jeong-Woo, Gi-Eun, Ji-Hyang, & Se-Won, 2014) and also was within the range identified by the individual titration procedure used in Chapter 2. In the sham condition, stimulation was only feigned being switched on.

Electrophysiological Recording and Analysis

EEG recording and analysis was almost identical to that in Chapter 2. EEG activity was recorded using Brain Products BrainAmp DC system using Ag/AgCl electrodes in a standard 64 electrode arrangement (International 10/10 System.) FT9 and FT10 were removed and FT9 placed at the side of the left eye to record horizontal electro-oculogram (HEOG) and FT10 placed below the right eye to record vertical electro-oculogram (VEOG). Electrodes were referenced online to FCz, using AFz as the ground, and then re-referenced offline to an average reference. EEG electrodes overlying the GVS electrodes (TP7, TP8, TP9, TP10, P7 and P8) were removed and not included in the average reference. During recording, electrodes were sampled at 1000 Hz and impedences kept below 10kΩ. A 250Hz low pass filter was applied during recording to prevent aliasing of higher frequencies.

Trials in which no change occurred were discarded and ERP analysis focused on change trials. A .05 - 70 Hz band pass filter and a 50Hz notch filter was applied. Semi-automatic ocular ICA correction was used to correct for vertical and horizontal eye movements. Data was segmented into 900ms epochs from -100 to 800ms with zero set at the onset of S2. Non-ocular artifacts exceeding .75 μV were removed using Brain Vision Analyzer 2.1 software semi-automatic artifact rejection, and the resulting segments were aligned to a 100 ms pre-stimulus baseline, then averaged for each condition. Artifact rejection coupled with accuracy (seen or unseen) resulted in more segments for seen trials, $F(1, 45) = 63.03$, $p < .001$, $\eta_p^2 = .58$, and left sided trials, $F(1, 45) = 19.11$, $p < .001$, $\eta_p^2 = .30$. There was a target detection by target side interaction showing more seen segments were on the left and more unseen segments were on the right, $F(1, 45) = 11.79$, $p < .001$, $\eta_p^2 = .21$. Numbers of segments were not significantly altered by stimulation, all $Fs < 1.84$ and all $ps > .170$. Mean segment numbers for each condition are shown in table 3.1.

Table 3.1. Mean segment numbers for each condition

Condition		Mean Segment Numbers
Left Seen	Sham	87.41
	Neck Sham	100.31
	GVS	96.80
Right Seen	Sham	77.53
	Neck Sham	81.63
	GVS	82.00
Left Unseen	Sham	80.29
	Neck Sham	47.69
	GVS	43.27
Right Unseen	Sham	52.00
	Neck Sham	59.56
	GVS	53.27

N2pc. As in Chapter 2 and Tseng, et al. (2012), EEG signal from electrodes PO7 and PO8 was averaged separately for each participant over a time range of 250-320ms. ERP waveforms were combined over hemisphere to preserve the target side relative to the electrode location (ipsilateral and contralateral).

P3. Signal from electrodes P3, Pz, P4, C3, Cz, C4, F3, Fz and F4 was averaged separately for each participant, over a time window of 500-700ms (Eimer & Mazza, 2005).

Results

Electrophysiological Data

N2pc. A 3x2x2x2 ANOVA was conducted to compare N2pc amplitude for effects of stimulation type (sham, neck sham or GVS), target detection (seen or unseen), target side (left or right) and ipsi/contra (ipsilateral or contralateral). Mean amplitudes for each condition

are presented in Figure 3.2. Full ERP waveforms are presented in Figures 3.3, 3.4 and 3.5. Topography maps are presented in Figure 3.6. In keeping with Chapter 2 and previous literature (e.g., Eimer & Mazza, 2005), an ipsi/contra by target detection interaction, $F(1, 45) = 11.65$, $p < .001$, $\eta_p^2 = .21$, showed that the N2pc was larger when targets were seen versus unseen. There was also a main effect of target detection, $F(1, 45) = 11.79$, $p < .001$, $\eta_p^2 = .21$. A main effect of ipsi/contra, $F(1, 45) = 11.79$, $p < .001$, $\eta_p^2 = .21$, further demonstrated that as expected, amplitude was more negative over the contralateral than ipsilateral electrode. Paired samples *t*-tests comparing ipsilateral and contralateral separately for seen versus unseen targets replicated effects in Chapter 2 by showing that a clear N2pc was only elicited when targets were seen, $t(47) = 4.99$, $p < .001$, $d = .75$, and not when they were unseen, $t(47) = .13$, $p = .898$, $d = .02$. This is presented in Figure 3.7.

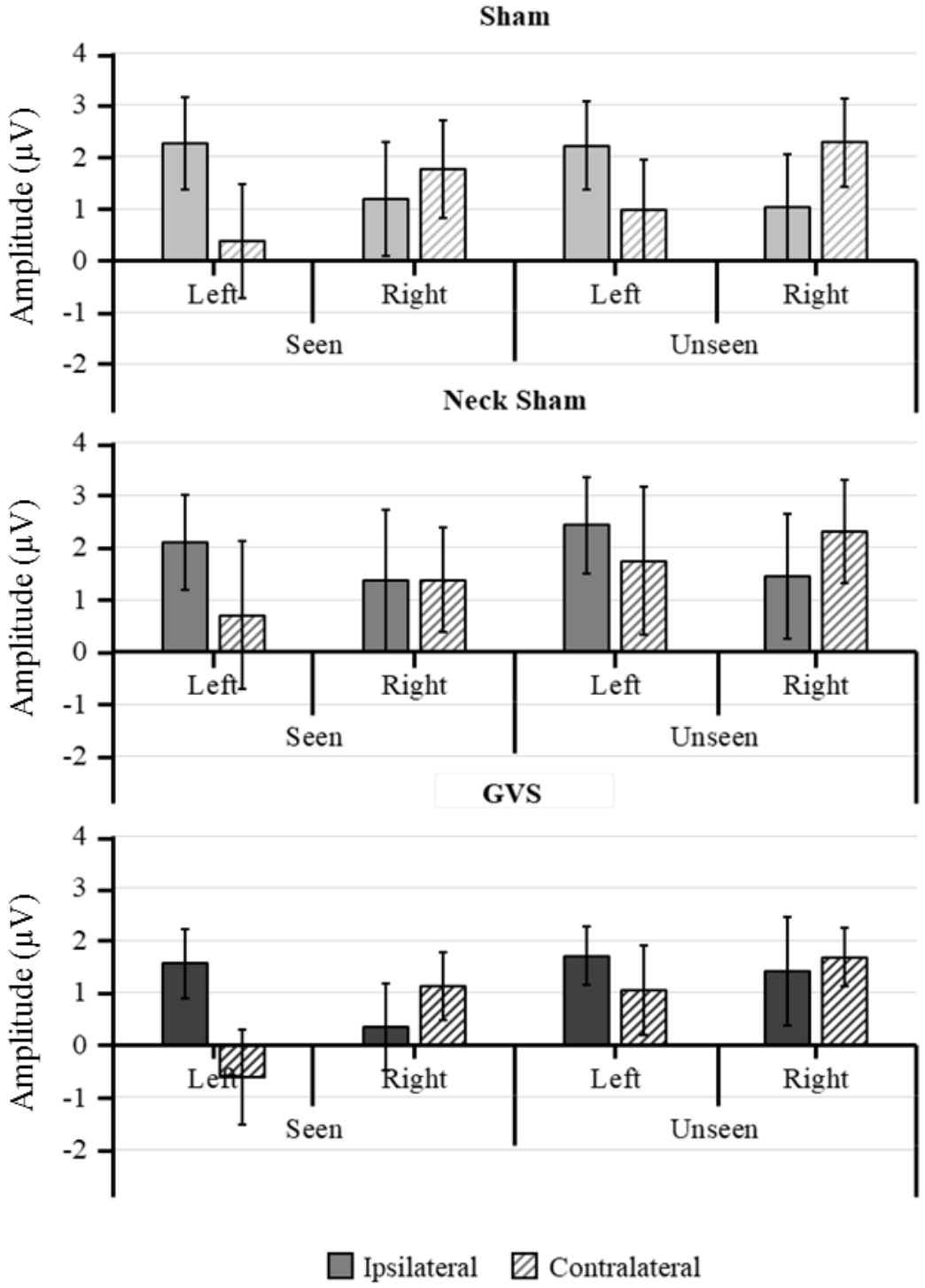

Figure 3.2. Mean amplitude plotted as a function of ipsi/contra, target detection and target side, separately for each stimulation condition. Top: Sham (n = 17). Middle: Neck Sham (n = 16). Bottom: GVS (n = 15). Error bars indicate standard errors.

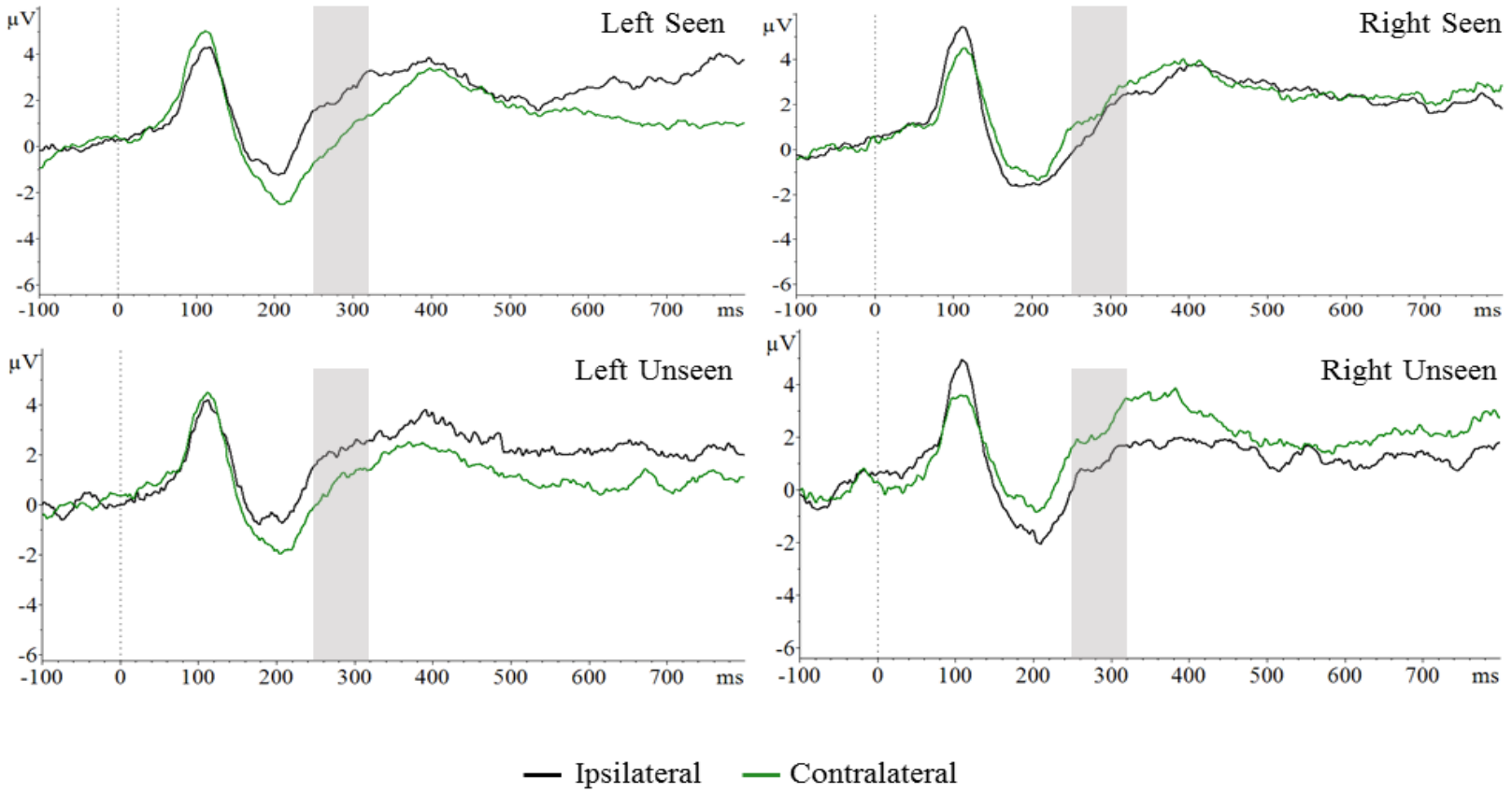

Figure 3.3. Grand averaged ERPs elicited from lateral posterior electrodes (PO7/PO8) during a time window of 250-320ms. Waveforms depict response to left seen targets (top left), right seen target (top right), left unseen targets (bottom left) and right unseen targets (bottom right) during sham stimulation.

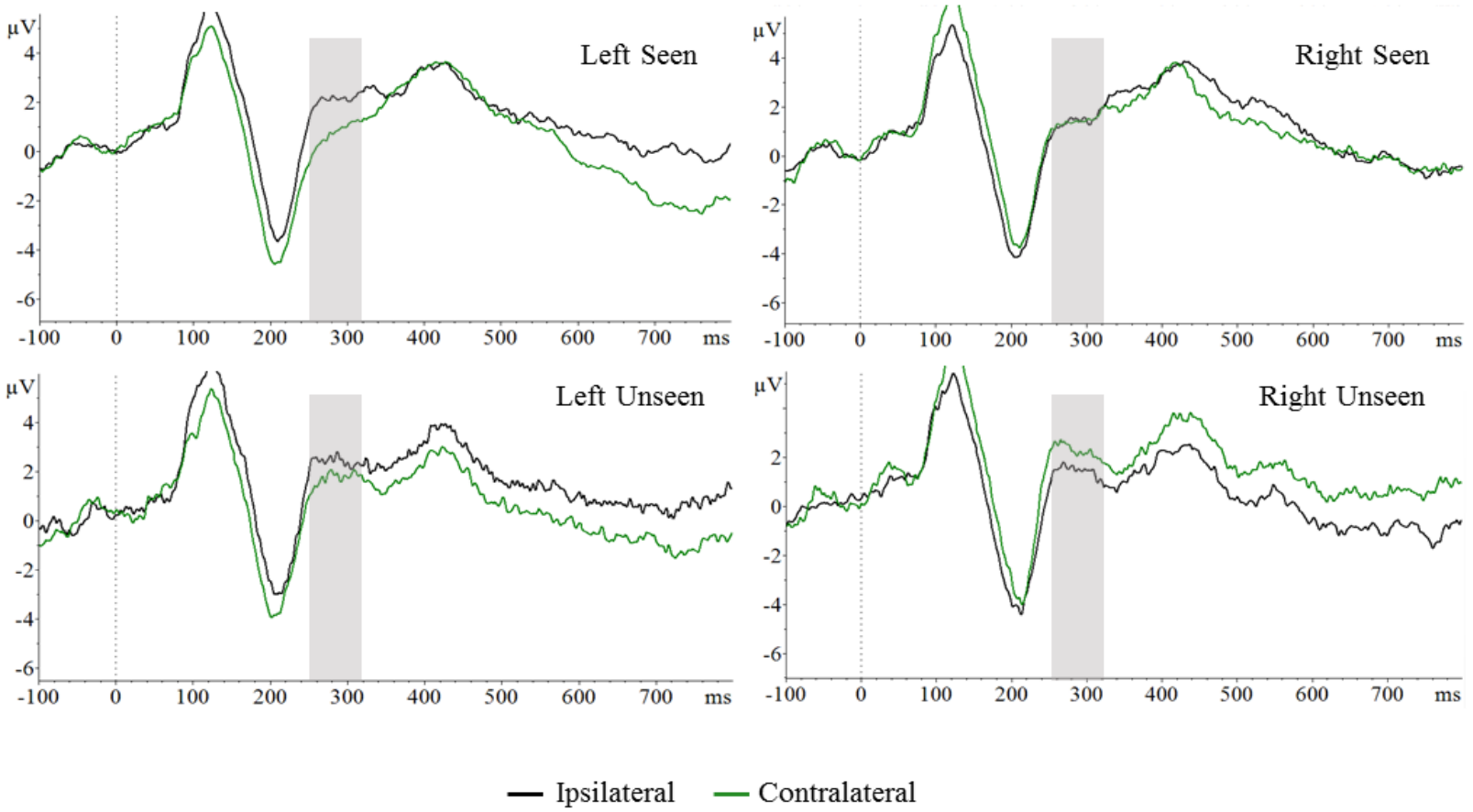

Figure 3.4. Grand averaged ERPs elicited from lateral posterior electrodes (PO7/PO8) during a time window of 250-320ms. Waveforms depict response to left seen targets (top left), right seen target (top right), left unseen targets (bottom left) and right unseen targets (bottom right) during neck sham stimulation.

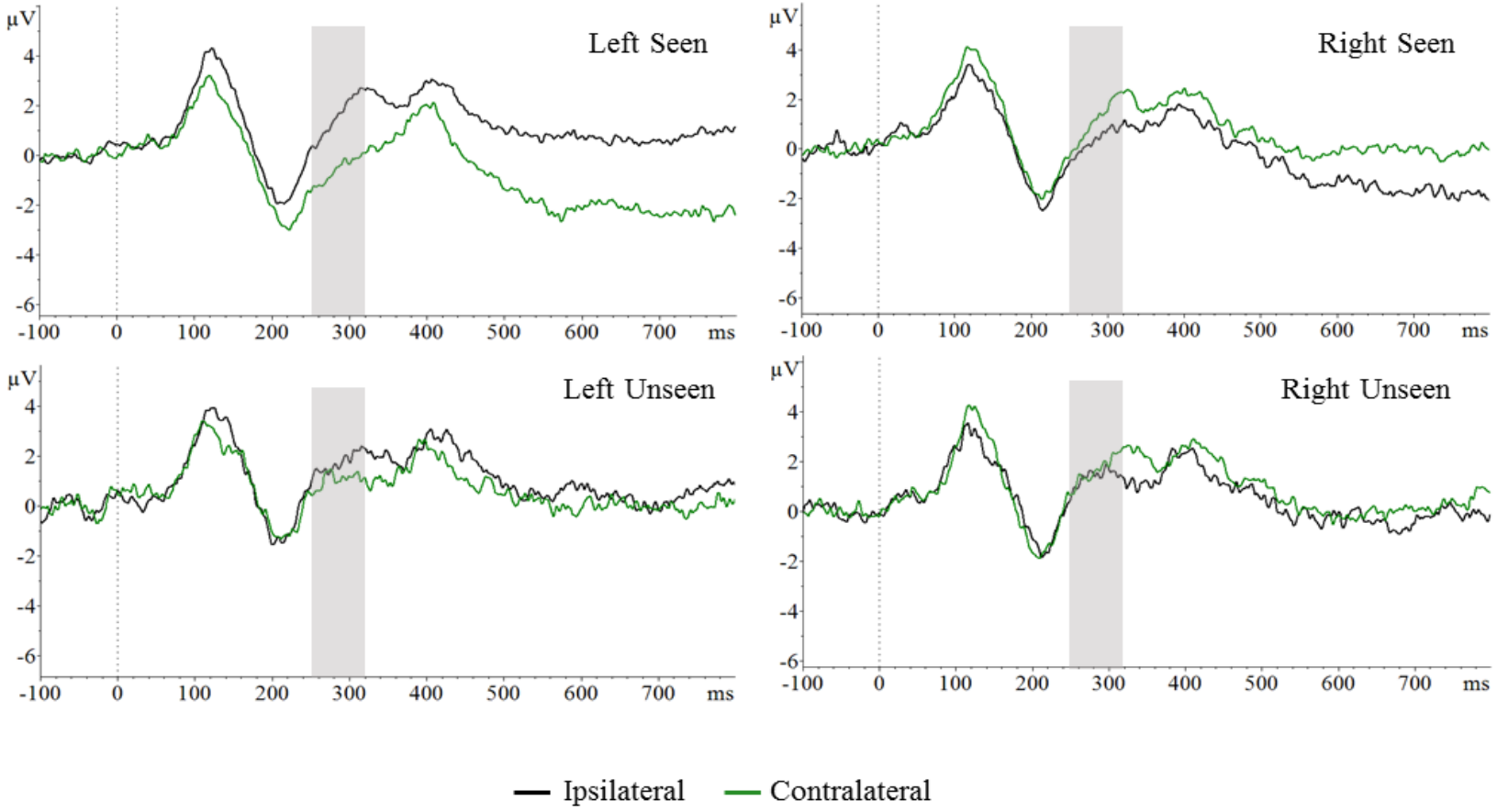

Figure 3.5. Grand averaged ERPs elicited from lateral posterior electrodes (PO7/PO8) during a time window of 250-320ms. Waveforms depict response to left seen targets (top left), right seen target (top right), left unseen targets (bottom left) and right unseen targets (bottom right) during GVS.

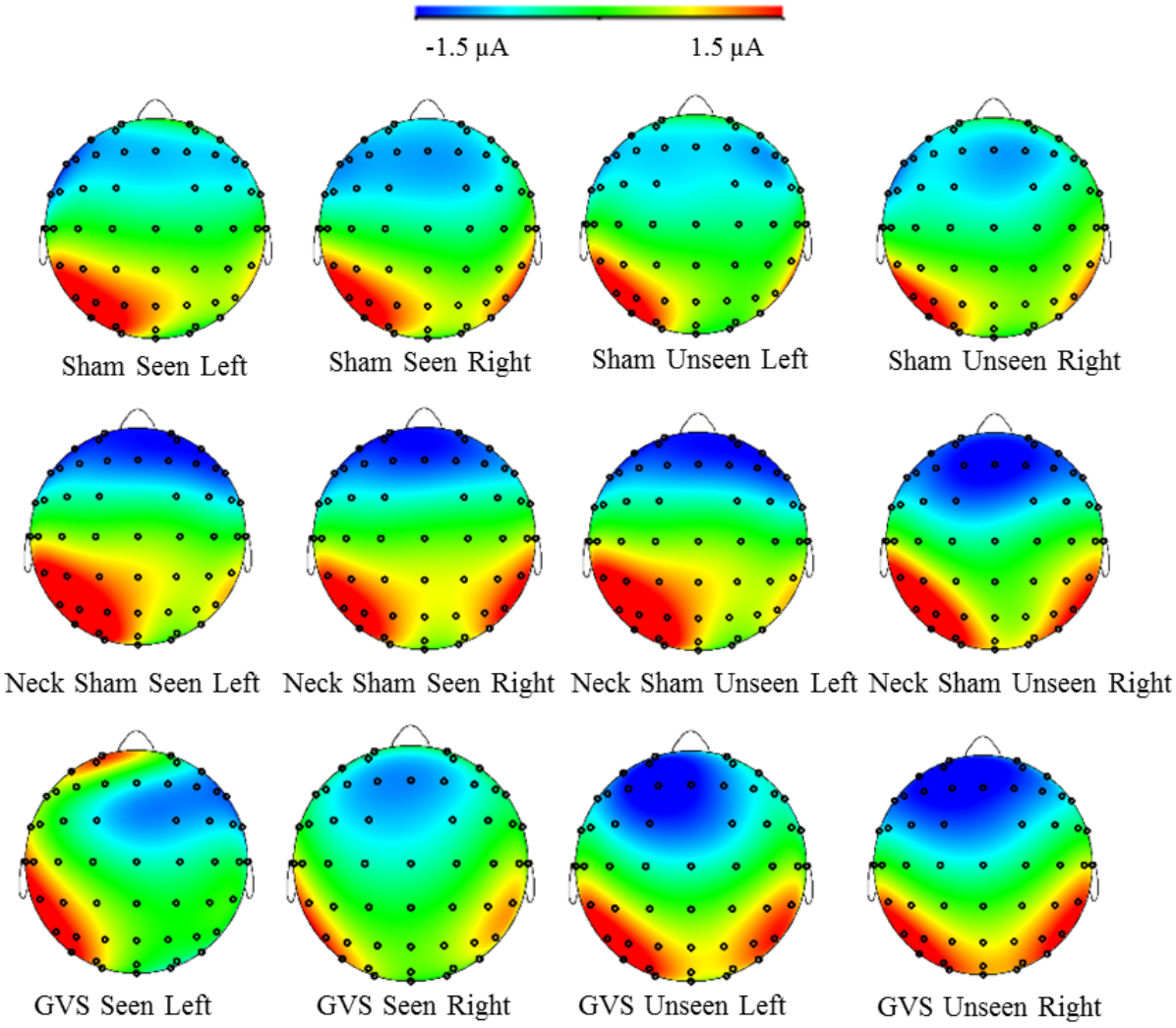

Figure 3.6. Topography maps for each condition within the N2pc time window (250-320 ms).

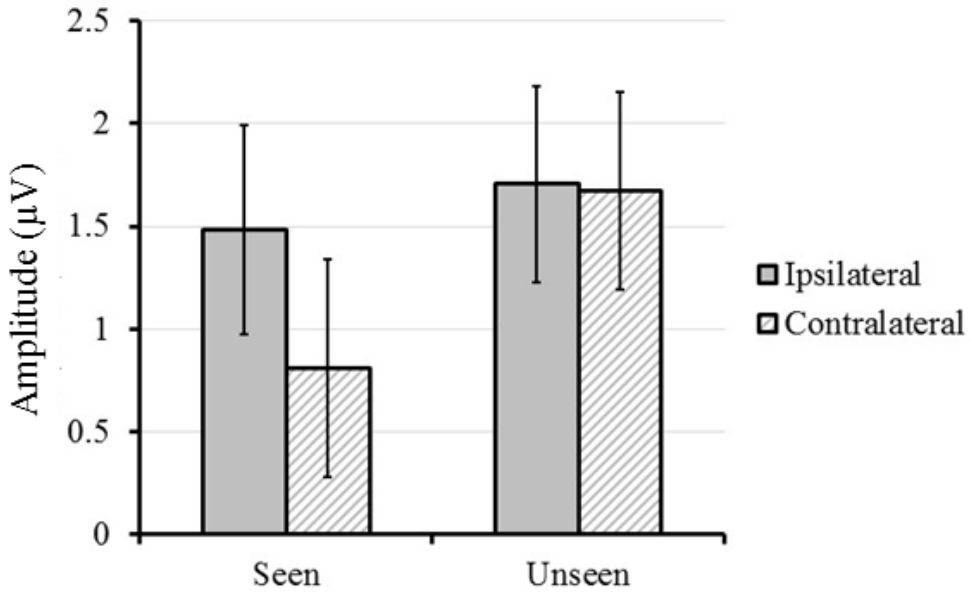

Figure 3.7. Mean amplitude plotted as a function of target detection and ipsi/contra, collapsed over stimulation and target side. Error bars indicate standard errors.

Unlike in Chapter 2, there was no hint of a significant interaction between target detection, ipsi/contra and stimulation, $F(1, 45) = .07$, $p = .948$, $\eta_p^2 = .00$, however the current data was impacted by target side. An interaction was found between target detection, ipsi/contra, target side and stimulation, $F(1, 45) = 3.478$, $p < .05$, $\eta_p^2 = .13$. To investigate these effects further, difference scores were computed in the same way as in Chapter 2, by calculating the mean differences between ipsilateral and contralateral amplitudes. Three ANOVAs were conducted on these difference scores, comparing effects of target detection (seen or unseen) and target side (left or right) separately for each stimulation type (sham, neck sham and GVS). A significant interaction between target side and target detection was found only during GVS, depicted in Figure 3.8. To investigate this interaction, paired samples *t*-tests (with alpha corrected at .05 / 4 = .013) compared target detection (seen or

unseen) separately for left and right targets for GVS participants only, finding that N2pc amplitude was higher for seen targets versus unseen targets only when the target appeared on the left, $t(14) = .2.91$, $p < .05$, $d = .84$. There was no difference between N2pc amplitude for seen and unseen targets when the target appeared on the right, $t(14) = 1.02$, $p = .325$, $d = .28$. Separate comparisons of left and right for seen and unseen targets revealed no effects, $t(14) = 1.76$, $p = .108$, $d = 1.30$[2] and $t(14) = .55$, $p = .591 = d = .62$, respectively. These results therefore broadly replicate the marginal finding from Chapter 2 that GVS impacts N2pc amplitude. This is such that seen and unseen targets are no longer significantly different from one another, but in the current data this only occurred for targets that appeared on the right[3]. No other main effects were found to be significant, all $Fs < 1.60$, and all $ps > .284$, nor were there any further interactions, all $Fs < 3.27$ and all $ps > .077$.

[2] This non-significant result is accompanied by a large effect size (*d*). On closer inspection of the individual participant scores, 12 of 15 show larger N2pc for left targets while three show larger N2pc for right targets. In two of these three participants, the right target advantage is numerically large. In this context, the difference between the *t*-test and Cohen's *d* is likely to reflect sample size, which is somewhat limited for this study and not taken into account for calculation of the effect size measure.

[3] N2pc was analysed according to target side to follow the method in Tseng et al. (2012) and because of the previously demonstrated lateral effects of GVS (e.g., Wilkinson et al., 2012). Another way to analyse N2pc data however is to compare electrode hemisphere instead of target side. This method can investigate if there are baseline differences in electrode hemisphere. Since it was noted that clear N2pcs were absent for right targets, coupled with the target-side effect, for completeness, an analysis by hemisphere was also carried out. The full analysis is presented in Appendix B. No significant baseline difference between electrode hemisphere was detected. It was however marginal ($p = .077$). Furthermore, no meaningful effect of stimulation was detected when analysed by electrode hemisphere. Therefore, the current findings are interpreted with caution. One explanation is that the GVS effect on N2pc really was effective only for one target side, hence why significant effects of stimulation do not appear when target side is removed from analysis. This is strengthened by the fact that stimulation effects do not occur in either no stimulation sham or neck sham. Replication however is required to rule out complicating factors of electrode hemisphere.

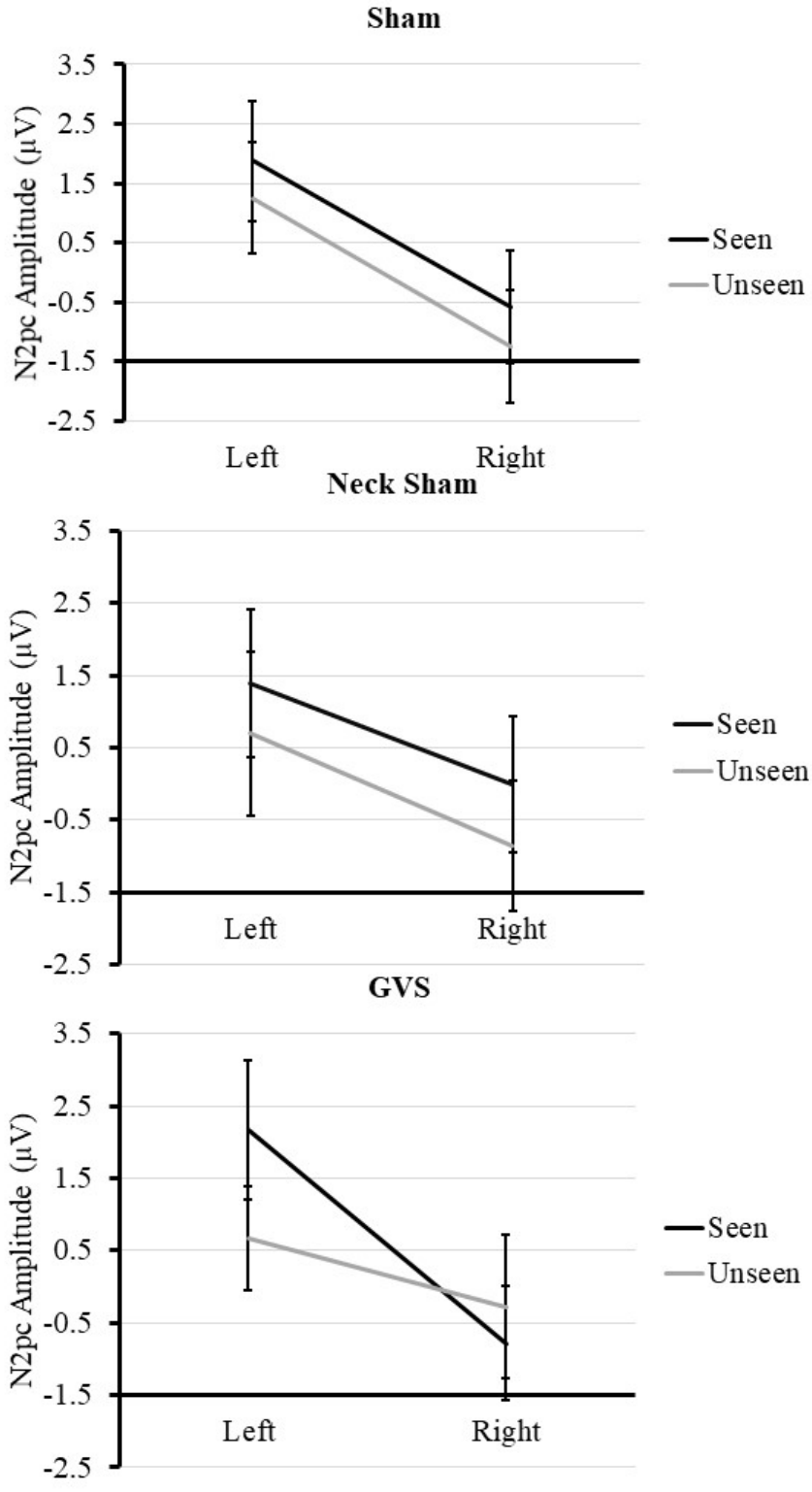

Figure 3.8. Mean (n = 48) N2pc amplitudes plotted as a function of target detection and target side separately for each stimulation condition. A significant target detection by target side interaction was detected only in the GVS condition.

P3. A 5-way ANOVA compared P3 amplitude for effects of stimulation (sham, neck sham or GVS), electrode (frontal, central or parietal), electrode laterality (left, midline or right), target detection (seen or unseen) and target side (left or right). Mean P3 amplitudes are presented in Figure 3.9. The full P3 waveforms for each condition are presented in Figures 3.10, 3.11 and 3.12. Topography maps are presented in Figure 3.13.

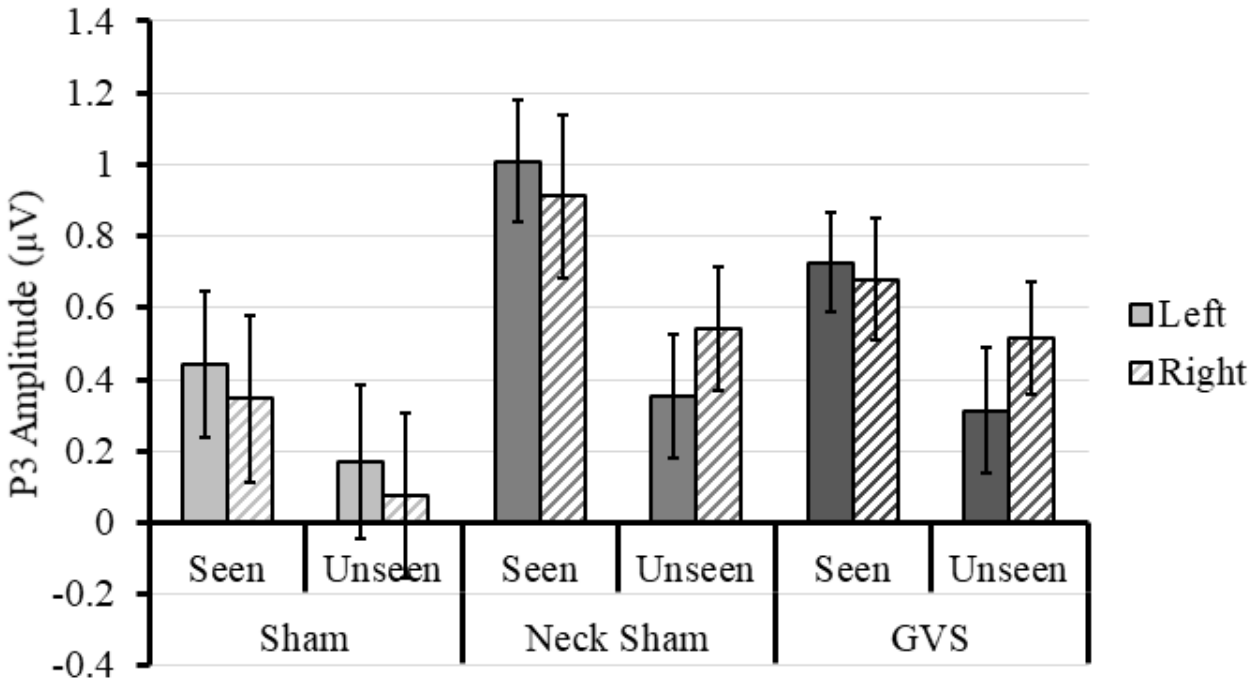

Figure 3.9. Mean (n = 48) P3 amplitudes plotted as a function of stimulation, target detection and target side, averaged across electrode location. Error bars indicate standard errors.

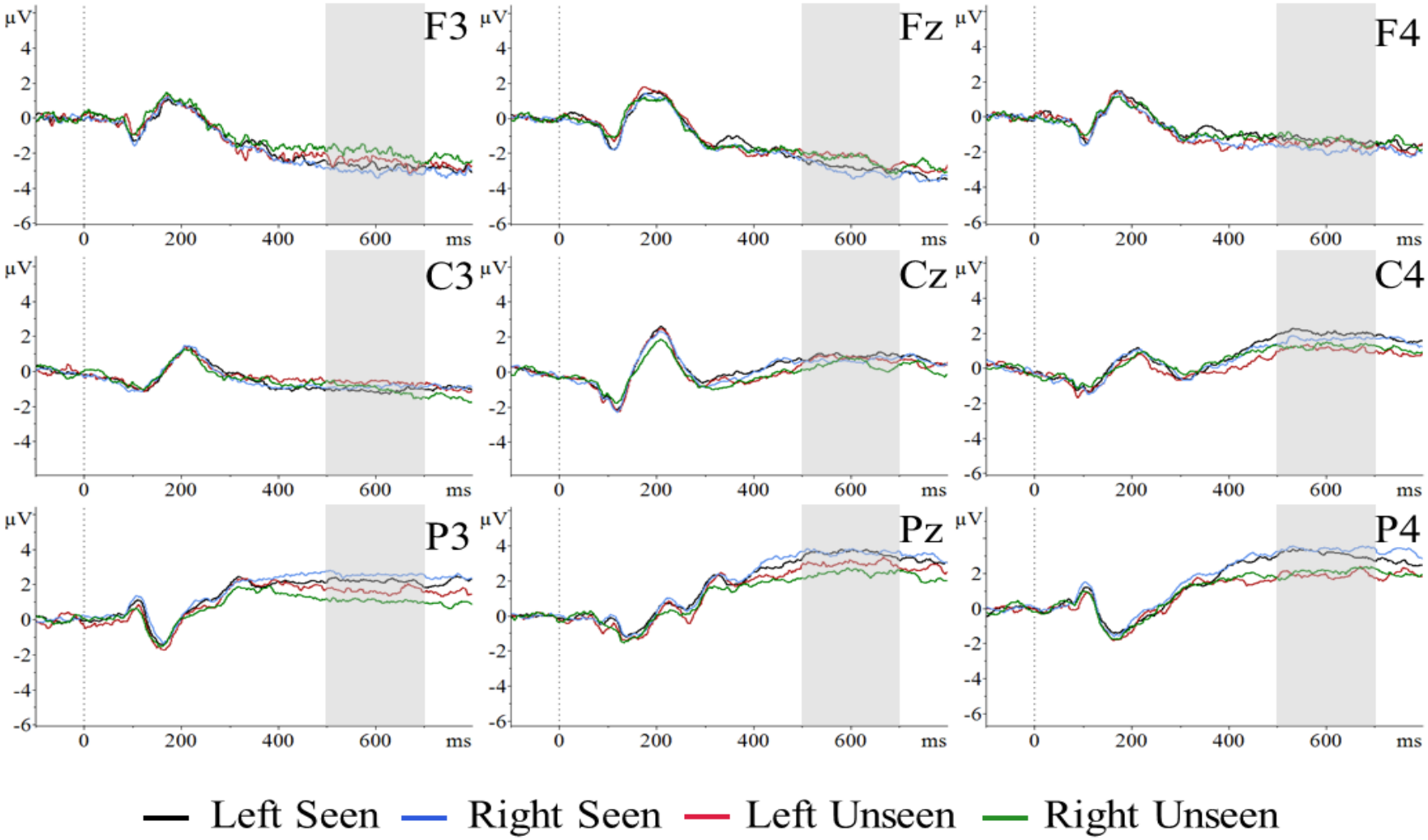

Figure 3.10. Grand average ERPs elicited in a time window of 500-700ms during sham stimulation.

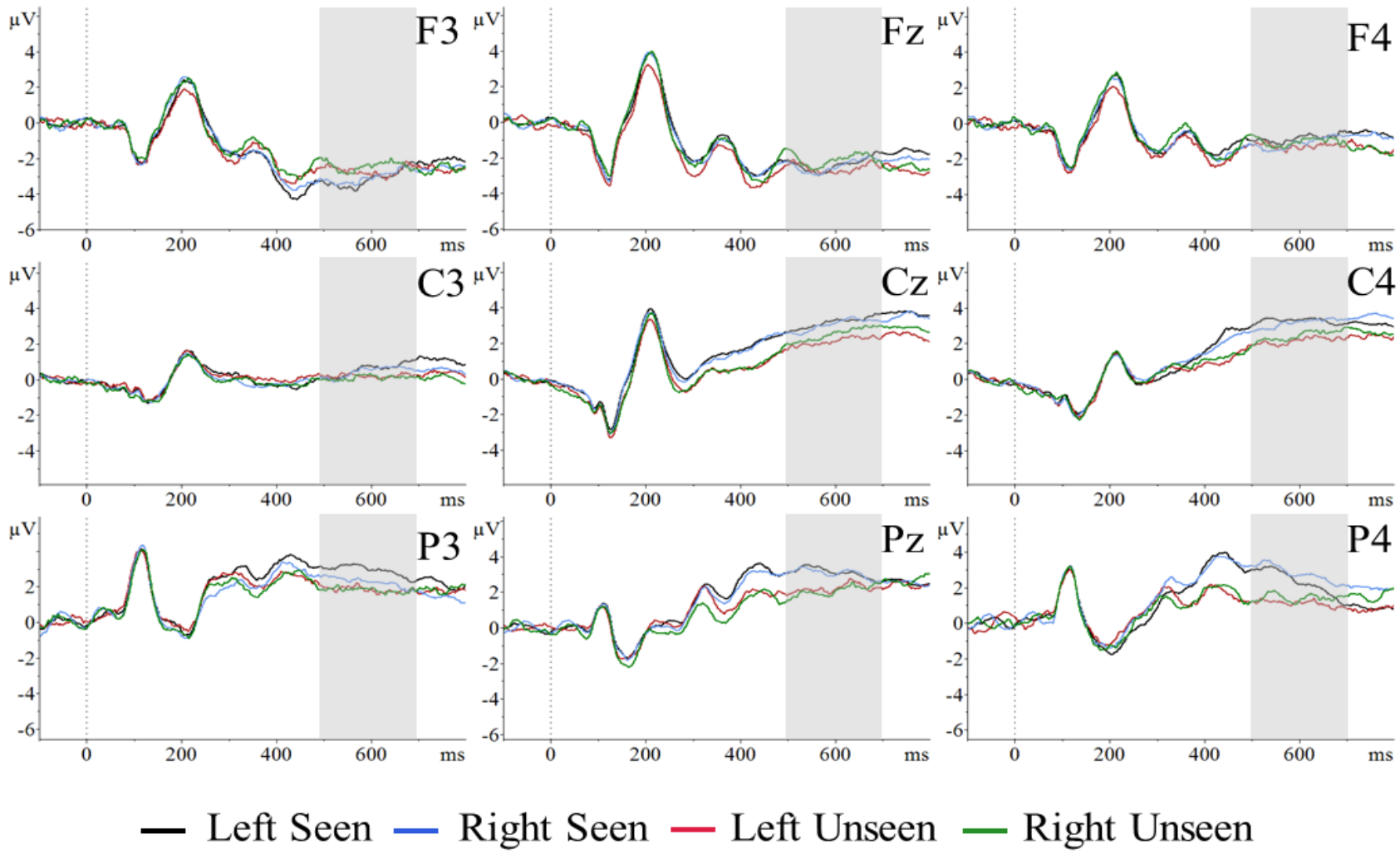

Figure 3.11. Grand average ERPs elicited in a time window of 500-700ms during neck sham stimulation.

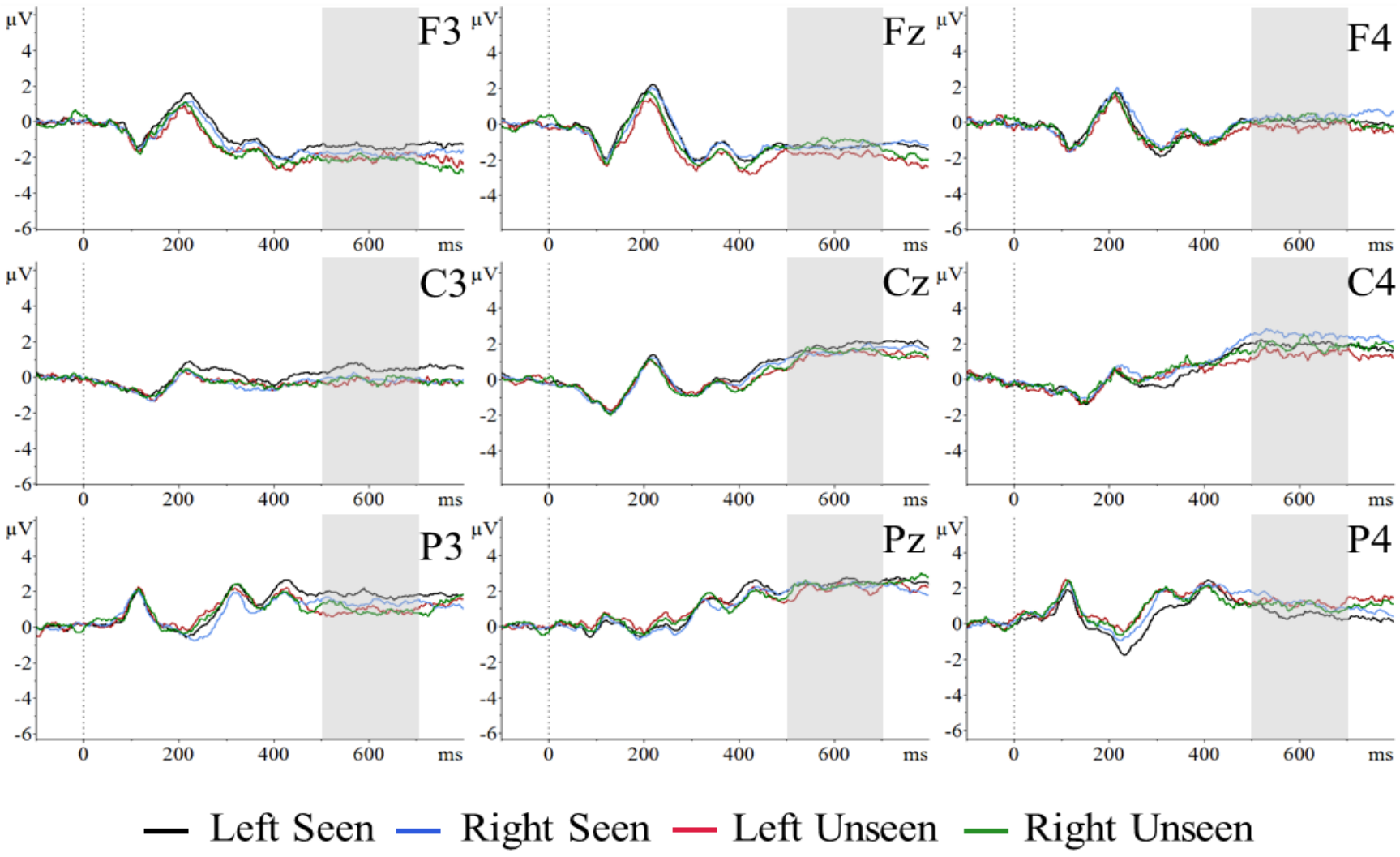

Figure 3.12. Grand average ERPs elicited in a time window of 500-700ms during GVS stimulation.

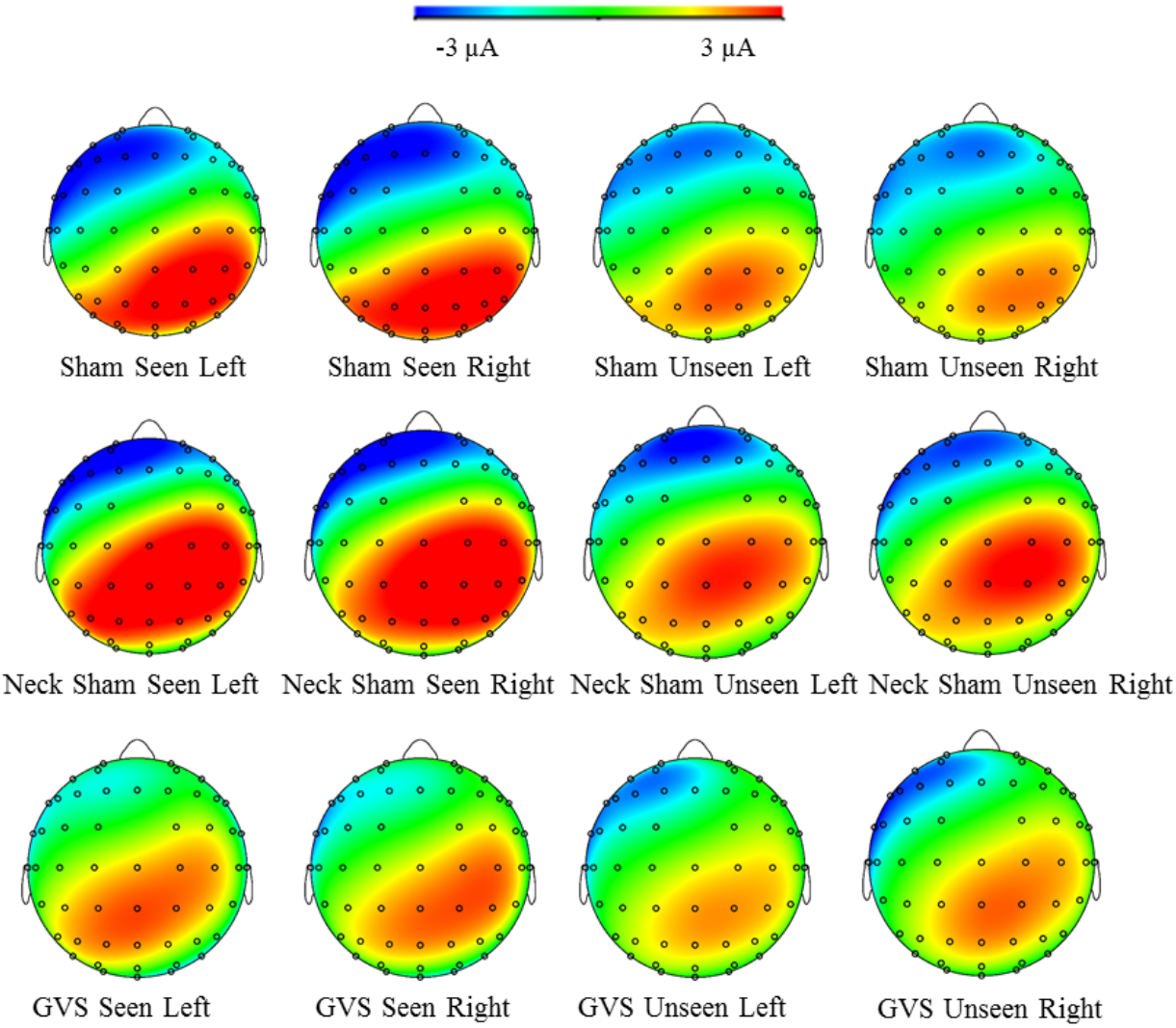

Figure 3.13. Topography maps for each condition within the P3 time window (500-700 ms).

The basic effects broadly replicated the findings of Chapter 2. P3 amplitude was higher when targets were seen versus unseen $F(1, 45) = 29.79$, $p < .001$, $\eta_p^2 = .48$ (e.g., Eimer & Mazza, 2005). P3 topography also replicated that of Chapter 2 and was in line with predictions from previous literature (e.g., Patel & Azzam, 2005). As expected, P3 was maximal at parietal electrodes, $M = 2.11$ µV, followed by central, $M = 1.18$ µV, and then frontal electrodes, $M = -1.77$ µV, $F(2, 45) = 44.48$, $p < .001$, $\eta_p^2 = .50$. Amplitude at parietal electrodes was more positive than central, $t(47) = 2.59$, $p = .013$, $d = .37$, and frontal electrodes, $t(47) = 6.74$, $p = < .001$, $d = .97$, and amplitude at central electrodes was more

positive than at frontal electrodes, $t(47) = 9.03$, $p < .001$, $d = .97$. As in Chapter 2, interactions were detected between electrode and target detection, $F(1, 45) = 8.02$, $p < .001$, $\eta_p^2 = .151$, electrode and electrode laterality, $F(1, 45) = 24.94$, $p < .001$, $\eta_p^2 = .36$, and between electrode, electrode laterality and target detection, $F(1, 45) = 2.80$, $p < .05$, $\eta_p^2 = .06$.

Three ANOVAs investigated effects underlying this three-way interaction by comparing target detection (seen or unseen) and electrode laterality (left electrodes, midline electrodes or right electrodes) separately for frontal, central and parietal electrode sites. The full ANOVA results are presented in Table 3.2. These results demonstrate that as in Chapter 2, P3 amplitude was larger when targets were seen, both at parietal and central, but not frontal electrode sites. Also as in Chapter 2, all electrode sites demonstrated a main effect of electrode laterality. P3 was most positive at the midline electrode for parietal sites but in the right hemisphere in central and frontal electrodes. Again as in Chapter 2, an electrode laterality by target detection interaction was found only at central electrode sites. Paired samples *t*-tests (with alpha corrected at .05 / 3 = .017 for multiple comparisons) compared seen and unseen targets separately for each electrode laterality group, finding that P3 was more positive for seen versus unseen targets at midline, $t(47) = 2.53$, $p = .015$, $d = .038$ and right electrodes, $t(47) = 5.06$, $p < .001$, $d = .72$, but there was no difference between seen and unseen at left electrodes, $t(47) = 1.96$, $p = .278$, $d = .16$.

Table 3.2. *ANOVA results to investigate a significant electrode by electrode laterality by target detection interaction. * p < .05, ** p < .01, *** p < .001*

	Electrode Laterality ($df = 2, 47$)	Target Detection ($df = 1, 47$)	Electrode Laterality x Target Detection ($df = 2, 47$)
Frontal Electrodes	$F = 16.72$, $\eta_p^2 = .26$	$F = .50$, $\eta_p^2 = .01$	$F = 2.25$, $\eta_p^2 = .05$
	$p < .001$***	$p = .482$	$p = .111$
Central Electrodes	$F = 28.70$, $\eta_p^2 = .38$	$F = 16.64$, $\eta_p^2 = .26$	$F = 3.45$, $\eta_p^2 = .07$
	$p < .001$***	$p < .001$***	$p < .05$*
Parietal Electrodes	$F = 5.42$, $\eta_p^2 = .10$	$F = 23.37$, $\eta_p^2 = .33$	$F = .52$, $\eta_p^2 = .01$
	$p < .01$**	$p < .001$***	$p = .594$

Additional basic effects also replicated Chapter 2. A marginal target side by target detection interaction was found, $F(1, 45) = 3.99$, $p = .053$, $\eta_p^2 = .08$, which was investigated as it replicated Chapter 2 and was very close to significance. Paired sample *t*-tests (with alpha corrected at .05 / 4 = .013 for multiple comparisons) compared left and right target trials separately for seen targets, $t(47) = .45$, $p = .155$, $d = .22$, and unseen targets, $t(47) = 1.42$, $p = .163$, $d = .20$, and found no differences. Seen and unseen trials were also compared separately for left and right targets, finding that P3 was higher for left targets when they were seen, $t(47) = 6.63$, $p < .001$, $d = .97$, but higher for right targets when they were unseen, $t(47) = 2.97$, $p < .01$, $d = .43$. Additionally, unlike in Chapter 2 there was no main effect of target side, but target side was incorporated in an electrode laterality by target side, $F(1, 45) = 3.79$, $p < .05$, $\eta_p^2 = .078$, and an electrode laterality by electrode by target side interaction, $F(1, 45) = 3.40$, $p < .05$, $\eta_p^2 = .07$.

Three ANOVAs comparing electrode laterality (left, midline or right electrodes) and target side (left or right) were conducted separately for frontal, central and parietal electrodes. The results are presented in Table 3.3. Findings indicate that the electrode laterality by target

side interaction only occurred at parietal electrode sites. Paired samples *t*-tests compared left and right targets separately for parietal left, parietal midline and parietal electrodes. Findings demonstrated that numerically, P3 was most positive to left targets in the left hemisphere and at the midline, and P3 more positive to right targets in the right hemisphere. However, after correcting for multiple comparisons (alpha corrected at .05 / 3 = .017), none of these were significant; left electrodes: $t(47) = 1.84$, $p = .073$, $d = .28$, midline electrodes: $t(47) = .74$, $p = .465$, $d = .11$, and right electrodes: $t(47) = 2.37$, $p = .022$, $d = .37$.

Table 3.3. *ANOVA results to investigate significant electrode laterality by electrode by target side interactions. * p < .05, ** p < .01, *** p < .001*

	Electrode Laterality ($df = 2, 47$)	Target Side ($df = 1, 47$)	Electrode Laterality x Target Side ($df = 2, 47$)
Frontal Electrodes	$F = 25.37$, $\eta_p^2 = .35$ $p < .001$***	$F = .33$, $\eta_p^2 = .01$ $p = .570$	$F = .32$, $\eta_p^2 = .01$ $p = .724$
Central Electrodes	$F = 28.70$, $\eta_p^2 = .38$ $p < .001$***	$F = .20$, $\eta_p^2 = .01$ $p = .661$	$F = 2.29$, $\eta_p^2 = .05$ $p = .107$
Parietal Electrodes	$F = 5.42$, $\eta_p^2 = .10$ $p < .01$**	$F = .01$, $\eta_p^2 < .001$ $p = .920$	$F = 6.84$, $\eta_p^2 = .13$ $p < .01$**

The most interesting findings are those that concern the effect of stimulation, where a 5-way interaction was found, $F(8, 45) = 2.23$, $p = .026$ $\eta_p^2 = .09$. This interaction was investigated through ANOVAs comparing target detection (seen or unseen), target side (left or right) and stimulation (sham, neck sham and GVS) conducted separately for each of the nine electrodes. These results are presented in Table 3.4.

Table 3.4. *ANOVA results to investigate five-way interaction. * p < .05, ** p < .01, *** p < .*

	Target Detection ($df = 1, 45$)	Target Side ($df = 1, 45$)	Stimulation ($df = 2, 45$)	Target Detection xStimulation ($df = 2, 45$)	Target Side xStimulation ($df = 2, 45$)	Target Detection xTarget Side ($df = 1, 45$)	Target Detection xTarget Side xStimulation ($df = 2, 45$)
F3	$F = 1.87$ $p = .179$ $\eta_p^2 = .04$	$F = .01$ $p = .965$ $\eta_p^2 < .001$	$F = .68$ $p = .511$ $\eta_p^2 = .03$	$F = 3.38$ $p = .043$* $\eta_p^2 = .13$	$F = 1.71$ $p = .192$ $\eta_p^2 = .07$	$F = 2.13$ $p = .152$ $\eta_p^2 = .05$	$F = .53$ $p = .591$ $\eta_p^2 = .02$
Fz	$F = .80$ $p = .375$ $\eta_p^2 = .02$	$F = .82$ $p = .369$ $\eta_p^2 = .02$	$F = 1.11$ $p = .339$ $\eta_p^2 = .05$	$F = 1.08$ $p = .350$ $\eta_p^2 = .05$	$F = 1.27$ $p = .292$ $\eta_p^2 = .05$	$F = 3.31$ $p = .076$ $\eta_p^2 = .07$	$F = .34$ $p = .711$ $\eta_p^2 = .02$
F4	$F = .17$ $p = .681$ $\eta_p^2 = .01$	$F = .17$ $p = .679$ $\eta_p^2 = .01$	$F = 2.62$ $p = .084$ $\eta_p^2 = .10$	$F = .55$ $p = .583$ $\eta_p^2 = .02$	$F = 1.50$ $p = .234$ $\eta_p^2 = .06$	$F = 5.02$ $p = .030$* $\eta_p^2 = .10$	$F = .59$ $p = .559$ $\eta_p^2 = .03$
C3	$F = 1.36$ $p = .249$ $\eta_p^2 = .03$	$F = 2.58$ $p = .116$ $\eta_p^2 = .05$	$F = 2.02$ $p = .144$ $\eta_p^2 = .08$	$F = 1.18$ $p = .318$ $\eta_p^2 = .05$	$F = .17$ $p = .847$ $\eta_p^2 = .01$	$F = .06$ $p = .810$ $\eta_p^2 = .01$	$F = 2.06$ $p = .139$ $\eta_p^2 = .08$
Cz	$F = 6.53$ $p = .014$* $\eta_p^2 = .13$	$F = .86$ $p = .360$ $\eta_p^2 = .02$	$F = 4.16$ $p = .022$* $\eta_p^2 = .16$	$F = 1.47$ $p = .240$ $\eta_p^2 = .06$	$F = 2.48$ $p = .096$ $\eta_p^2 = .10$	$F = 1.44$ $p = .237$ $\eta_p^2 = .03$	$F = .61$ p = .549 $\eta_p^2 = .03$
C4	$F = 24.81$ $p <.001$*** $\eta_p^2 = .36$	$F = 1.64$ $p = .207$ $\eta_p^2 = .04$	$F = 2.08$ $p = .137$ $\eta_p^2 = .09$	$F = .45$ $p = .642$ $\eta_p^2 = .02$	$F = 2.13$ $p = .131$ $\eta_p^2 = .09$	$F = 1.36$ $p = .249$ $\eta_p^2 = .03$	$F = .76$ $p = .472$ $\eta_p^2 = .03$
P3	$F = 21.22$ $p < .001$*** $\eta_p^2 = .32$	$F = 3.30$ $p = .076$ $\eta_p^2 = .07$	$F = 1.45$ $p = .246$ $\eta_p^2 = .06$	$F = .37$ $p = .696$ $\eta_p^2 = .02$	$F = .36$ $p = .699$ $\eta_p^2 = .02$	$F = .13$ $p = .721$ $\eta_p^2 = .01$	$F = 5.38$ $p = .008$** $\eta_p^2 = .19$
Pz	$F = 13.04$ $p = .001$** $\eta_p^2 = .23$	$F = .47$ $p = .499$ $\eta_p^2 = .01$	$F = .56$ $p = .578$ $\eta_p^2 = .02$	$F = 1.78$ $p = .180$ $\eta_p^2 = .07$	$F = .37$ $p = .690$ $\eta_p^2 = .02$	$F = .11$ $p = .740$ $\eta_p^2 = .01$	$F = .78$ $p = .467$ $\eta_p^2 = .03$
P4	$F = 21.32$ $p < .001$** $\eta_p^2 = .32$	$F = 5.42$ $p = .024$* $\eta_p^2 = .11$	$F = 1.44$ $p = .248$ $\eta_p^2 = .06$	$F = 8.07$ $p = .001$** $\eta_p^2 = .26$	$F = .23$ $p = .799$ $\eta_p^2 = .01$	$F = 1.76$ $p = .192$ $\eta_p^2 = .04$	$F = .75$ $p = .477$ $\eta_p^2 = .03$

The results presented in Table 3.4 demonstrate that the stimulation by target detection by target side interaction was only present at the left, parietal electrode P3[4]. This interaction, is presented in Figure 3.14. To investigate this interaction, three follow-up ANOVAs compared target detection (seen or unseen) and target side (left or right) separately for each stimulation condition (sham, neck sham, GVS). The results are presented in Table 3.5. The findings demonstrate that the target detection by target side interaction only occurs during sham stimulation, and not during neck sham or GVS. The similarity between neck sham and GVS conditions therefore means it cannot be concluded that this is a GVS specific effect and therefore does not support the hypothesis that GVS impacts the amplitude of the P3. No other significant effects were detected from the original ANOVA, all *F*s < 2.27 and all *p*s > .068.

Table 3.5. *ANOVA results to investigate target detection x target side interaction separated by stimulation condition*

	Target Detection	Target Side	Target Detection x Target Side
Sham	$F = 11.82$	$F = .37$	$F = 6.93$
	$p = .003$, $\eta_p^2 = .43$	$p = .55$, $\eta_p^2 = .02$	$p = .018$*, $\eta_p^2 = .30$
Neck Sham	$F = 5.29$	$F = 2.68$	$F = 3.44$
	$p = .036$*, $\eta_p^2 = .26$	$p = .122$, $\eta_p^2 = .15$	$p = .083$, $\eta_p^2 = .19$
GVS	$F = 5.33$	$F = .77$	$F = 1.35$
	$p = .037$*, $\eta_p^2 = .28$	$p = .396$, $\eta_p^2 = .05$	$p = .264$, $\eta_p^2 = .09$

[4] When more conservative correction for multiple comparisons is applied (alpha corrected at .05 / 9 = .006, this interaction falls just short of significance ($p = .008$).

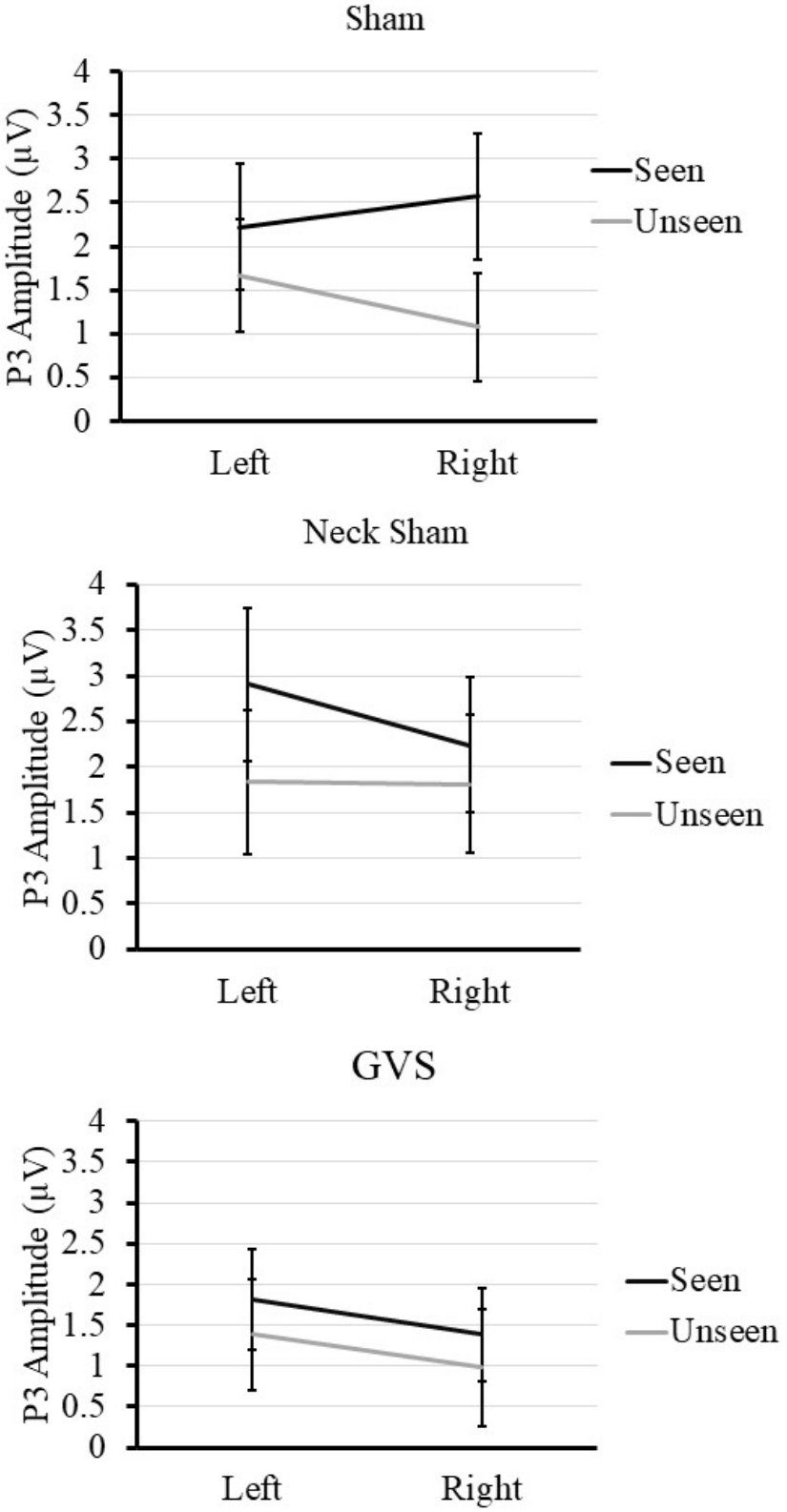

Figure 3.14. Mean P3 amplitude at electrode P3 only, plotted as a function of target detection and target side, separately for each stimulation type.

Behavioural Data

GVS was well tolerated by all participants with only mild tingling reported as side effects. As expected, overall accuracy was higher than in Chapter 2, with 64% in sham, 66% in neck sham and 67% in GVS. This was a little lower than the 71% accuracy aimed for using the Levitt (1970) staircase procedure.

d'. Average *d'* scores were computed separately for the three stimulation conditions. A 3x2 ANOVA was conducted comparing stimulation (sham, neck sham or GVS) and target side (left or right.) Mean *d'* for each condition are shown in Figure 3.15. As expected, overall *d'* was higher than in Chapter 2 across all stimulation conditions; sham: $M = 1.16$, neck sham: $M = 1.26$ and GVS: $M = 1.34$. As in Chapter 2 and in-line with previous literature (e.g., Iyilikci et al., 2010; Verleger et al., 2010), *d'* was higher for targets that appeared on the left versus targets that appeared on the right, $F(1, 45) = 16.90$, $p < .001$, $\eta_p^2 = .275$. Again, as expected due to the low levels of stimulation there were no effects of stimulation, both $Fs < .30$, and both $ps > .572$.

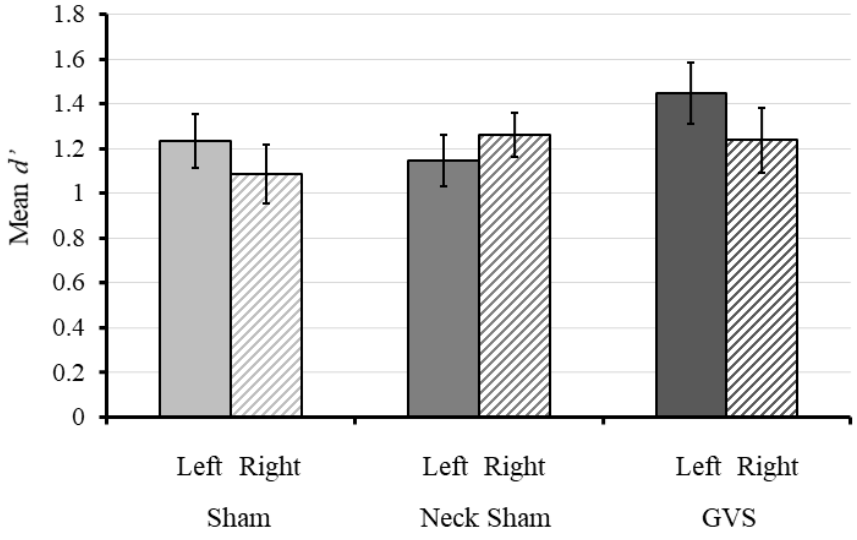

Figure 3.15. Mean (n = 48) d' scores, plotted as a function of stimulation and target side. Accuracy was higher for targets appearing in the left visual field versus the right visual field. Error bars indicate standard errors.

Reaction Time. Mean reaction times were calculated for target-present trials only. These are displayed in Figure 3.16. A 3x2x2 ANOVA was conducted comparing stimulation (sham, neck sham or GVS), target detection (seen or unseen) and target side (left or right). In contrast to the *d'* results and findings from Chapter 2, reaction times were equally quick for both left and right targets, $F(1, 45) = .03$, $p = .874$, $\eta_p^2 = .001$. Chapter 2 found a marginal interaction ($p = .052$) between stimulation and target side, however no hint of this effect was found in the current data, $F(2, 45) = .72$, $p = .494$, $\eta_p^2 = .031$. No other effects were significant, all $Fs < 2.54$ and all $ps > .118$.

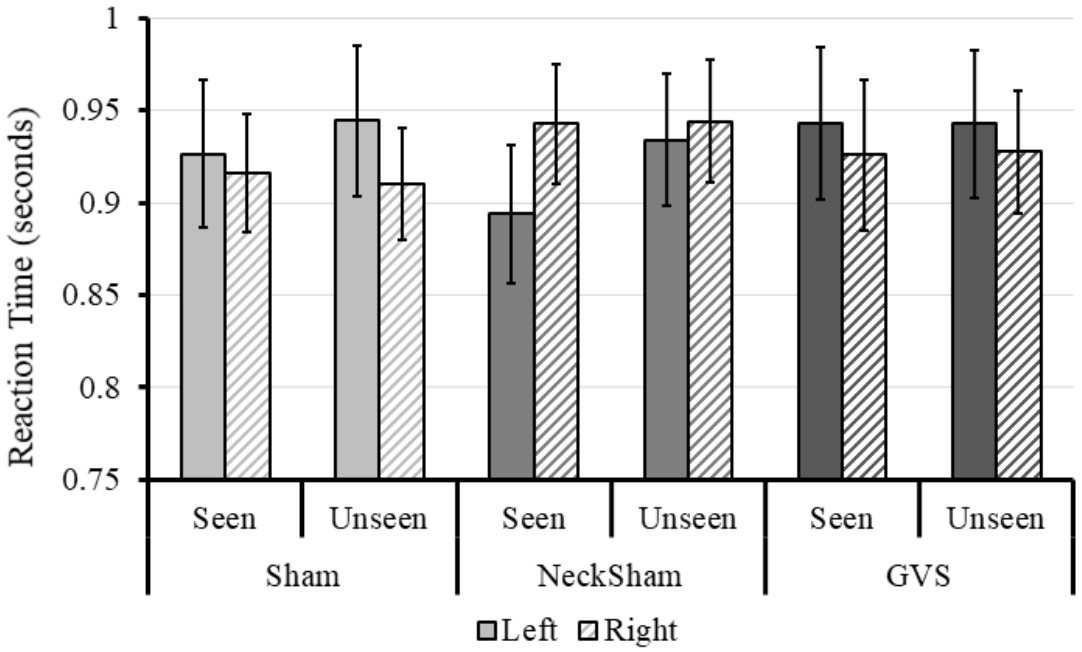

Figure 3.16. Mean (n = 48) reaction times plotted as a function of stimulation, target detection and target side. Error bars indicate standard errors.

Discussion

Chapter 2 hinted that GVS might impact the amplitude of the attention related ERP component N2pc. The effects however were not significant and there were limitations in the paradigm, including poor accuracy scores and the finding that GVS might not be completely sub-sensory. The current chapter therefore aimed to address these issues and improve the paradigm to investigate whether the marginal effects of GVS demonstrated in Chapter 2 could be replicated and extended. Accuracy was improved by increasing stimuli size and by aiming for higher accuracy output using the Levitt (1970) staircase procedure. To address the issue that GVS might not be sub-sensory, a second sham condition was included where active stimulation was applied to the neck to mimic any physical sensations of GVS, but not to stimulate the vestibular organs. Similar to Chapter 2, the current study found that during sham conditions, the N2pc was larger for seen versus unseen targets. This difference was removed during GVS. Differently to Chapter 2 however, the difference between seen and unseen N2pc amplitude with GVS was removed only for targets that appeared on the right side of the screen. In addition to the N2pc, the current chapter also investigated the impact of GVS on the ERP component P3, finding no specific GVS effects. Finally, the marginal effect on reaction time shown in Chapter 2 failed to replicate in the current study. This chapter therefore provides very tentative evidence that GVS may impact the amplitude of the N2pc in a lateral manner, potentially reflecting its ability to improve target detection among distractors.

The notion that GVS might impact N2pc amplitude was based on findings that GVS can improve performance on tasks which require detection of targets amongst distractors (e.g., Rorsman, Magnusson, & Johansson, 1999; Wilkinson et al., 2014; Zubko et al., 2013). It was hypothesised that relative to two sham conditions, one with no stimulation and one with active stimulation delivered away from the mastoids, that GVS would impact the

amplitude of the N2pc such that the response to unseen targets was not significantly different to seen targets. This hypothesis was supported, but GVS only removed the difference between seen and unseen for targets that appeared on the right side of the screen. Lateral effects of GVS have been shown previously, for example GVS has been demonstrated to relieve lateral attentional bias in sufferers of hemi-spatial neglect (e.g., Rorsman et al., 1999; Wilkinson et al., 2014; Zubko et al., 2013). In addition, lateral effects of GVS have been shown to be polarity specific, with left-anodal/right-cathodal electrode set-ups resulting in leftward attention shifts, where right-anodal, left-cathodal either have no effect (e.g., Patel et al., 2015), or produce rightward attention shifts (e.g. Ferrè et al., 2013). Since the current study used a left-anodal, right cathodal GVS set-up, the data appear to contrast with the majority of this previous literature as the effect in the current study seemed to occur mostly on right targets.

There are several important points to be taken into account when considering why the current data produced effects mainly for right-sided targets where previous literature might suggest GVS should predominantly affect left-sided targets. Firstly, as noted in the marginal behavioural effect in Chapter 2, there is an obvious additional complexity between the change-detection task used in the current study and the line-bisection and cancellation tasks used in previous GVS studies that require lower level cognitive processing (e.g., Ferrè et al., 2013). Further, the lateral findings of GVS are not without contradiction. For example, Nakamura et al. (2015) demonstrated no effect of left-anodal GVS but beneficial effects of right-anodal GVS in hemi-spatial neglect patients. Indeed, many lateral effects of GVS are based on literature from hemi-spatial neglect patients with left inattention, (e.g., Wilkinson et al., 2014; Zubko et al., 2013), as compared to the healthy participants in the current study who showed left attention advantages. This therefore complicates comparisons across the two. Thirdly, it is noted that the left-target advantage shown in the current study resulted in a

difference in segment numbers between left and right targets, which may have impacted power and results. Finally, it is possible that the N2pc is not the best measure for investigating lateral electrophysiological effects of GVS, since its calculation is based on the differences between ipsilateral and contralateral hemispheric response, inevitably complicating interpretation. Given these discrepancies and difficulties with interpretation, lateral electrophysiological responses to GVS are further investigated in Chapter 5.

In contrast to the N2pc findings, no clear evidence was found to support that the P3 is influenced by GVS in either Chapters 2 or 3. The notion that GVS would increase P3 amplitude was based on findings that the P3 is suppressed in patients with hemi-spatial neglect (Saevarsson et al., 2012), a condition that research has demonstrated to be improved with GVS (e.g., Oppenländer et al., 2015; Rorsman et al., 1999; Schmidt et al., 2013; Wilkinson et al., 2014; Zubko et al., 2013). Additionally, P3 amplitude to auditory stimuli has shown to be modulated by synchronised vestibular signals delivered via GVS and to visual stimuli by right-anodal GVS (Lee, Park, & Yoon, 2016). In Chapter 2, no effects of GVS on the P3 were detected. In the current chapter, P3 amplitude was impacted by stimulation, however, this occurred in both GVS and neck sham conditions relative to a no stimulation sham condition. This prevents the conclusion that this was a GVS specific effect. Additionally, follow-up tests which compared stimulation, target detection and target side separately for each electrode, fell just short of significance when corrected for multiple comparisons. This correction however was fairly conservative.

The neck-sham condition mimics any tingling sensation of GVS but does not activate the vestibular nerves (e.g., Ferrè et al., 2013). Therefore, one possible explanation for the impact of neck sham on P3 amplitude might be placebo. In particular, some studies have linked P3 in change detection with decision confidence (e.g., Bergmann, Schubert, & Hagemann, 2016; Eimer & Mazza, 2005), which could be influenced by a sense of receving

stimulation. If so, then this would explain why the effects of neck sham are not seen in either the N2pc or behavioural findings. Another explanation might be that sensory effects of stimulation increase general arousal, impacting performance. This seems a less likely explanation, however, since it is unclear why increased general arousal would not impact the N2pc. Again, these findings have important methodological implications for non-invasive neural stimulation research, since if no neck-sham condition was included here, it would be concluded that GVS impacts the amplitude of the P3.

Finally, Chapter 2 hinted at an effect of GVS on reaction time. This was such that during sham stimulation, there was a clear advantage for targets that appeared on the left. In GVS however, this difference between left and right was removed. This effect was not replicated in the current study. Given the marginal nature of the effect in Chapter 2y coupled with the lack of replication in this chapter's improved design, it is likely that this was a false positive. Important for this interpretation, however, is the fact that the GVS effect demonstrated on reaction time in Chapter 2 relies on there being a difference between left and right targets during sham, which was not present in the current chapter. This is unexpected since a clear left-side advantage was present in accuracy and reaction time in Chapter 2, and in accuracy in Chapter 3, and it is in line with previous literature (e.g., Iyilikci et al., 2010; Verleger et al., 2010). Therefore, it is possible that rather than a null effect, GVS was not able to impact reaction time in the way hinted at in Chapter 2 since the left-target advantage was not present during sham stimulation.

To summarise, the current chapter provides tentative indication that GVS may impact the N2pc, removing the difference in response to seen and unseen targets, at least when they appear on the right side of the screen. This may represent the ability of GVS to improve target detection amongst distractors in a lateral manner, and is investigated further in Chapter 5. In contrast, no evidence has been provided to support that the P3 in change detection is

impacted by GVS. The P3 data provide important methodological implications, however, for sham conditions in future brain-stimulation research, since similar responses were seen in both neck-sham and GVS conditions. Finally, the effect of GVS on reaction time remains unclear due to discrepancies in findings between Chapters 2 and 3. Therefore, Chapter 4 seeks to further investigate the behavioural effects of GVS in change detection, to resolve these discrepancies and to explore the effects of higher intensity and different GVS waveforms, before the laterality of GVS effects is investigated further in Chapter 5.

Chapter 4:

Do “noisy” GVS waveforms alter performance on a change-detection task?

Introduction

Chapters 2 and 3 demonstrated that left-anodal Galvanic Vestibular Stimulation (GVS) might be able to affect the amplitude of the attention-related ERP component, the N2pc. This may reflect the ability of GVS to improve target detection and better suppression of distractors in visuospatial tasks (e.g., Eimer, 1996; Tseng et al., 2012; Woodman, Arita, & Luck, 2009). Despite this electrophysiological effect, and though previous literature has demonstrated that GVS can alter performance on attention and visuospatial tasks in healthy participants (e.g., Blini, Tilikete, Farne, & Hadj-Bouziane, 2018; Ferrè, Longo, Fiori, & Haggard, 2013; Patel et al., 2015), the behavioural findings from Chapters 2 and 3 were mixed and have failed to demonstrate robust effects. Chapter 2 hinted at an effect of GVS and target side on reaction time, such that while a clear left-target advantage can be seen during sham, this was removed during GVS. This effect failed to replicate in Chapter 3, however, though so did the left target advantage during sham. No effects of GVS on accuracy were detected. One reason for this might be that lower intensity stimulation was used than in previous literature (e.g., Blini et al., 2018; Ferrè et al., 2013), between .28 and .45 mA in Chapters 2 and 3 respectively, versus 1mA, preventing behavioural improvement. The current chapter therefore seeks to resolve the discrepancies between the behavioural findings of Chapters 2 and 3 and investigate whether the hint of behavioural improvement demonstrated in Chapter 2 can be replicated and extended with higher-intensity stimulation. In addition, the current chapter also sought to investigate whether different types of GVS waveform are more efficient in producing behavioural improvement.

One limitation of Chapters 2 and 3 was that EEG measures prevented use of GVS waveforms that create large amounts of electrical noise in the EEG data. One such waveform that has been used frequently in previous GVS literature is known as “noisy” GVS. Noisy GVS involves applying electrical current with random fluctuations in intensity (e.g., Lee et

al., 2015; Wilkinson et al., 2014). This contrasts with the square current used in Chapters 2 and 3 in which intensity remained constant, aside from a short fade in and out period. Although improvements in attention and visuospatial tasks have been demonstrated using square current GVS (e.g., Blini et al., 2018; Ferrè et al., 2013; Oppenländer et al., 2015), there is evidence that noisy GVS might be more beneficial for improving some aspects of cognitive performance (e.g., Wilkinson, Nicholls, Pattenden, Kilduff, & Milberg, 2008). One theory for why this might be is that the addition of random noise may boost detection of weak, otherwise sub-threshold signals, for example trains of action potentials (e.g., Kim et al., 2013; McDonnell & Abbott, 2009; Moss, Ward, & Sannita, 2004). In other words, random fluctuations may "kick" neural systems into a more sensitive and dynamic state (Soma, Kwak, & Yamamoto, 2003). This is known as stochastic resonance. Taken together, these findings suggest that performance on the change-detection task used in Chapters 2 and 3 might be best improved through the use of noisy as opposed to square GVS current.

The rationale behind the decision to use low intensity current in Chapters 2 and 3 was to prevent behavioural improvement, since the primary focus was to compare ERP amplitude for seen and unseen targets across GVS and sham stimulation. An improvement in accuracy may have caused trials that were previously unseen with sham to become seen with GVS, thus masking any increase in ERP amplitude in the unseen condition. Despite this attempt, Chapter 2 revealed a marginal interaction between stimulation and target side for reaction time (p = .052). This interaction demonstrated that there was a clear left target advantage in reaction times during sham but not during GVS. The left-target advantage was also present in *d'* in both Chapters 2 and 3 and is consistent with previous literature (e.g., Iyilikci, Becker, Gunturkun, & Amado, 2010; Verleger et al. 2010). One reason the hint of the stimulation by target side effect failed to replicate in Chapter 3 might be that the left-sided advantage was not present in reaction times during sham either. Therefore, the current chapter aims to

resolve the discrepancies between the behavioural findings of Chapters 2 and 3 and to determine whether there is a left target advantage in reaction time and whether this interacts with stimulation. Further, the current chapter seeks to extend findings of Chapters 2 and 3 by maximising possibility for producing behavioural improvement by using the higher intensities of stimulation used in previous literature (e.g., Blini et al., 2018; Ferrè et al., 2013).

The current chapter therefore uses the same change-detection task as in Chapter 3 and aims to answer three questions remaining from Chapters 2 and 3. Firstly, given that a left target advantage is present in *d'* in both Chapters 2 and 3, and in reaction time in Chapter 2, it is hypothesised that participants will be more accurate at detecting and quicker to respond to targets that appear on the left side of the screen. Secondly, it is hypothesised that by using 1mA of GVS, based on previous literature (e.g., Blini et al., 2018; Ferrè et al., 2013; Oppenländer et al., 2015; Tseng et al., 2012), both square current and noisy current GVS will improve performance relative to a no stimulation sham condition. Finally, based on the evidence that "noisy" GVS may be most beneficial for cognitive performance (e.g., Wilkinson et al., 2008), it is expected that noisy GVS in particular will improve performance relative to both sham and square current GVS conditions.

Method

Participants

Sixty participants were recruited from the University of Kent in exchange for course credit. Three participants were removed from the analysis; one for failure to complete the study protocol and two for colour vision deficiency, defined as scores of less than 17 on the Ishihara Tests for Colour Blindness (Ishihara, 1994). As in Chapters 2

and 3, participants were screened for suitability to receive GVS, ensuring they had no history of seizures, vestibular or neurological disease. This left 45 females and 12 males, all right handed, aged between 18 and 32 years, M = 19.5 SD = 1.94. All participants gave informed consent and the procedures were approved by the University of Kent Psychology Ethics Committee.

Stimuli and Apparatus

Stimuli were identical to that described in Chapter 3 (see Figure 4.1). Displays of rectangles were coloured by selecting randomly from red, blue, violet, green, yellow, black and white. Rectangles were sized at 2.20° high and 2.01° wide, with a minimum of 3.01° horizontal and 1.01° vertical distance kept between them. Rectangle distance from fixation ranged from 11.92° horizontally and 6.43° vertically. The same number of rectangles were presented on the right and left sides of the screen. The number of rectangles used was individually titrated using a 1-up 2-down staircase procedure as described in Levitt, (1970). For each incorrect answer, one pair of rectangles, one left and one right, was removed while one pair was added for two consecutive correct answers. This continued for 20 reversals, where an average number of rectangles was taken and used in the main experiment. The number of rectangles ranged from 6 to 14, M = 3.55. Stimuli were presented on a 1920x1080 BenQXL2420T monitor with a 100Hz refresh rate. The experimental protocol was controlled by PsychoPy (Peirce, 2007).

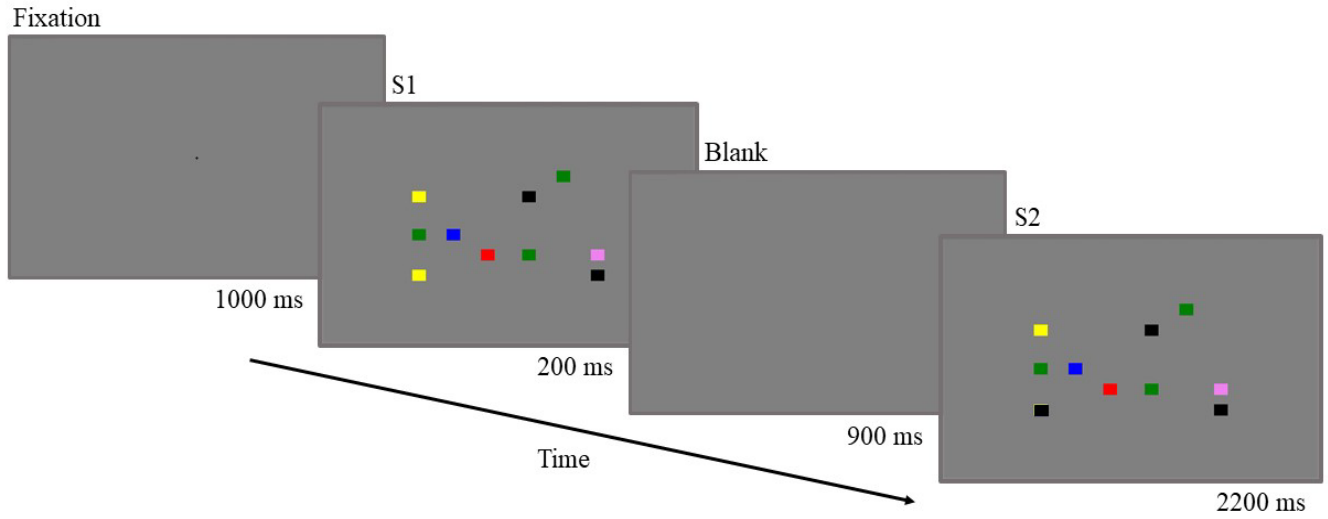

Figure 4.1. Stimuli and timeline for each trial. In this example, the change target appears in the lowe left corner and changes from yellow to black.

Procedure

Following GVS set-up, participants were seated in the lab 57 cm from the screen. Participants first completed 30 practice trials to create familiarity with the task. Difficulty of the task was then individually adjusted using a 1-up 2-down staircase procedure as described in Levitt, (1970). After this, participants completed a second practice followed by six experimental blocks. The practice trials, staircase procedure and experimental blocks were all comprised of the same task as follows. Two displays of coloured rectangles were shown briefly, separated by a short blank. The first display (S1) was displayed for 200ms, followed by a blank of 900ms, followed by the second display (S2) that was displayed for 2200ms, or until a response was made. A centrally located fixation marker was displayed at the start of each trial for 1000ms. On 75% of trials, one of the rectangles changed colour. Participants were required to indicate whether they saw one of the rectangles change colour by two forced choice. As in Chapters 2 and 3, there were 426 trials in total, including 320 trials where a target changed colour, 160 on the left and 160 on the right. Additionally, there were 106 trials

in which no change occurred. Following participation, subjects were debriefed and informed of the sham condition and were asked to make a forced choice on whether they received active or sham stimulation.

GVS Protocol

GVS was set-up following the practice trials and switched on for the duration of the experimental blocks. The skin behind the ears was cleansed using an alcohol swab and conductive gel, before applying carbon rubber, auto-adhesive electrodes over the mastoids. The electrodes were connected to a NeuroConn DC-Stimulator Plus device. As in Chapters 2 and 3, left-anodal/right-cathodal stimulation was applied, but at the higher intensity of around 1mA with a 60 second fade in and out period. Participants either received broadband noise-enhanced GVS (n = 20), square current GVS (n = 19) or sham stimulation (n = 18)[5]. Noisy current was generated from random numbers following a gaussian distribution, with 99% of numbers falling within .5 to 1.5 mA. This waveform generated a wide-band noise signal of 0 – 250 Hz. For those in the sham condition, electrodes were set up in the same way but the switching on of the stimulation was only feigned (as in Chapter 2). Following participation, participants were asked whether they thought they had received active or sham stimulation.

Results

Overall accuracy was close to that predicted by the up-down staircase procedure described in Levitt (1970), with 70% for sham, 64% for square current and 67% for noisy current.

d'. Average *d'* scores were computed separately for noisy GVS, square-current GVS and sham stimulation. To test the hypothesis that GVS would improve *d'* scores relative to a sham condition, and most maximally with noisy GVS current, a 3 x 2 ANOVA was

[5] Unlike Chapter 3, no neck-sham condition was included in the current study. This is because preliminary analysis gave indications that the neck-sham condition was also reaching vestibular nerves. This later proved to be incorrect, nonetheless, no neck sham data was collected for this or the following chapters.

conducted comparing stimulation (noisy, square or sham GVS) and target side (left or right.) Mean *d'* plotted as a function of stimulation and target side is presented in Figure 4.2.

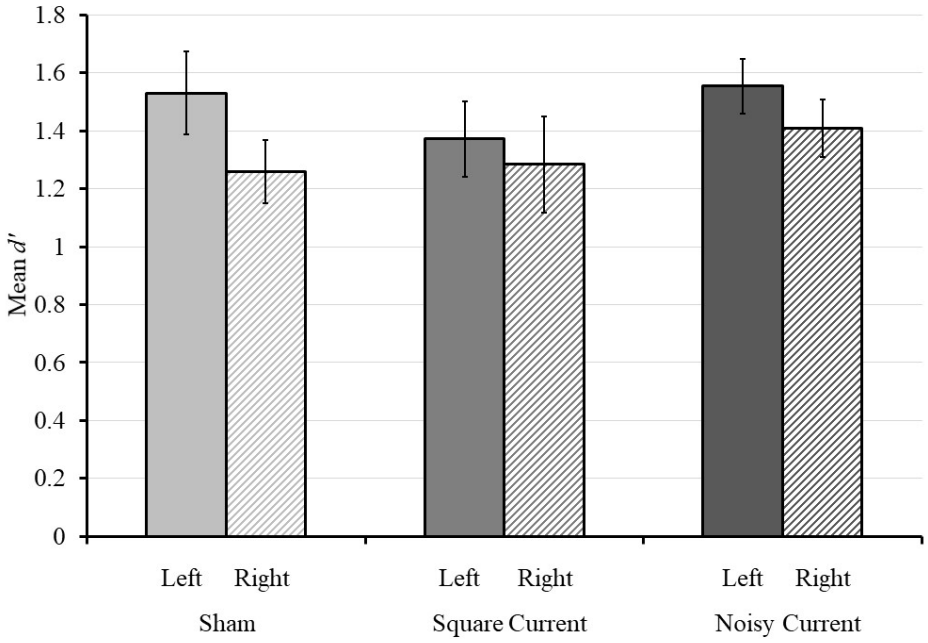

Figure 4.2. Mean (n = 57) d-prime plotted as a function of stimulation and target side. Error bars indicate standard errors.

As in Chapters 2 and 3, and in line with previous literature demonstrating a natural leftward bias in healthy individuals (e.g., Iyilikci et al., 2010; Verleger et al., 2010), participants more accurately detected targets on the left, M = 1.49, than on the right, M = 1.32, $F(1, 54) = 17.36$, $p < .001$, $\eta_p^2 = .24$. There was no main effect of stimulation, $F(1,54) = .41$, $p = .666$, $\eta_p^2 = .02$, and no stimulation by target side interaction $F(1,13) = 1.75$, $p = .184$, $\eta_p^2 = .06$.

Reaction Time. Average reaction time for noisy GVS, square GVS and sham stimulation were computed for target-present trials only. To test the hypothesis that noisy GVS would improve reaction time most, followed by square GVS and sham stimulation, a 3

x 2 x 2 ANOVA was conducted comparing the effects of stimulation (noisy, square or sham GVS), target side (left or right) and target detection (seen or unseen). Mean reaction times for each condition are presented in Figure 3.3. As in Chapter 2, a natural leftward bias was detected through a main effect of target side $F(1,54) = 7.67$, $p < .01$, $\eta_p^2 = .12$. Mean reaction time was quicker for left targets, $M = .92$s, than right targets, $M = .94$. There were no other main effects, all $Fs < .53$, all $ps > .590$, and no interactions, all $Fs < .74$, all $ps > .482$.

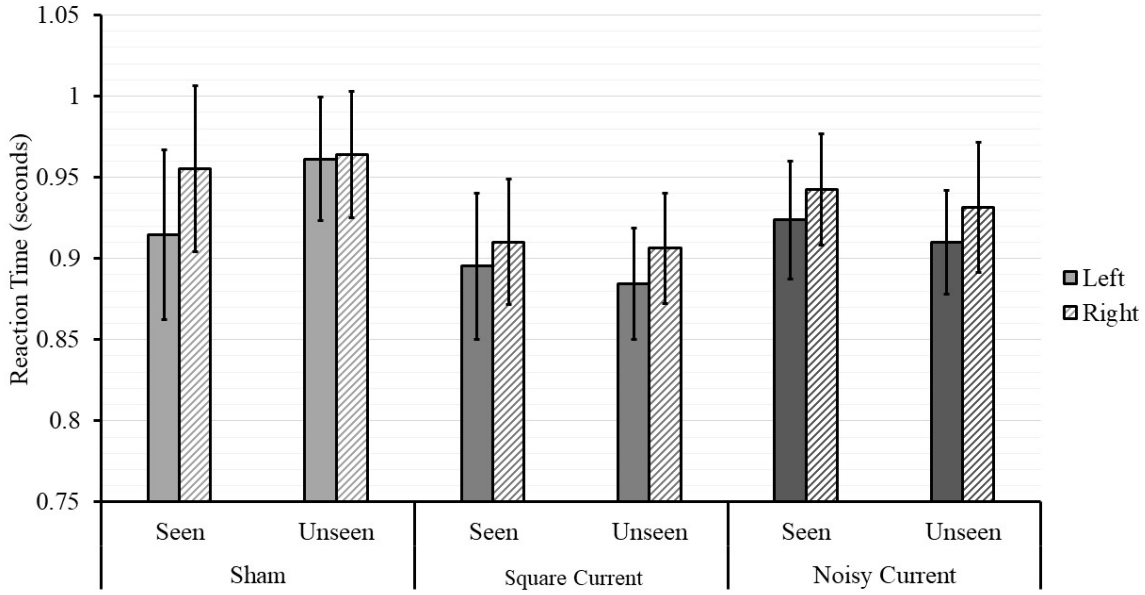

Figure 3.3. Mean reaction times (n = 57) plotted as a function of stimulation, target detection and target side. Error bars indicate standard error.

Despite the higher intensity of stimulation compared to Chapters 2 and 3, GVS was well tolerated by all participants, who only reported tinging and itching as side effects. 40 participants were asked following debrief whether they thought they had received active or sham stimulation. 73.91% of the 23 participants who received active stimulation (either noisy or square) correctly identified that they had received active stimulation. 47.01% of the 17 participants who received sham stimulation also reported that they felt they had received active stimulation. A chi-square test of independence demonstrated that although there was a

numerical difference, this did not reach significance X^2 (1, N = 40) = 3.01, p = .083. Failure to reject the null hypothesis therefore provides no evidence of an association between receiving active stimulation and believing that active stimulation was received.

Discussion

Chapters 2 and 3 demonstrated that square current GVS might be able to impact electrophysiological correlates of a change-detection task. Behavioural results however were mixed. Chapter 4 aimed to resolve discrepancies between the behavioural findings of Chapters 2 and 3 and to extend them by maximising the potential for behavioural improvement using higher-intensity stimulation as used in previous GVS literature (e.g., Blini et al., 2018; Ferrè et al., 2013; Oppenländer et al., 2015). Additionally, based on findings that fluctuating GVS current might be more effective at improving cognitive performance than square GVS current (Wilkinson et al., 2008), Chapter 4 aimed to compare performance on a change detection task under these two stimulation conditions. The results demonstrated that even with the higher intensity of stimulation, no behavioural improvement was induced with GVS relative to a no-stimulation sham condition. In addition, noisy GVS was no more effective at improving behavioural performance than square current GVS was. Taken together, these findings suggest that the GVS protocols used in previous literature are insufficient to induce behavioural improvement on a change-detection task, at least in this context.

Chapter 2 hinted at an effect of stimulation on reaction time through a marginal stimulation by target side interaction. The marginal nature of the effect coupled with the lack of replication likely suggests the Chapter 2 result was a false positive. An alternative explanation might be the differences in paradigm between that used in Chapter 2 and in Chapters 3 and 4, including the use of a between-participants design as opposed to within-

participants and differences in accuracy scores. Performance generally was much lower in Chapter 2 in terms of *d'*. Tseng et al. (2012) demonstrated using the same change-detection paradigm that tDCS only improved behavioural performance in low performing individuals. This might suggest that the lower accuracy performance in Chapter 2 enabled the reaction time effect with GVS whereas the higher accuracy in Chapters 3 and 4 did not. Although beyond the scope of this thesis, this possibility could be tested by repeating the experiment in Chapter 4 but using the Levitt (1970) individual difficulty staircase procedure to produce accuracy similar to that in Chapter 2. Alternatively, a within-participants design could be used and participants split into low and high performing groups based on their accuracy during sham (as in Tseng et al., 2012), to investigate whether low performing individuals showed improvement with GVS. Comparison of low and high performing individuals was not possible in the current study since a between-participants design was used, making it unclear how low and high performing sham participants should be paired with GVS counterparts.

An obvious difference between the protocols used in Chapter 2 and Chapter 4 is the different intensities of GVS, with an average of .35 mA in Chapter 2 and 1 mA in Chapter 4. The rationale behind using 1 mA in Chapter 4 was to mirror the intensities given in previous GVS literature that have been shown to induce behavioural effects (e.g., Blini et al., 2018; Ferrè et al., 2013; Oppenländer et al., 2015) in an effort to extend the marginal behavioural effect shown in Chapter 2. Evidence from tDCS, TMS and limited GVS literature, however, has demonstrated that the relationship between amount of stimulation and behavioural improvement is not linear and higher intensity or more stimulation does not necessarily result in greater improvement (e.g., Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Schwarzkopf, Silvanto, & Rees, 2011; Wilkinson et al., 2014). Benwell et al. (2015), for example, demonstrated that tDCS effects on lateralised attention involved a complicated

interaction between stimulation dose and baseline performance, such that in some groups participants with lower doses of stimulation showed greater improvement. Similarly, Wilkinson et al. (2014) demonstrated that one session of GVS was equally effective as 10 sessions in improving attention bias in hemi-spatial neglect participants. It is possible therefore that in this context, the lower intensity stimulation used in Chapter 2 was more beneficial.

One suggestion put forward to explain the paradoxical effects of stimulation dose as shown in Benwell et al. (2015), is stochastic resonance. Stochastic resonance refers to the phenomenon where application of noise can boost the detection of a weak signal (e.g., McDonnell & Abbott, 2009; Moss et al., 2004). TMS studies such as that by Schwarzkopf et al. (2011) have demonstrated that under different conditions, low intensity stimulation can improve cognitive performance while high intensity stimulation impairs performance. As in Benwell et al. (2015) this has also shown to be affected by a complex relationship with baseline performance and individual differences. At this stage, it is only possible to speculate on whether stochastic resonance might offer an explaination for the marginal stimulation effect with lower intensities in Chapter 2, but not higher intensity in Chapter 4, especially since it is unclear how far square current in particular can be considered a source of physiological noise (Benwell et al., 2015). However, the possibility opens up new avenues of research into investigating optimal levels of stimulation in different paradigms and its relationship to baseline performance and individual differences.

The final finding of the current chapter has methodological implications for the use of control groups in non-invasive brain stimulation studies. In Chapter 2, a within-participants design was used with levels of stimulation adjusted to be sub-sensory, following protocols described in previous GVS research (Wilkinson et al., 2008). Findings demonstrated that although participants reported they were unable to feel stimulation, almost all correctly

identified when they had received active GVS versus sham stimulation in a forced choice. The current chapter therefore used a between-participants design and following debrief, asked participants whether they felt they had received active or sham stimulation. Only around half of those who received sham stimulation believed they had received active stimulation. This demonstrates that setting up of electrodes and feigning switching them on may not be sufficient to be convincing with 1 mA of stimulation, however it may be at lower intensities. The current chapter did however demonstrate that there was no association between receiving active stimulation and believing to have received active stimulation, therefore suggesting that between-participants designs might be a more effective method for sham controlling GVS and dissociating specific effects from placebo.

In summary, Chapter 4 demonstrated that 1 mA of GVS did not improve performance on a change-detection task relative to a no-stimulation sham condition. Additionally, the findings demonstrate that "noisy" current GVS was no more effective at improving performance than square current GVS. These findings are in partial contrast to a marginal stimulation effect on reaction time demonstrated in Chapter 2. Given the marginal nature of the effect in Chapter 2, coupled with the failure to replicate the effect in both Chapters 3 and 4, it is likely that the effect of GVS on reaction time was a false positive. It is important to note however that there were some key differences between the protocols used in Chapter 2 and in Chapters 3 and 4 that might also explain the null effects. For example, Chapter 2 used a within-participants design and had low accuracy scores as compared to the higher accuracy scores and between-participants design used in Chapters 3 and 4. It is possible therefore that individual differences may influence GVS effects. The findings presented here therefore open up further avenues of research into the effect of baseline performance and optimal levels of stimulation on change-detection performance.

The final empirical chapter of this thesis investigates an unresolved issue arising from Chapters 2 to 4 on the interaction between GVS and target side. The lateral effects of GVS have been documented previously (e.g., Ferrè et al., 2013; Patel et al., Wilkinson et al., 2014; Zubko et al., 2013). However, the effects of target side in the previous Chapters have been mixed. Chapter 5 therefore aims to investigate the lateral effects of GVS further, using an electrophysiological technique known as steady-state visual-evoked potentials (SSVEP).

Chapter 5:

The effect of galvanic vestibular stimulation on visual-evoked potentials

Introduction

Chapters 2 and 3 demonstrated that left-anodal GVS may improve target detection and suppression of distractors, indicated by an impact of GVS on the amplitude of ERP component N2pc. The lateralisation of GVS effects through the previous chapters, however, have been mixed. In particular, Chapter 3 demonstrated that the N2pc was only impacted for targets that appeared on the right side of the screen. This appears in contrast to much of the previous literature on the lateral effects of GVS, since the majority of findings suggest that left-anodal GVS should be better at shifting attention, and therefore lead to greater improvement, towards the left (e.g., Ferrè, Longo, Fiori, & Haggard, 2013; Rorsman, Magnusson, & Johannson, 1999; Utz, Keller, Kardinal, & Kerkhoff, 2011; Wilkinson et al., 2014). This evidence though is not without contradiction (e.g., Nakamura, Kita, Kojima, Okada, & Shomoto, 2015). These previous studies use much simpler tasks than that used in Chapters 2 to 4, such as line-bisection and cancellation tasks. Additionally, their findings are based on behavioural rather than electrophysiological measures. Importantly, interpretation of the lateral findings of Chapter 3 are complicated due to how the N2pc is calculated. The current chapter therefore aims to further investigate lateral-electrophysiological effects of GVS using a technique known as steady-state visual-evoked potentials (SSVEPs). SSVEPs are well suited to answering attention-related questions, since they provide measures of neural responses that can be unambiguously associated with specific external stimuli (Norcia, Appelbaum, Ales, Cottereau, & Rossion, 2015).

A difficulty in interpretting the lateral effect of GVS on the N2pc is that the calculation of the N2pc is based on the difference between ipsilateral and contralateral hemispheric response. That is, the N2pc for a left target, for example, is calculated by subtracting the amplitude at the ipsilateral (left) hemisphere, from the amplitude at the contralateral (right) hemisphere. This makes it impossible to exclude complicating factors of

hemisphere, for example, potential baseline differences between the two, from the interpretation of lateral effects. Another way to analyse N2pc data is to compare hemisphere instead of target side. That is, compare the amplitude separately in the left hemisphere and in the right hemisphere, collapsed over left and right targets. Of course, this also raises issues as this would mask modulations of the N2pc that only occur for one target side. Both target side and hemisphere effects cannot be investigated in one ANOVA, because it would be impossible to have, for example, a left hemisphere ipsilateral response to a right target, since right targets are contralateral to the left hemisphere. Chapter 3 compared effects of target side based on the method by Tseng et al. (2012), who investigated the effects of tDCS on the N2pc in change detection. Due to the finding that GVS affected different target sides differently, coupled with difficulties in interpretting purely target-side effects using the N2pc, further investigation into the lateral electrophysiological effects of GVS is warranted.

SSVEPs are measurable neural oscillations that occur in response to flickering visual stimuli at a constant frequency (e.g., İşcan & Nikulin, 2018). The neural oscillations occur at the same frequency and higher harmonics of the flickering stimuli. SSVEPs are particularly useful for measuring the spatial distribution of attention, since neural responses can be monitored across different spatial positions by flickering stimuli in various locations at different frequencies (e.g., Hillyard & Anllo-Vento, 1998; Morgan, Hansen, & Hillyard, 1996; Muller et al., 1998; Pitzalis, Spinelli, Vallar, & Di Russo, 2013; Toffanin, Jonga, Johnson, & Martens, 2009). This technique is known as frequency tagging. Previous literature has demonstrated that attending to a specific spatial location increases the SSVEP amplitude at only the frequency associated with the attended object (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Toffanin et al., 2009). For example, Morgan et al. (1996) presented participants with two rapid steams of letters played over the top of flickering stimuli at two distinguishable frequencies. When asked to identify numbers

in one stream and ignore the other, SSVEP amplitude at the associated background frequency increased. SSVEPs, therefore, provide an ideal measure to examine lateral influences on attention caused by GVS, since any shifts should be reflected in SSVEP power.

Lateral effects of GVS on spatial perception and attention have been found to be polarity specific (e.g., Ferrè et al., 2013; Patel et al., 2015; Saj, Honoré, & Rousseaux, 2006). For example, Ferrè et al., (2013) demonstrated that while left-anodal/right-cathodal stimulation resulted in a bias toward the left side in a line-bisection task in healthy participants, left cathodal/right anodal stimulation resulted in the opposite. This is in line with GVS protocols used in a number of studies on participants with hemi-spatial neglect, who use left-anodal/right-cathodal GVS to ameliorate left-sided inattention (e.g., Rorsman et al., 1999; Wilkinson et al., 2014; Zubko et al., 2013). A smaller number have also found right-anodal/left-cathodal to be effective for certain tasks (e.g., Nakumara et al., 2015; Oppenländer et al., 2015; Utz, Keller, Kardinal, & Kerkhoff, 2011). For example, Nakumara et al. (2015) found that only right-anodal stimulation ameliorated inattention in hemi-spatial neglect participants, while Oppenländer et al. (2015) demonstrated that left-anodal best improved figure-copying and cancellation tasks and right-anodal was best for line bisection.

A theory for these polarity effects, and in particular why the majority of studies demonstrate left-anodal GVS is most beneficial for ameliorating inattention in patients, is that left-anodal GVS has been demonstrated to result in higher increases in activity in the right posterior parietal cortex than right-anodal GVS (e.g., Fink et al, 2003). The right parietal cortex has been previously associated with directing attention to both visual fields, as compared to the left parietal cortex which is associated with directing attention primary to the right visual field only (e.g., Fink, et al., 2003; Heilman & Van Den Abell, 1980). Over-excitation of the right posterior parietal cortex with left-anodal GVS may therefore induce a contralateral attention bias (Ferrè et al., 2013).

Initially, ERP components that have been associated with shifts in attention were considered to investigate the lateral effects of GVS in this chapter. For example, the early directing attention negativity (EDAN) component has been associated with recognition of a spatial cue and the consequent redirection of attention (e.g., Harter & Anllo-Vento, 1991; Talsma, Slagter, Nieuwenhuis, Hage, & Kok, 2005). The anterior directing attention negativity (ADAN), on the other hand, has been suggested to reflect control of visuospatial attention (e.g., Eimer, van Velzen, Forster, & Driver, 2003; Talsma et al., 2005). Additionally, the late directing attention positivity (LDAP) has been taken to reflect changes in activity in visual sensory areas in anticipation of an expected stimulus (Eimer, 2014; Talsma et al., 2005). These components, however, like the N2pc, are calculated on the basis of ipsilateral and contralateral hemisphere response, and therefore involve the same complications of hemisphere in interpretation. Although these components would be of interest in future research, it was decided to use SSVEP amplitude as the measure for the current chapter as a clearer measure of unambiguous spatial attention.

SSVEPs have shown to be influenced by electrical stimulation previously. For example, Pitzalis et al. (2013) used transcutaneous electrical nerve stimulation (TENS), a related form of electrical stimulation, applied over the left trapezium muscle. In a sample of neglect patients, Pitzalis et al. (2013) found hemi-field assymetries in SSVEP latency were significantly reduced following TENS application. Importantly, similar, if smaller, effects on SSVEP latency were demonstrated in a sample of healthy participants. Though this study did not investigate polarity specific effects of stimulation, these findings demonstrate that SSVEPs are a useful tool for measuring electrophysiological spatial measures of attention.

The current chapter therefore measured SSVEPs to investigate lateral, electrophysiological effects of GVS. Based on a previous study demonstrating the impact of a different form of stimulation, transcutaneous electrical nerve stimulation (TENS), on

SSVEPs, stimuli consisted of sinusoidal gratings presented either unilaterally on the left or right, or bilaterally (Pitzalis et al., 2013). The contrast of the grating was reversed at either 6 Hz or 7.5 Hz, with these frequencies chosen to fall within the range used by Pitzalis et al. (2013) and to work with the refresh rate of the monitor. For consistency with previous studies that have demonstrated lateral effects of GVS (e.g., Ferrè et al., 2013; Wilkinson et al., 2013; Zubko et al., 2013), GVS was applied at an intensity of 1 mA. To investigate the polarity-specific effects of GVS, participants received either left-anodal/right-cathodal GVS, right-anodal/left-cathodal GVS, or sham stimulation in which no stimulation was applied. Based on the findings of Ferrè et al. (2013) and Patel et al. (2015) on healthy participants, it was hypothesised that left-anodal stimulation would increase SSVEP amplitude for left-sided stimuli while right-anodal stimulation would increase SSVEP amplitude for right-sided stimuli. Additionally, based on findings that SSVEP amplitudes are greater for focussed versus divided attention (Toffanin et al., 2009), it was expected that amplitude would be higher for unilateral stimuli displays.

Method

Participants

40 participants were recruited from the University of Kent in exchange for payment or course credit. Four participants were excluded for not completing the study protocol. The remaining sample included 23 females and 13 males, all right handed, aged between 18 and 23, $M = 19.8$, $SD = 1.4$. As in Chapters 2 to 4, participants were screened for suitability to receive GVS. In addition to GVS exclusion criteria, participants were also excluded from participating if they had a history of migraine or headaches, on account of the flickering stimuli. All participants reported normal or corrected to normal vision.

Stimuli

Stimuli were similar to that used in Pitzalis et al. (2013) study into the effect of TENS on SSVEPs. They consisted of horizontal sinusoidal 0.67 cycles per degree (cpd) gratings, presented on a grey background either side of a centrally located fixation cross (see figure 5.1). Gratings were 17.81º square with an 50% contrast and presented 2.67º from the fixation cross. SSVEPs were elicited by reversing the contrast of the grating at two temporal frequencies of either 6Hz or 7.5Hz. Stimuli were presented on a 1920x1080 BenQXL2420T monitor with a 120Hz refresh rate. The experimental protocol was controlled by PsychoPy (Peirce, 2007).

Procedure

Following GVS and EEG set-up, participants were seated in the lab and positioned in a chin rest 60cm from the screen. Participants were requested to passively observe the flickering grating presented on the screen, keeping fixation on the centrally located cross. They were not required to make any response or participate in a task. Each trial lasted for five seconds. Trials were separated with a random interval of 1 to 1.5 seconds in which only the fixation cross appeared on screen. Per block, eight trials presented a grating in the LVF, eight trials presented a grating in the RVF and eight trials presented gratings bilaterally. These were presented in random order. There were eight blocks, making 192 trials in total. A 10 second break was given between each block to allow participants a short rest. To control for order effects, half of the blocks flickered stimuli in the LVF at 6Hz and the RVF at 7.5Hz (sequence 1), and vice versa for the remaining half (sequence 2). A five minute break was given between sequence 1 and 2 blocks to prevent any carry over effects. The order of sequences 1 and 2 were counterbalanced between participants. Participants received either

sham stimulation (*N* = 11), left-anodal GVS (*N* = 13), or right-anodal GVS (*N* = 12) in a between-subjects design.

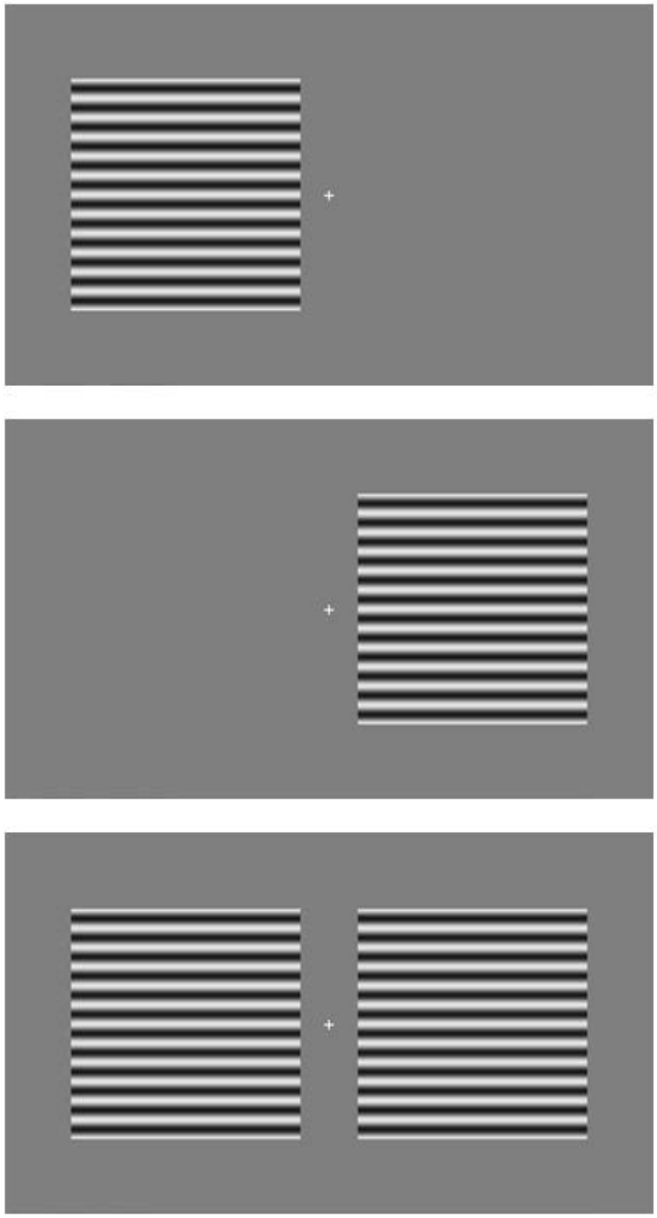

Figure 5.1. Examples of left unilateral, right unilateral and bilateral stimulus displays.

GVS Protocol

As in previous chapters, participants were prepared for GVS by cleansing the skin behind the ears with an alcohol swab and conductive gel. GVS electrodes were then placed

over the mastoids. Participants in the LGVS condition received bilateral, bipolar stimulation comprised of left-anodal and right-cathodal stimulation. Participants in the RGVS condition received right-anodal and left-cathodal stimulation. Participants in the sham condition had electrodes set up in the same way, however they were not switched on. Stimulation was applied at 1mA with a 60 second fade in and 30 second fade out period. Following debrief, participants were given a forced choice of what stimulation condition they thought they were in.

Electrophysiological Recording and Analysis

EEG was recorded using Brain Products BrainAmp DC system using Ag/AgCl electrodes in a standard 64 electrode arrangement (International 10/10 System.) FT9 and FT10 were removed and placed one at the side of the eye and one below the eye, to record electro-oculogram (EOG). Electrodes were referenced online to FCz using AFz as the ground, then re-referenced offline to Cz (as in Pitzalis et al., 2013). TP7, TP8, TP9, TP10, P7 and P8 were removed as these overlied the GVS electrodes. During recording, electrodes were sampled at 1000 Hz and impedences kept below 10kΩ. A 250Hz low pass filter was applied at recording to prevent aliasing of higher frequencies.

EEG data was analysed using Brain Vision Analyzer 2.2. The data were bandpass filtered at 1-100 Hz. Semi-automatic artifact rejection was conducted to remove non-ocular artifacts exceeding 75 μV. Ocular artifacts were corrected using semi-ocular ICA correction. Data were segmented into 3000 ms epochs, consisting of the middle three seconds of the trial's stimuli presentation. The first and last 1000 ms for each trial were removed. Artifact rejection resulted in an average of 31.44 segments for unilateral left displays. 31.19 for unilateral right and 31.46 for bilateral displays. Segment numbers were not significantly different between conditions, all Fs < 1.72 and all ps > .200. Similar to Pitzalis et al. (2013),

data was exported from Oz for the second harmonic, in windows of 11.75 – 12.25 Hz and 14.75 – 15.25 Hz. Data were then log transformed using the natural log.

Results

To test the hypothesis that left-anodal GVS would increase SSVEP for left stimuli and right-anodal GVS would increase SSVEP power right stimuli, a 3x2x2 ANOVA was conducted comparing factors of stimulation (between participants sham, left-anodal/right-cathodal GVS or right-anodal/left-cathodal GVS), display configuration (within participants unilateral or bilateral stimuli) and target side (within participants left or right). Mean SSVEP amplitudes for each condition are presented in Figure 5.2, with more power indicated by shorter bars.

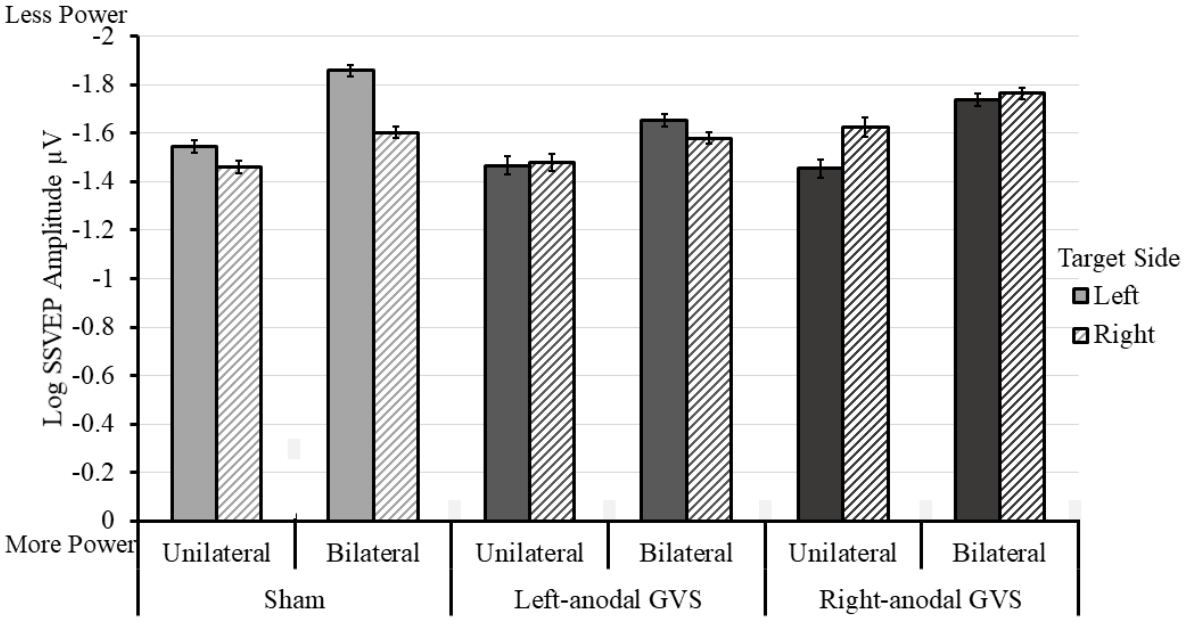

Figure 5.2. Mean SSVEP amplitudes for each condition. More positive scores indicate higher power. Error bars indicate standard error.

As predicted and in keeping with previous literature (Toffanin et al., 2009), SSVEP amplitude was higher for unilateral than bilateral displays, as demonstrated by a main effect of display configuration, $F(1, 33) = 30.87$, $p < .001$, $\eta_p^2 = .48$. There was also a display configuration by target side interaction, $F(1, 33) = 6.57$, $p = .015$, $\eta_p^2 = .17$, depicted in Figure 5.3. To investigate this interaction, paired-samples *t*-tests (with alpha corrected at .05 / 4 = .013) first compared left and right stimuli separately for unilateral, $t(35) = .68$, $p = .499$, $d = .09$, and bilateral stimulus displays, $t(35) = 1.75$, $p = .089$, $d = .28$, finding no differences. Next, unilateral and bilateral stimulus displays were compared separately for left and right stimuli, finding that power was greater for unilateral displays for both left and right displays, though this effect was larger for left than right displays $t(35) = 5.86$, $p < .001$, $d = .96$ and $t(35) = 3.02$, $p = .005$, $d = .56$, respectively.

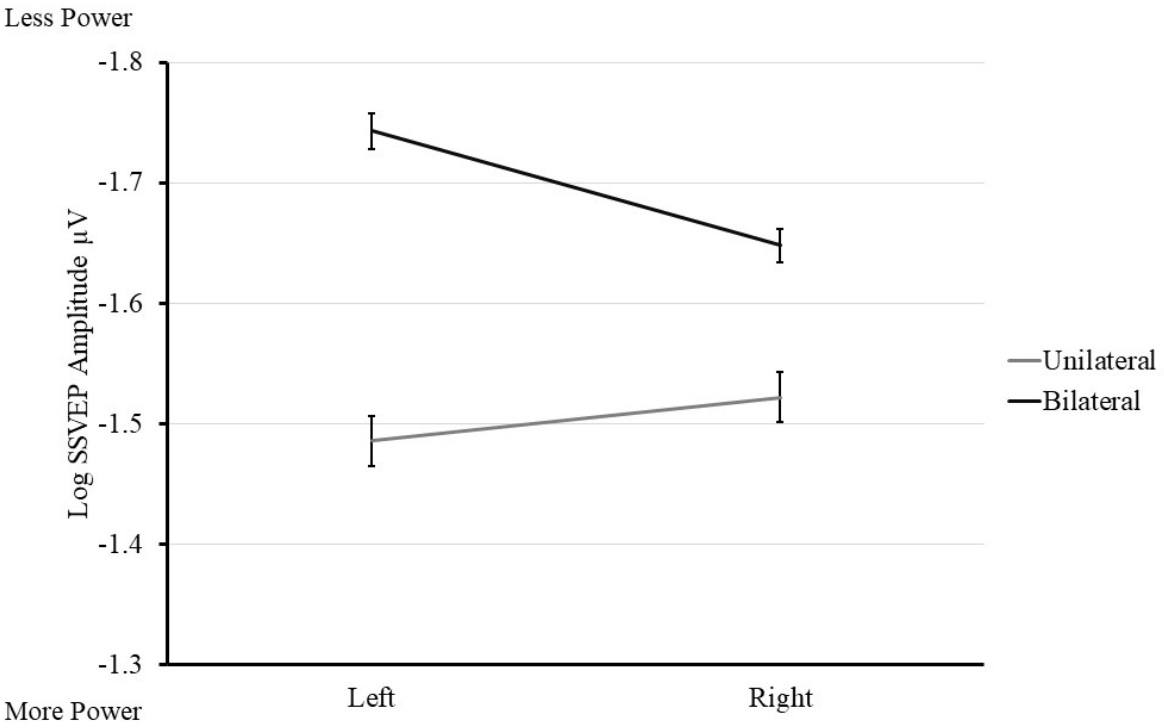

Figure 5.3. Mean SSVEP amplitude, plotted as a function of target side and display configuration. More positive scores indicate higher power.

No significant effects of stimulation were detected, however there was a marginal stimulation by target-side interaction, $F(2, 33) = 2.80$, $p = .075$, $\eta_p^2 = .15$, depicted in Figure 5.4. Due to the strong prediction of effects of stimulation on target side, this interaction was investigated further. Paired-samples *t*-tests (with alpha corrected at .05 / 3 = .017) compared left and right stimuli separately for sham, $t(10) = 1.24$, $p = .244$, $d = .37$, left-anodal GVS, $t(12) = .244$, $p = .811$, $d = .07$, and right-anodal GVS, $t(11) = 2.16$, $p = .054$, $d = .65$. No differences were detected, though right-anodal GVS was approaching significance, with higher amplitude for left versus right stimuli.

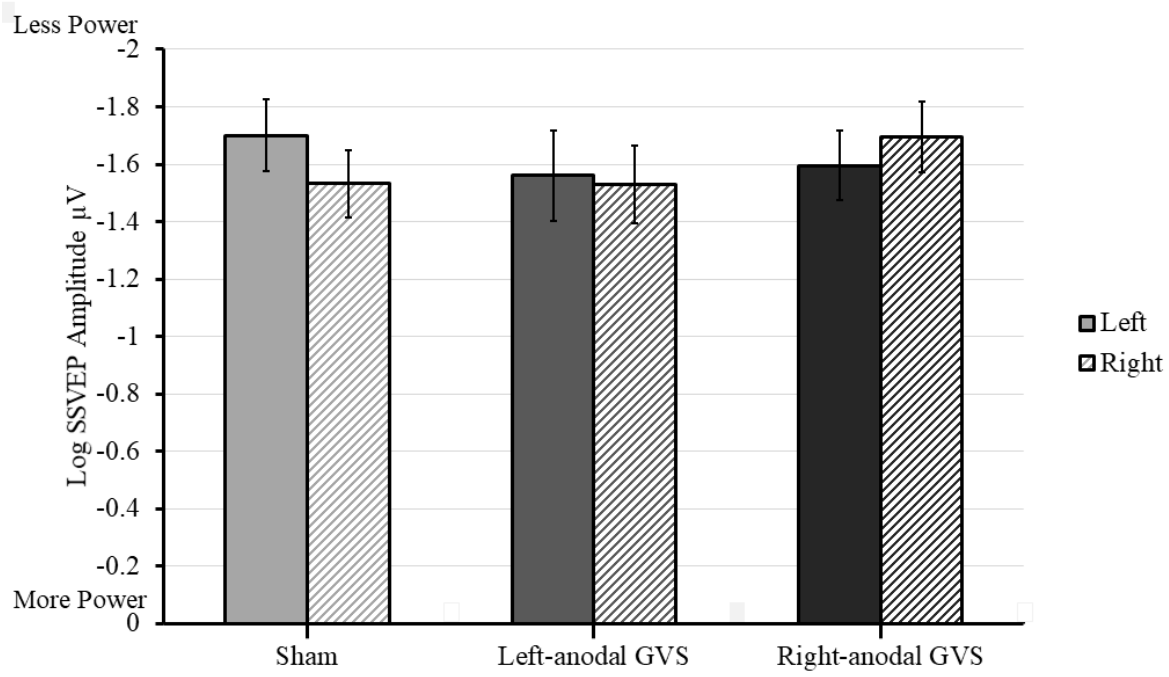

Figure 5.4. Mean SSVEP amplitude plotted as a function of stimulation and target side. More positive scores indicate higher power. Error bars represent standard error.

The remaining main effects, of stimulation and target side, were not significant, both Fs < .54, ps > .568, neither were there any further interactions, both Fs < .56 and both ps > .576.

Discussion

Chapters 2 and 3 indicated that GVS impacted the amplitude of the attention-related ERP component, the N2pc. This may reflect the ability of GVS to improve target detection among distractors. The lateral effects of GVS, however, were less clear. In particular, Chapter 3 demonstrated that N2pc was only affected for targets that appeared on the right side of the screen. Lateral effects of GVS have been shown previously, most evidently in its use to ameliorate symptoms of lateral attention impairments in hemi-spatial neglect participants (e.g., Rorsman et al., 1999; Utz et al., 2011; Wilkinson et al., 2014; Zubko et al., 2013). In healthy participants, the effects of GVS have been shown to be polarity specific, biasing line-bisection judgements in opposite directions depending on whether the anodal electrode appears on the left or the right (e.g., Ferrè et al., 2013). The current chapter therefore aimed to investigate the lateral effects of GVS in healthy individuals, using an electrophysiological measure of spatial attention, SSVEPs. Based on the findings that SSVEP amplitude increases with attention (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Toffanin et al., 2009) and the polarity-specific effects described by Ferrè et al. (2013) and Patel et al. (2015), it was hypothesised that a left-anodal/right-cathodal GVS set-up would increase SSVEP amplitude for left stimuli, while a right-anodal/left-cathodal GVS set-up would increase SSVEP amplitude for right stimuli. These predictions were not supported by the current data, which showed no significant changes to SSVEP amplitude occurred during GVS.

The paradigm used in the current study was based on the idea of "frequency tagging", a technique used to measure attendance to various spatial locations by flickering stimuli at different locations at different frequencies and measuring the resultant neural oscillations (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Pitzalis et al., 2013; Toffanin et al., 2009). SSVEPs therefore have an advantage for measuring lateral effects of GVS over the N2pc measure used in Chapters 2 and 3, since neural response can be unambiguously associated with attendance to a specific spatial location. The current chapter found that, consistent with previous literature (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Toffanin et al., 2009), SSVEP amplitude was higher when attending to unilateral stimuli rather than divided over bilateral stimuli. This finding therefore demonstrates that the basic paradigm was functioning as expected.

Contrary to expectations, no clear target side effects were found in the current data. There was an interaction between target side and display configuration (unilateral or bilateral). However, when broken down, this demonstrated that while numerically SSVEP amplitude was higher for right-sided targets during unilateral displays and left-sided targets during bilateral displays, there was no significant difference between left and right for either unilateral or bilateral display configurations. With the exception of reaction time in Chapter 3, the behavioural findings from Chapters 2 to 4 indicated a clear left-sided advantage in *d'* and reaction time in the basic (sham) conditions. Given therefore that the SSVEP paradigm used in the current study could measure levels of attending to either side, it could reasonably be expected to see this left-sided advantage reflected here, but this was not the case. A possible explanation for this discrepancy is that through Chapters 2 to 4, participants were engaged in a difficult change-detection task. Left-sided advantages in similarly demanding tasks have been shown previously (e.g., Verleger et al., 2010). In contrast, the current chapter involved participants sitting passively without a demanding cognitive load, which might

explain why the left-sided advantage did not occur. This paradigm was based on the study by Pitzalis et al. (2013), who investigated the effects of TENS on SSVEPs. Additionally, it was decided that participants would sit passively to enable measurement of purely GVS effects on lateral SSVEP amplitude, rather than alerting attention one way or another by introducing a task. Further research however could utilise a task played over the flickering gratings to investigate any target side differences while engaged in an active task.

No significant effects of GVS were detected in the current study. There was a marginal interaction between stimulation and target side (p = .075), which indicated a marginally higher (p = .054) SSVEP amplitude for left-sided targets during right-anodal/left-cathodal GVS only. There were no differences between left and right targets during left-anodal/right-cathodal stimulation or during sham. This finding is in contrast to that predicted, which was based on previous GVS literature in healthy participants, who found that right-anodal/left-cathodal GVS either induced rightward bias (e.g., Ferrè et al's. 2013) or had no effect (Patel et al., 2015). Some studies have reported effects on left inattention with right-cathodal/left-anodal GVS. For example Nakamura et al. (2015) found only right-anodal GVS ameliorated left inattention in hemi-spatial neglect participants. Additionally, Utz et al. (2011) demonstrated that right-anodal GVS was able to improve left inattention, albeit less successfully than left-anodal stimulation. The authors of the former study attribute this discrepancy to differences in pathology, however this should not be applicable to the neurologically healthy participants in the current study. Given therefore the inconsistency between the GVS findings of the current study and previous literature in healthy participants especially, coupled with the marginal nature, this finding may represent a false positive and requires further investigation for clearer interpretation.

One reason for the discrepancies between the GVS findings of the current study and previous literature in healthy participants might be due to differences in the tasks used. For

example, Ferrè et al. (2013) used a line-bisection task, which requires an allocentric spatial judgement, as opposed to the current study which required participants to passively attend. Patel et al. (2015), on the other hand, moved participants either to the left or right on a sled and asked them to estimate how far they had moved, therefore requiring a whole body spatial-perception judgement. In both of these cases, the effects demonstrated a shift in spatial attention induced by polarity-specific GVS, rather than compared to a sham condition as in the current study. It is possible, therefore, that the GVS effects demonstrated previously in healthy participants were specifically related to mechanisms not engaged in the current study's paradigm.

In keeping with this interpretation, an earlier study by Rorden, Karnath, and Driver (2001) demonstrated that a different form of vestibular stimulation, CVS, was able to induce shifts in covert attention in hemi-spatial neglect participants but not in healthy participants. From this, it was concluded that the effects in neglect patients may be due to changes in egocentric space representations rather than attention shifts. Similarly, Ferrè, Bottini, & Haggard, (2012) also demonstrated that CVS had no effect on attention-related VEPs in healthy participants. On the other hand, Figliozzi, Guariglia, Silvetti, Siegler, & Doricchi, (2005) did find effects on covert attention orienting in healthy participants through vestibular rotary accelerations. In this study, a pair of stimuli were presented simultaneously while participants were asked which appeared "first". Based on findings that preferential choices are given towards the attended stimulus, it was found that vestibular stimulation induced covert attention shifts towards the direction of the rotation. The authors of the latter study speculate that the discrepancy may be due to different levels of vestibular input, since Rorden et al. (2001) only applied CVS to one ear while Figliozzi et al. (2005) stimulated bilaterally. This theory would not explain the findings of the current chapter, however, since GVS was applied bilaterally. More likely, the authors suggest that since response keys were positioned

along the line of rotation (left or right of the body), this may have induced a motor-response bias towards the side of the rotation. This would be in keeping with the current findings, since no responses were required during the stimuli presentation. The findings of the current chapter are therefore in agreement with Rorden et al. (2001), that vestibular stimulation does not effect lateral covert shifts of attention.

A second possibility for the null result is that the current study may be under-powered due to the small sample size. The sample size of 12 per condition was chosen to be in keeping with a previous study, which looked at the effect of TENS on SSVEPs (Pitzalis et al., 2013). It is possible, however, that this sample size was insufficient to capture any significant effects of GVS. A final important reason that may explain the lack of effects is that GVS changes in SSVEP amplitude may be too subtle to measure. Pitzalis et al. (2013) studied the effect of TENS on SSVEPs, and found that rather than changes in amplitude, tens was associated with changes in SSVEP onset latency. SSVEP amplitude was measured in the current study since previous research has demonstrated that this increases with attention (e.g., Hillyard & Anllo-Vento, 1998; Morgan et al., 1996; Muller et al., 1998; Toffanin et al., 2009). Therefore, amplitude made most sense theoretically for investigating biases in attention with GVS. The possibility that GVS may instead impact SSVEP latency, however, opens up further avenues of research.

In summary, the aim of Chapter 5 was to investigate the lateral effects of GVS in an electrophysiological paradigm that could measure changes in attending to various locations on screen. This question arose on account of previous literature which demonstrated polarity effects of GVS, and the fact that the N2pc measure used in Chapters 2 and 3 may not be the most suitable for capturing lateral effects. No clear lateral effects of GVS were demonstrated in the current study. The chapter did, however, highlight that SSVEPs may be a suitable tool in measuring electrophysiological changes in spatial attention with GVS. In addition, Chapter

5 has opened up further research questions beyond the scope of this thesis, including the effects of GVS on SSVEP amplitude during an active task and the effects of GVS on other SSVEP measures, including onset latency.

Chapter 6

Summary, Conclusions and Future Directions

6.1. The aim of this thesis

The aim of this thesis was to investigate underlying mechanisms of GVS by measuring electrophysiological changes in response to stimulation. A number of studies have demonstrated the effect of GVS in ameliorating symptoms of attention disorders such as hemi-spatial neglect (e.g., Rorsman, Magnusson, & Johannson, 1999; Saj, Honore, & Rosseaux, 2006; Utz, Keller, Kardinal, & Kerkhoff, 2011; Wilkinson et al., 2014; Zubko, Wilkinson, Langston & Sakel, 2013) and extinction (e.g., Kerkhoff et al., 2011; Schmidt et al., 2013). In addition, GVS has been shown to modulate reward-based and spatial attention and perception in healthy participants (e.g., Blini, Tilikete, Farne, & Hadj-Bouziane, 2018; Ferrè, Longo, Fiori, & Haggard, 2013; Patel et al., 2015). These studies build on earlier work that demonstrate the effects of other forms of vestibular stimulation, such as motion devices and cold water irrigation (CVS), on attention in both healthy and attention-impaired individuals (e.g., Figliozzi, Guariglia, Silvetti, Siegler, & Doricchi, 2005; Moon, Lee, & Na, 2006; Rubens, 1985). Taken together, these studies present a growing body of evidence that GVS may provide an ideal tool for improving attention deficits.

Despite the known therapeutic potential of GVS, little is known of the underlying mechanisms that drive these changes. Lesion and neuroimaging investigation has revealed overlap in neural areas associated with hemi-spatial neglect and areas receiving projections from vestibular stimulation (e.g., Bense, Stephan, Yousry, Brandt, & Dieterich 2001; Buxbaum et al., 2004; Committeri et al., 2007; Fink et al., 2003; Karnath & Dieteric, 2006; Karnath & Rorden, 2012; Lobel, Kleine, Le Bihan, Leroy-Willig, & Berthoz, 1998; Mort et al., 2003; Stephan, Hufner, & Brandt, 2009). Some studies have used electrophysiological measures to demonstrate that GVS modulates neural oscillations (e.g., Kim et al., 2013; Lee et al., 2014; Wilkinson, Ferguson, & Worley, 2012). In an effort to associate electrophysiological changes with specific cognitive functions, others have measured ERP

components in response to GVS during cognitive tasks (e.g., Lee, Park, & Yoon, 2016; Schmidt-Kassow, Wilkinson, Denby, & Ferguson 2016; Wilkinson et al., 2012). These latter studies demonstrate EEG as a suitable tool for measuring underlying changes with GVS. Changes in EEG, however, have not previously been investigated with regard to sub-components of attention and cognitive functions that may underlie improvement in hemi-spatial neglect.

6.2. Summary of findings

Chapter 2 investigated the effect of GVS on the ERP component N2pc in a change detection task. The N2pc has been associated with detection of target-relevant information among distractors and/or suppression of irrelevant distractors (e.g., Brisson & Jolic, 2007; Eimer, 1996; Hickey, McDonald, & Theeuwes, 2006; Luck, Girelli, McDermott, & Ford, 1997; Luck & Hillyard, 1994). Based on findings that GVS can improve performance on tasks that require target detection among distractors (e.g., Wilkinson et al., 2014; Zubko et al., 2013), it was predicted that GVS would impact the amplitude of the N2pc relative to a sham group. Although significant effects were not found, Chapter 2 demonstrated marginal effects broadly in support of the hypothesis. This was demonstrated through a marginal interaction between stimulation and target detection (p = .068). It was predicted that changes would primarily be reflected in trials where targets were unseen, with the assumption that seen trials would have already reached a near-ceiling N2pc amplitude. This prediction was partially supported. While a significant difference between N2pc amplitude for seen and unseen targets was clear in sham, this difference was removed during GVS. This might suggest that GVS enhanced target-relevant information, or improved suppression of irrelevant distractors, to make the N2pc response to unseen targets more similar to seen targets.

Chapter 2 also investigated the effect of GVS on the ERP component P3. The P3 has been interpretted as reflecting updating of stimulus representations (e.g., Donchin & Coles, 1988; Polich, 1993; Zhou & Thomas, 2015). Based on the fact that the P3 has shown to be suppressed in hemi-spatial neglect participants (Saevarsson, Kristjánsson, Bach, & Heinrich, 2012), and that modulation of the P3 with GVS has been demonstrated previously (Lee et al., 2016; Schmidt-Kassow et al., 2016), along with links between GVS and memory, which might aid change detection (e.g., Adel Ghahraman et al., 2016; Lee et al., 2014; Wilkinson et al., 2012), it was predicted that GVS would increase the amplitude of the P3 relative to a sham control group. This prediction, however, was not supported, with no change in P3 detected between GVS and sham conditions.

Measures of *d'* and reaction time were also investigated in Chapter 2. In an effort to avoid masking N2pc and P3 effects for unseen trials by inducing a behavioural improvement, stimulation intensity was kept low and task difficulty high. Despite this, a marginal effect of stimulation and target side was detected on reaction time ($p = .052$). This was such that while a clear advantage was seen during sham for targets that appeared on the left, in line with previous research (e.g., Iyilikci, Becker, Gunturkun, & Amado, 2010), this difference was removed with GVS. This finding was surprising, not only because of the intention to prevent behavioural improvement, but because previous studies suggest that left-anodal/right-cathodal GVS should, if anything, compound the left-attention advantage in healthy participants (e.g., Ferrè et al., 2013; Patel et al., 2015). This finding was therefore revisited in Chapters 3 and 4. As intended, overall performance on the task was generally low, around chance.

A final important finding of Chapter 2 was that despite following previously defined protocols to ensure that stimulation was below the sensory threshold (e.g., Schmidt-Kassow et al., 2016), the majority of participants were able to detect which day they had received

active and sham stimulation in a forced choice. Similarly to Schmidt-Kassow et al. (2016), mild super-sensory stimulation was first applied, reducing the intensity until participants reported they no longer felt any sensation. After a few minutes, the intensity was readministered to ensure no sensation. Previous studies have taken this as evidence of sub-sensory stimulation, without requiring participants to make a forced choice on whether they received stimulation or not. However, Chapter 2 demonstrated that despite feeling no conscious sensation, the majority of participants were able to make accurate judgements when forced. Therefore, it may not be appropriate to take lack of sensory experience of GVS as sufficient for studies aiming to have participants blind to the condition. The data from Chapter 2 shows that participants still seemed to have a clear sense of which condition they were in.

Given that N2pc findings were in the predicted direction but marginal in Chapter 2, Chapter 3 aimed to improve the paradigm in an effort to replicate and extend findings of the effect of GVS on the N2pc, the P3 and on reaction time. Based on the possibility that very high task difficulty in Chapter 2 might have limited the scope for improvement with GVS, task difficulty was reduced by increasing stimulus size and decreasing the number of distractors in the same change-detection task. Additionally, following the finding that almost all participants could detect when they received active versus sham stimulation, Chapter 3 utilised a between-participants design to control for placebo effects. A second sham condition was also included where active stimulation was delivered, but electrodes were placed over the neck rather than the mastoids. This additional sham control group served the purpose of mimicking any sensory effects of GVS, such as heat or tingling, but without stimulating the mastoids. This was done to rule out the possibilities that GVS effects may be due to placebo or that sensory sensation acted as a cue to alert attention.

The predictions in Chapter 3 were the same as those in Chapter 2. In a broad replication of the trends demonstrated in Chapter 2, Chapter 3 found a significant difference between N2pc amplitude for seen and unseen trials in the two sham conditions (no stimulation and neck stimulation). However, this difference was removed during GVS. This may indicate that a mechanism underlying GVS improvement is the ability to enhance target-relevant information and/or better suppress distractors, so that responses to unseen and seen trials more closely resemble one another. Unlike in Chapter 2, however, this effect was only present for targets that appeared on the right side of the screen. This was contrary to expectation, since previous research appears to suggest that left-anodal/right-cathodal stimulation, as used in this study, should primarily affect targets that appear on the left, since attention should shift this way (Ferrè et al., 2013; Fink et al., 2003; Patel et al., 2015). Lateral effects of GVS were therefore revisited in Chapter 5.

As in Chapter 2, Chapter 3 demonstrated no effect of GVS on the amplitude of the P3. Although there was an effect of stimulation, changes were seen in both the GVS and neck-sham conditions relative to a no-stimulation sham, suggesting this was not a GVS specific effect. Behaviourally, *d'* was higher than in Chapter 2, as anticipated following the changes to the paradigm to lower task difficulty. However, no effect of GVS was detected on either *d'* or reaction time. Therefore, the finding from Chapter 2 of a stimulation by target side interaction on reaction time was not replicated in Chapter 3.

Following the mixed behavioural findings of Chapters 2 and 3, Chapter 4 aimed to resolve these discrepancies through means of replication. Additionally, while Chapters 2 and 3 aimed to prevent behavioural improvement to avoid masking EEG effects, Chapter 4 sought to maximise the potential for behavioural improvement. Based on the fact that stimulation intensity in Chapters 2 and 3 was lower than that used in previous studies (e.g., Ferrè et al., 2013; Wilkinson et al., 2014), stimulation intensity was increased from an average of .35 mA

to 1 mA, to be in keeping with this previous literature. It was predicted that relative to a sham condition, GVS would increase *d'* and decrease reaction time. This finding was not supported, with no difference in either measure between sham and GVS conditions. Additionally, based on findings that GVS current with random fluctuations in intensity might be more effective at modulating cognitive function (e.g., Wilkinson, Nicholls, Pattenden, Kilduff, & Milberg, 2008; Schwarzkopf Silvanto, & Rees, 2011), "noisy" GVS was compared to square current and sham stimulation. It was predicted that noisy GVS would have most impact on *d'* and reaction time. Contrary to this prediction, however, no difference was found between any of the stimulation conditions.

Finally, Chapter 5 investigated whether GVS induced lateral shifts of attention using SSVEPs. The lateral effects through Chapters 2 to 4 were mixed, in particular with the finding in Chapter 3 that N2pc was only effected for targets that appeared on the right side of the screen. This appeared contradictory to previous research, which would seemingly suggest that the left-anodal/right-cathodal set-up used should shift attention leftwards in healthy participants (e.g., Ferrè et al., 2013; Fink et al., 2003; Patel et al., 2015.) The N2pc measure used in Chapter 3 however is not ideally suited to measuring purely lateral effects, since it's calculation is based on the difference between ipsilateral and contralateral hemispheric responses, complicating interpretation, (see Chapter 5 introduction for full explanation). Chapter 5 therefore compared left-anodal/right cathodal GVS, right-anodal/left-cathodal GVS, and sham stimulation to investigate the effect on SSVEP amplitude, a measure more suited to spatially selective attention (Norcia, Appelbaum, Ales, Cottereau, & Rossion, 2015). Previous literature has demonstrated that SSVEP amplitude is increased with attention to particular spatial locations (e.g., Hillyard & Anllo-Vento, 1998; Morgan, Hansen, & Hillyard 1996; Muller et al., 1998; Toffanin, Jonga, Johnson, & Martens, 2009). Therefore, based on previous findings (e.g., Ferrè et al., 2013; Patel et al., 2015), it was predicted that left-

anodal/right-cathodal GVS would increase SSVEP amplitude for targets appearing on the left, while right-anodal/left-cathodal GVS would increase SSVEP amplitude for targets appearing on the right. These predictions were not supported, with no differences in SSVEP amplitude detected between stimulation conditions.

6.3. Conclusions

6.3.1. N2pc

The main effects of GVS in this thesis were demonstrated on the N2pc. Chapter 3 demonstrated an impact of GVS on N2pc amplitude, resulting in electrophysiological responses to seen and unseen targets more closely resembling one another. This might suggest that GVS influenced N2pc response to unseen targets to move them closer to a threshold at which they might be seen. Similar trends were seen in Chapter 2, but these effects were not significant. GVS has been shown to improve performance on attention tasks in attention-impaired patients (e.g., Wilkinson et al., 2014). Attention, however, is a broad term that can describe many sub-components. Indeed, a key debate in the vestibular stimulation literature is whether the beneficial effects demonstrated are the result of general arousal or a more specific mechanism (e.g., Bottini & Gandola, 2015). The finding of this thesis that GVS selectively impacted N2pc, but not P3 amplitudes under the same conditions, lends support towards a specific mechanism. In particular, an improvement in enhancing target information, or in better suppressing distractors, might underlie GVS effects on cancellation tasks.

Why this effect occurred only in right-sided targets is less clear. Although effects of target side were not a primary research question in this study, if it were, an *a priori* hypothesis might have been that targets on the left would be primarily affected. This is because previous research has demonstrated that left-anodal/right cathodal GVS, as used in

Chapter 3, is most associated with leftward attention shifts, which might facilitate improvement (e.g., Ferrè et al., 2013; Fink et al., 2003; Patel et al., 2015). One explanation might have been that sensory cues, felt most strongly under the cathodal (right) electrode (Ferrè et al., 2013), alerted attention towards this direction. This explanation is unlikely, however, since we then would have expected to see the same effect in the neck sham condition, where active stimulation was also applied. Other possible explanations might be to do with the better baseline performance for left-sided targets, which may have interacted to produce different effects of target side (e.g., Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Schwarzkopf et al., 2011).

The N2pc may not be the best measure for observing lateral effects of GVS. This is because its calculation is based on the difference between ipsilateral and contralateral hemispheric response relative to target side. Therefore, the effects of target side cannot be disentangled from hemisphere, which complicates interpretation (see Chapter 5 introduction for further explanation). Hemispheric differences have been demonstrated to impact the N2pc previously. For example, Eimer (1996) found hemispheric differences in the N2pc on a task where participants were asked to search for words. It was speculated that the reason behind this finding might be due to preferential language processing in the left hemisphere. Importantly to the current study, similar findings have been demonstrated when participants were required to distinguish between colours (e.g., Liu et al., 2009). The authors similarly speculated that this may be due to hemispheric differences in language processing, due to categorising colours. N2pc has been viewed according to target side previously, indeed the study by Tseng et al. (2012) on the effects of tDCS on N2pc partially informed the rationale for the method used in Chapters 2 and 3, but target side did not form a primary research question in either study. Therefore, at present it is only possible to speculate on the reasons behind the target side effect in Chapter 3. Importantly, however, the findings of the current

thesis demonstrate an impact of GVS on the N2pc relative to two sham conditions, including a neck sham condition where active stimulation was administered. These findings therefore rule out the effects of placebo and point to a specific mechanism of GVS.

6.3.2. P3

The findings of the current thesis do not support an effect of GVS on P3 amplitude, at least in a change-detection paradigm. Modulation of P3 amplitude has been demonstrated previously with GVS (Lee et al., 2016; Schmidt-Kassow et al., 2016), but there are notable differences between those studies and the studies in this thesis. For example, in Schmidt-Kassow et al. (2016), P3 was elicited during an auditory odd-ball paradigm, where a deviant tone was played amongst uniform tones. Not only does this represent a much lower task load than in the current set of studies, but delivery of GVS also varied. P3 was only modulated when alternating polarity GVS was paired with the timing of the tones. The authors have previously shown a similar effect when auditory tones were synchronised with cycling rhythm (Schmidt-Kassow, Heinemann, Abel, & Kaiser, 2013). These findings may therefore reflect a consequence of timing properties of synchronised multi-sensory input rather than GVS *per se*.

Lee et al. (2016) likewise used an odd-ball paradigm, but did not pair GVS timing with stimuli, ruling out the effects as purely timing-properties. In contrast to the current study, however, Lee et al. (2016) used left-cathodal/right-anodal stimulation to demonstrate an increase in P3 amplitude. It is known that different set-ups of GVS differentially affect patterns of neural activity (Fink et al., 2003). The left-anodal/right-cathodal set-up in Chapters 2 to 4 of this thesis was chosen to mimick protocols used in the majority of hemi-spatial neglect studies (e.g., Wilkinson et al., 2014) and to primarily activate attention structures of the right hemisphere (Fink et al., 2003). Given, however, that the P3 has been

linked with other functions such as working memory (e.g., Saliasi, Geerligs, Lorist, & Maurits, 2013), it is possible both that the task load in the current study was too high, or that modulation of cognitive functions best reached with left-cathodal stimulation underlie the effect in Lee et al. (2016).

6.3.3. *d'* and Reaction Time

The primary focus of this thesis was the effects of GVS on electrophysiological correlates of attention, but behavioural measures were also collected through Chapters 2 to 4. In Chapters 2 and 3, in an effort to prevent behavioural improvement masking ERP effects (see Chapter 2 introduction for an explanation of this rationale), GVS intensity was kept low and task difficulty high to prevent behavioural improvement. Despite this, Chapter 2 found an interaction between stimulation and target side that was very close to significance ($p = .052$). This effect failed to replicate in either Chapter 3 or 4. Given the marginal nature, coupled with the lack of replication, this result likely represented a false positive.

There are, however, some important points to note. Firstly, the effect in Chapter 2 demonstrated that there was a clear left advantage in reaction time during sham stimulation, which was removed during GVS. Therefore, to replicate this finding, the left-sided advantage has to be present during sham, which was not the case in Chapter 3. A natural left advantage was seen consistently in *d'* through Chapters 2, 3 and 4, and in reaction time in Chapters 2 and 4. This is in-line with previous literature (e.g., Iyilikci, Becker, Gunturkun, & Amado, 2010; Verleger et al., 2010). Therefore, the absence of this advantage in reaction time in Chapter 3 is an anomaly, which may explain the lack of replication in this chapter. Additionally, overall accuracy was lower in Chapter 2 than in Chapters 3 and 4. Tseng et al. (2012) found that another form of neural stimulation, tDCS, was only effective at modulating change-detection performance when accuracy was low, after participants were split into high

and low performers for analysis. Therefore, the lower accuracy in Chapter 2 could have enabled an effect of stimulation that was prevented in Chapters 3 and 4.

Chapter 4 investigated behavioural measures of GVS in more depth by both increasing stimulation intensity to be more in-line with previous literature (e.g., Wilkinson et al., 2014), and by comparing "noisy" GVS current to square current and sham stimulation. Previous literature has demonstrated that randomly fluctuating or "noisy" GVS current may be more effective at improving cognitive function than square current (e.g., Wilkinson et al., 2008). One theory for why this might be is the phenomenon of stochastic resonanse, or the idea that application of random noise may be able to boost detection of a weak signal (e.g., McDonnell & Abbott, 2009; Moss, Ward, & Sannita, 2004). The findings of the current thesis, however, do not support a beneficial effect of higher intensity or noisy GVS current on change detection, since no difference was found between stimulation conditions in either *d'* or reaction time.

Chapter 4 constituted a relatively exploratory study into the potential effects of GVS on change detection, with stimulation intensity and GVS waveforms informed by the available literature. This study adds to a body of evidence in the wider brain stimulation literature that the relationship between stimulation intensity and cognitive effects is not strictly linear (e.g., Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Schwarzkopf, Silvanto, & Rees, 2011; Wilkinson et al., 2014). For example, TMS studies have demonstrated that under different conditions, low-intensity stimulation can improve performance while high-intensity impairs performance (e.g., Schwarzkopf et al. 2011). Moreover, tDCS literature has demonstrated that the most effective stimulation intensity interacts with level of baseline performance (Benwell et al., 2015). The low stimulation intensity and poor accuracy in Chapter 2, coupled with the higher accuracy and higher

stimulation intensity of Chapter 4, may therefore offer one potential explanation for why the marginal stimulation effect on reaction time was not replicated in Chapter 4.

A second possible explanation for the null effects of Chapter 4 might be that previous findings of the effects of GVS may be task dependent. Particularly in healthy participants, studies such as by Ferrè et al. (2013) and Patel et al. (2015) involve spatial perception processes and lateral effects, which may not have been strongly related to the change-detection task. Change detection is not a task used commonly with hemi-spatial neglect participants either. This paradigm was chosen as it was visually similar to traditional hemi-spatial neglect tasks and requires many of the same mechanisms for completion, such as target detection among distractors. Traditional cancellation tasks were unsuitable for the current thesis, since they would likely result in ceiling effects in healthy participants, masking improvement. Additionally, the lack of awareness of obvious visual stimuli in change blindness has been compared with the lack of awareness in hemi-spatial neglect (Pisella & Mattingley, 2004). Inevitably, however, the cognitive load of the task in Chapter 4 was higher than in many previous studies, which may have prevented behavioural improvement. Further, effects of GVS in hemi-spatial neglect participants have been shown to be much stronger than in healthy participants (e.g., Oppenländer et al., 2015; Utz, Keller, Kardinal, & Kerkhoff, 2011). It is therefore possible that although GVS was able to impact underlying electrophysiological mechanisms, this was insufficient to produce a behavioural effect. Although these findings and considerations open up questions for future research, at present, this thesis does not provide support for the effect of GVS on change-detection behavioural performance.

6.3.4. Lateral effects of GVS

Lateral effects of GVS were investigated in Chapter 5, but no impact on the amplitude of the SSVEP was found with either left-anodal or left-cathodal GVS. This was contrary to predictions, since previous research has demonstrated that left-anodal GVS biases attention leftwards while right-anodal either biases rightwards (Ferrè et al., 2013) or had no effect (Patel et al., 2015) in healthy participants. These previous studies have differences with the current study, however. Ferrè et al. (2013), for example, used a line-bisection task which requires an allocentric spatial judgement. Patel et al. (2015), on the other hand, asked people to make judgements about lateral whole-body movements. In contrast, Chapter 5 had participants passively attend to stimuli while fixating on a centrally-located marker. Effects of GVS, therefore, would have indicated shifts in covert attention. This was necessary as eye movements would have created artifacts in the EEG data. It is possible, however, that mechanisms underlying the lateral effects demonstrated previously with GVS do not extend to covert shifts of attention.

In support of this interpretation, Rorden, Karnath, and Driver (2001) demonstrated that a different form of vestibular stimulation, CVS, was not able to elicit lateral effects on covert attention in healthy participants. In contrast, Figliozzi et al. (2005) demonstrated that vestibular stimulation through rotation did influence covert-attention orienting in healthy participants. These two studies represent very different approaches in terms of type of stimulation used. Although there is clear overlap, different methods of vestibular stimulation are known to induce variations in brain activity (e.g., Bense et al., 2001; Suzuki et al., 2001). Therefore one possible explanation is that GVS differs in type and intensity of vestibular input from the rotation used in Figliozzi et al. (2005), which may not engage mechanisms of lateral shifts of covert attention. A more likely explanation, however, is to do with differences in paradigm and methods used. A key difference in Figliozzi et al. (2005), was that response

keys were presented along the line of rotation, while Rorden et al. (2001) used one centrally located response key. Chapter 5 did not require any response. It is possible, therefore, that the response method, coupled with the method of stimulation used in Figliozzi et al. (2005), produced a motor-response bias. This may have contributed to shifts in covert attention that were not present in either Rorder et al. (2001) or in Chapter 5.

A further potential explanation for the absense of lateral effects in Chapter 5 might be that the study involved no task and consequently, viewing stimuli passively may have caused participants to disengage. This would have resulted in fluctuations of SSVEP amplitude across time, that were different across participants and therefore may be have been masked when averages were calculated. The paradigm used was based on that by Pitzalis, Spinelli, Vallar, and Di Russo (2013), who demonstrated an effect of TENS on SSVEPs. Other research, however, has demonstrated that allocation of attention modulates SSVEP amplitude even when the flickering stimuli used to induce the SSVEP are task-irrelevant (e.g., Morgan et al., 1996). Such studies instead use flickering stimuli as a background, while participants engage in a task. Future research could therefore utilise a task to ensure engagement of participants, while monitoring the background effects of GVS on SSVEP amplitude. Another approach could be to monitor smaller time windows than the broad three seconds used in Chapter 5. This would be an interesting question, not only because of potential disengagement of participants over longer periods, but also because GVS has been shown to induce greater neural responses at onset and offset (Stephan et al., 2005).

6.3.5. Methodological Implications

The findings in this thesis also provide some important metholodological implications for future neural stimulation studies. In Chapter 2, protocols from previous literature were followed to ensure subsensory stimulation (e.g., Schmidt-Kassow et al., 2016). This included

a titration procedure where stimulation was applied and adjusted in intensity until participants reported no sensation. A few minutes break was then given and the stimulation intensity readministered. If the participant reported sensation, the titration procedure was repeated. In previous studies, lack of conscious sensation has been taken as evidence for subsensory stimulation, without requiring the participants to make a forced choice of whether they received stimulation or not (e.g., Schmidt-Kassow et al., 2016). The findings of this thesis, however, indicate that self report may be inadequate, since almost all participants were able to correctly identify which day they received active versus sham stimulation in a forced choice. Chapters 3, 4 and 5 therefore utilised between-participants designs. This has important implications since placebo effects have been demonstrated in other forms of brain stimulation (e.g., Mercado et al., 2006).

Additionally, findings of this thesis provide some considerations for appropriate sham conditions for neural stimulation. In Chapter 3, a significant stimulation interaction was detected on P3 amplitude. However, this interaction implicated both GVS and a sham condition where stimulation was delivered to the neck, relative to a no stimulation sham condition. The neck-sham used in the current study was based on the method of Ferrè et al. (2013), where neck sham electrodes were placed 5 cm below usual placement of GVS electrodes. Though the electrodes cover a fairly large area, previous studies on various cognitive functions have demonstrated that the effects of neck sham are distinguishable from GVS, therefore suggesting neck stimulation does not reach vestibular organs (e.g., Ferrè et al., 2013; Ferrè, Day, Bottini, & Haggard, 2013). Furthermore, if neck sham was able to reach vestibular nerves, then it would be expected to see neck sham effects also in the N2pc, which was not the case. One possible explanation for the findings of neck sham effects on the P3 in Chapter 3 is, therefore, placebo. In particular, some studies have made links between P3 amplitude and confidence in response decisions (e.g., Bergmann, Schubert, & Hagemann,

2016; Eimer & Mazza, 2005). If participants were able to sense unusual stimulation in both GVS and neck sham, this may have created a placebo effect on confidence, impacting P3 amplitude. These findings therefore demonstrate that active stimulation delivered away from the mastoids may be a useful method of sham-controlling GVS studies, particularly for measures that may likely be influenced by placebo.

6.3.6. Potential Mechanisms

The modulations demonstrated in this thesis may reflect a number of potential mechanisms. Previously, it has been debated whether the effects of GVS on attention disorders such as hemi-spatial neglect are due to a non-specific effect (Schiff and Pulvar, 1999). For example, given GVS influences on control of balance and posture, findings of improvement in hemi-spatial neglect may be explained by compensatory postural adjustments towards the anode, or an increase in general arousal (e.g., Day & Fitzpatrick, 2005; Ferrè et al., 2013). These explanations seem unlikely however, since different polarity set-ups of GVS have been demonstrated to have different, task-dependent, therapeutic effects, suggesting against general arousal (e.g., Oppenländer et al., 2015). Moreover, polarity-specific lateral attention shifts have been demonstrated after the effects of compensatory postural sway should have stabilized, ruling out simply balance and posture explanations (Ferrè et al., 2013). Importantly, such general explanations cannot explain non-lateral effects of GVS, such as on figure copying (Wilkinson, Zubko, DeGutis, Milberg, & Potter, 2010) or face processing (Wilkinson, Ko, Kilduff, McGlinchey, & Milberg, 2005). These findings therefore point to a more specific mechanism of GVS.

In the current thesis, the selective modulation of the N2pc, but not the P3, provides additional support for specific mechanisms underlying GVS effects. In this case, the findings may demonstrate the ability of GVS to improve attentional selection of targets in multi-

stimulus displays (e.g., Eimer, 1996). This may underlie improvements in target detection in hemi-spatial neglect participants, such as during cancellation tasks (e.g., Wilkinson et al, 2014; Zubko et al., 2013.) One potential mechanism that may explain these findings is that GVS may project to specific neural areas associated with target detection. For example, GVS has been shown to activate areas including the anterior and posterior insula and the inferior parietal lobe (e.g., Bense et al., 2001; Fink et al., 2003; Lobel et al., 1998; Stephan et al., 2009), both of which have been associated with target detection in attention tasks (e.g., Linden, et al., 1999). Neuroimaging has demonstrated that projections of vestibular stimulation are widespread (e.g., Bense et al., 2001). Therefore, that GVS projects to specific, but widespread networks associated with various cognitive functions, may provide one explanation underlying GVS effects (Smith et al., 2010). Further research is required however to elucidate whether the effects of GVS across cognitive functions reflect one or many different mechanisms (Oppenländer et al., 2015).

6.4 Remaining Questions and Future Directions

One question that remains following this thesis is the effect that larger sample sizes might have had on findings. The sample sizes used in the current studies were based on those used in previous literature in identical or very similar paradigms. The paradigm in Chapters 2 and 3 was based on Tseng et al. (2012), who investigated the effect of tDCS on the amplitude of the N2pc in change detection. In this study, 19 participants were included per condition. Therefore, 20 participants per condition were recruited in Chapter 3. However, following participant removal, this was reduced to 15, 16 and 17 for the three stimulation conditions. Although fewer participants were used, it is worth noting that the current studies used many more trials than in Tseng et al. (2012), with 320 change trials as compared to 144. This was because the maximum number of trials were included that would allow for online delivery of

GVS, without exceeding the 30 minutes shown to be a safe stimulation duration (Wilkinson et al., 2009).

The paradigm in Chapter 4 was identical to Chapter 3 and based on a behavioural only experiment also in Tseng et al (2012). This study demonstrated effects of tDCS on change detection in 10 participants, as compared to an average of 19 per condition in the current study. As in Chapters 2 and 3, many more trials were used in the current thesis than in Tseng et al. (2012). Finally, the paradigm in Chapter 5 was based on Pitzalis et al. (2013), who investigated the effects of TENS on SSVEPs. Chapter 5 employed an average of 18 participants per condition, where Pitzalis et al. (2013) had used 12. Therefore, although the sample sizes in the current studies are small, the numbers chosen appear sufficiently justified by previous literature. In particular, since the participant numbers exceed that previously used in similar research questions and paradigms, the non-significant effects of Chapters 4 and 5 would not appear to be explained by insufficient sample size. Having said this, recent research has demonstrated that whilst commonly done, basing sample sizes on that used in previous literature may not be the most appropriate method (e.g., Anderson, Kelley, & Maxwell, 2017). This is because publication bias leads to over-estimation of effect sizes, where the real effect sizes are much smaller. Thus, future research perhaps needs to overcompensate for this when basing sample sizes on previous literature.

Future research could also address some limitations of the current studies. For example, Chapters 2 and 3 used very low-intensity stimulation of around .4 mA. This was to ensure that stimulation was subsensory, following previously described protocols (Schmidt-Kassow et al., 2016). It has been shown previously that stimulation intensities of < .5 mA do not elicit postural sway and eye-movement responses, which provide an objective measure of vestibular response (e.g., Fitzpatrick & Day, 2004; Kim et al., 2013). Despite this, GVS effects on behavioural and EEG measures have been shown previously, when stimulation is

applied at .4 mA and less (e.g., Kim et al., 2013; Wilkinson et al., 2012). Therefore, this supports that even low amounts of stimulation are able to elicit vestibular effects. Future studies however should consider including objective measures of vestibular response, such as changes in eye-movements.

An additional question arising from the current thesis is the potential effect habituation to the GVS may have had on results. It is known that GVS has the largest effects at onset and offset of the stimulation (Stephan et al., 2005). The current studies applied GVS in blocks of a few minutes. This was to ensure sufficient numbers of trials were collected while keeping within known safe amounts of stimulation (Wilkinson et al., 2008). It is likely however that vestibular receptors did not stay active for this whole period of time. An investigation into the time course of GVS effects would therefore comprise an important question for further studies.

A further avenue for future research is to examine the effects of different GVS polarities on the change-detection paradigm used in the current thesis. Chapters 2 to 4 used left-anodal GVS only, which was compared to a sham condition. This was to replicate protocols used in earlier studies into the effects of GVS on hemi-spatial neglect (Wilkinson et al., 2014; Zubko et al., 2013). In healthy participants, however, some studies have demonstrated that the smaller effect sizes in healthy populations are best measured by comparing different polarity GVS, rather than comparing only to a sham group (e.g., Ferrè et al., 2013). Left-anodal and right-anodal GVS could therefore be compared to investigate if this strengthens the effects demonstrated on the N2pc in the current thesis.

An obvious extension to the findings of this thesis, particularly those on the N2pc, would be to replicate findings in hemi-spatial neglect participants. As an initial set of studies, this thesis recruited healthy participants to first allow effects to be viewed in a more homogenous sample, without complicating factors of differing pathology and cognitive

deficits. Similar investigations recruiting hemi-spatial neglect participants would provide further evidence on whether improved target detection and suppression of distractors, as indicated by the N2pc, does indeed underlie GVS improvement on certain hemi-spatial neglect tasks. Additionally, findings from the behavioural study of Chapter 4 and SSVEP study of Chapter 5, if applied to in hemi-spatial neglect patients, may provide insight into these mechanisms, since it has been demonstrated that effects of GVS appear stronger in patients than in healthy participants (e.g., Oppenländer et al., 2015).

In healthy participants, an interesting avenue of further research would be into the effects of different GVS waveforms and stimulation intensities and how these interact with baseline performance. The findings of Chapter 4 are in-line with a body of wider brain stimulation literature that demonstrate the relationship between stimulation amount and intensity and cognitive enhancement is not linear (e.g., Benwell et al., 2015; Schwarzkopf et al., 2011; Wilkinson et al., 2014). Although research into this area in GVS is limited, Wilkinson et al. (2014) demonstrated, for example, that 10 sessions of GVS in hemi-spatial neglect patients was no more beneficial than one session, indicating that more stimulation is not necessarily better. Benwell et al. (2015), using tDCS, demonstrated that the most effective stimulation intensity was related to baseline performance. Such investigation with GVS therefore may help to refine protocols for maximum cognitive enhancement, and for targeting type and degree of cognitive deficits most likely to benefit.

Finally, there are a wealth of attention-related ERP components that remain unexplored with reference to the effects of GVS. In particular, components relating to cueing and preparatory shifts of attention, such as the anterior attention-directing negativity (ADAN), the early attention-directing negativity (EDAN) and the late direction attention positivity (LDAP) (see Chapter 5 introduction for discussion of these components), provide markers for tasks also known to be impaired in hemi-spatial neglect participants (e.g., Norcia

et al., 2015; Posner, Walker, Friedrich, & Rafal, 1984). Investigation into the effects of GVS on these markers could provide more specific insight into which cognitive functions can be modulated by GVS.

References

Adel Ghahraman, M., Zahmatkesh, M., Pourbakht, A., Seifi, B., Jalaie, S., Adeli, S., & Niknami, Z. (2016). Noisy galvanic vestibular stimulation enhances spatial memory in cognitive impairment-induced by intracerebroventricular-streptozotocin administration. *Physiology and Behaviour, 157*, 217-224. doi:10.1016/j.physbeh.2016.02.021

Ales, J. M., & Norcia, A. M. (2009). Assessing direction-specific adaptation using the steady-state visual evoked potential: Results from EEG source imaging. *Journal of Vision, 9*, 1-13. doi:10.1167/9.7.8

Anderson, S. F., Kelley, K., & Maxwell, S. E. (2017). Sample-Size Planning for More Accurate Statistical Power: A Method Adjusting Sample Effect Sizes for Publication Bias and Uncertainty. *Psychological Science, 28*, 1547-1562. doi:10.1177/0956797617723724

Angelaki, D. E. (2004). Eyes on Target: What Neurons Must do for the Vestibuloocular Reflex During Linear Motion. *Journal of Neurophysiology, 92*, 20-35. doi:10.1152/jn.00047.2004

Angelaki, D. E., & Cullen, K. E. (2008). Vestibular system: the many facets of a multimodal sense. *The Annual Review of Neuroscience, 31*, 125–150. doi:10.1146/annurev.neuro.31.060407.125555

Angelaki, D. E., & Hess, B. J. (2005). Self-motion-induced eye movements: effects on visual acuity and navigation. *Nature Reviews Neuroscience, 6,* 966-976. doi:10.1038/nrn1804

Angelaki, D. E., Klier, E. M., & Snyder, L. H. (2009). A vestibular sensation: probabilistic approaches to spatial perception. *Neuron, 64,* 448–461. doi:10.1016/j.neuron.2009.11.010

Balter, S. G., Stokroos, R. J., Eterman, R. M., Paredis, S. A., Orbons, J., & Kingma, H. (2004). Habituation to Galvanic Vestibular Stimulation. *Acta Otolaryngol, 124*, 941/945. doi:10.1080/00016480410017350

Barrett, D. J., Edmondson-Jones, M., & Hall, D. A. (2010). Attention in neglect and extinction: Assessing the degree of correspondence between visual and auditory impairments using matched tasks. *Journal of Clinical and Experimental Neuropsychology, 32*, 71–80. doi:10.1080/13803390902838058

Becker, D. E., & Shapiro, D. (1980). Directing attention toward stimuli affects the P3 but not the orienting response. *Psychophysiology, 17*, 385-389. doi:10.1111/j.1469-8986.1980.tb00168.x

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*, 886-899. doi: 10.1152/jn.2001.85.2.886

Bergmann, K., Schubert, A. L., Hagemann, D., & Schankin, A. (2016). Age-related differences in the P3 amplitude in change blindness. *Psychological Research, 80,* 660–676. doi:10.1007/s00426-015-0669-6

Bigelow, R. T., & Agrawal, Y. (2015). Vestibular involvement in cognition: Visuospatial ability, attention, executive function and memory. *Journal of Vestibular Research, 25,* 73–89. doi:10.3233/VES-150544

Blini, E., Tilikete, C., Farne, A., & Hadj-Bouziane, F. (2018). Probing the role of the vestibular system inmotivation and reward-based attention. *Cortex, 103,* 82-89. doi:10.1016/j.cortex.2018.02.009

Bolognini, N., Pascual-Leone, A., & Fregni, F. (2009). Using non-invasive brain stimulation to augment motor training-induced plasticity. *Journal of Neuroengineering and Rehabilitation, 6*. doi:10.1186/1743-0003-6-8

Bottini, G., & Gandola, M. (2015). Beyond the Non-Specific Attentional Effect of Caloric Vestibular Stimulation: Evidence from Healthy Subjects and Patients. *Multisensory Research, 28,* 591-612. doi:10.1163/22134808-00002504

Brisson, B., & Jolic, P. (2007). The N2pc component and stimulus duration. *Neuroreport, 18*, 1163-1166. doi:10.1097/WNR.0b013e3281e72d1b

Brozzoli, C., Demattè, M. L., Pavanic, F., Frassinetti, F., & Farnè, A. (2006). Neglect and extinction: Within and between sensory modalities. *Restorative Neurology and Neuroscience, 24*, 217–232.

Bucker, B., & Theeuwes, J. (2014). The effect of reward on orienting and reorienting in exogenous cuing. *Cognitive, Affective, & Behavioral Neuroscience, 14*, 635-646. doi:10.3758/s13415-014-0278-7

Buxbaum, L., Ferraro, M., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., Cosletta, H. B. (2004). Hemispatial neglect subtypes, neuroanatomy and disability. *Neurology, 62*, 749-756. doi:10.1212/01/WNL.0000113730.73031.F4

Coats, A. C. (1972). The sinusoidal galvanic body-sway response. *Acta oto-laryngologica*, *74*, 155-162. doi: 10.3109/00016487209128436

Colclasure, J. C., & Holt, J. R. (2004). Transduction and adaptation in sensory hair cells of the mammalian vestibular system. *Gravitational and Space Biology Bulletin, 16*, 61-70.

Committeri, G., Pitzalis, S., Galati, G., Patria, F., Pelle, G., Sabatini, U., Castriota-Scanderbeg, A., Piccardi, L., Guariglia, C., Pizzamiglio, L. (2007). Neural bases of

personal and extrapersonal neglect in humans. *Brain, 130,* 431-441. doi:10.1093/brain/awl265

Czernuszenko, A., & Czlonkowska, A. (2009). Risk factors for falls in stroke patients during inpatient rehabilitation. *Clinical Rehabilitation, 23*, 176-188. doi: 10.1177/0269215508098894.

Day, B. L., & Fitzpatrick, R. C. (2005). The vestibular system. *Current Biology, 15*, 1-4. doi:10.1016/j.cub.2005.07.053

De Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience, 14,* 1245–1246. doi:10.1038/nn.2905.

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

Donchin, E., & Coles, M. (1988). Is the P3 component a manifestation of context updating? *Behavioral and Brain Sciences, 11,* 357-427. doi:10.1017/S0140525X00058027

Eimer, M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalography and clinical neurophysiology, 99,* 22-234. doi:10.1016/0013-4694(96)95711-9

Eimer, M. (2014). The time course of spatial attention: insights from event related brain potentials. In A. C. Nobre, & S. Kastner, *The Oxford handbook of attention* (pp. 289–317). Oxford: Oxford Handbooks Online.

Eimer, M., & Mazza, V. (2005). Electrophysiological correlates of change detection. *Psychophysiology, 42,* 328-342. doi:10.1111/j.1469-8986.2005.00285.x

Eimer, M., van Velzen, J., Forster, B., & Driver, J. (2003). Shifts of attention in light and in darkness: an ERP study of supramodal attentional control and crossmodal links in

spatial attention. *Cognitive Brain Research, 15,* 308-323. doi:10.1016/S0926-6410(02)00203-3

Fellrath, J., Blanche-Durbec, V., Schnider, A., Jacquemoud, A. S., & Ptak, R. (2012). Visual search in spatial neglect studied with a preview paradigm. *Frontiers in Human Neuroscience, 6*. doi:10.3389/fnhum.2012.00093

Ferrè, E. R., Bottini, G., & Haggard, P. (2012). Vestibular inputs modulate somatosensory cortical processing. *Brain Structure and Function, 217,* 859–864. doi:10.1007/s00429-012-0404-7

Ferrè, E. R., Day, B. L., Bottini, G., & Haggard, P. (2013). How the vestibular system interacts with somatosensory perception: A sham-controlled study with galvanic vestibular stimulation. *Neuroscience Letters, 550,* 35-40. doi:10.1016/j.neulet.2013.06.046

Ferrè, E., Longo, M. R., Firori, F., & Haggard, P. (2013). Vestibular modulation of spatial perception. *Frontiers in human neuroscience, 7*. doi:10.3389/fnhum.2013.00660

Ferrè, E. R., Vagnoni, E., & Haggard, P. (2013). Vestibular contributions to bodily awareness. *Neuropsychologia, 51,* 1445-1452. doi:10.1016/j.neuropsychologia.2013.04.006

Figliozzi, F., Guariglia, P., Silvetti, M., Siegler, I., & Doricchi, F. (2005). Effects of vestibular rotatory accelerations on covert attentional orienting in vision and touch. *Journal of Cognitive Neuroscience, 17,* 1638-1651. doi:10.1162/089892905774597272

Fink, G. R., Marshall, J. C., Weiss, P. H., Stephan, T., Grefkes, C., Shah, N. J., Zilles, K., Dieterich, M. (2003). Performing allocentric visuospatial judgements with induced distortion of the egocentric reference frame: An fMRI study with clinical implications. *Neuroimage, 20,* 1505-1517. doi:10.1016/j.neuroimage.2003.07.006

Fitzpatrick, R. C., & Day, B. L. (2004). Probing the human vestibular system with galvanic stimulation. *Journal of applied physiology, 96*, 2301–2316. doi:10.1152/japplphysiol.00008.2004

Geminiani, G., & Bottini, G. (1992). Mental representation and temporary recovery from unilateral neglect after vestibular stimulation. *Journal of Neurology, Neurosurgery & Psychiatry, 55*, 332–333. doi:10.1136/jnnp.55.4.332-a

Grabherr, L., Macauda, G., & Lenggenhager, B. (2015). The moving history of vestibular stimulation as a therapeutic intervention. *Multisensory Research, 28*, 653-687. doi:10.1163/22134808-00002495

Harter, M. R., & Anllo-Vento, L. (1991). Visual-spatial attention: preparation and selection in children and adults. *Electroencephalography and Clinical Neurophysiology, 42*, 183-194.

Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention. The mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology, 30*, 327-330. doi:10.1212/WNL.30.3.327

Hickey, C., McDonald, J. J., & Theeuwes, J. (2006). Electrophysiological Evidence of the Capture of Visual Attention. *Journal of Cognitive Neuroscience, 18*, 604-613. doi:10.1162/jocn.2006.18.4.604

Highstein, S. M., & Holstein, G. R. (2012). The anatomical and physiological framework for vestibular prostheses. *The Anatomical Record, 295*, 2000–2009. doi:10.1002/ar.22582

Hillyard, S. A., & Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of the United States of America, 95*, 781-787. doi:10.1073/pnas.95.3.781

İşcan, Z., & Nikulin, V. V. (2018). Steady state visual evoked potential (SSVEP) based brain-computer interface (BCI) performance under different perturbations. *Plos One, 13,* 1-17. doi:10.1371/journal.pone.0191673

Ishihara, S. (1994). *Ishihara's tests for colour blindness. 38 plates edition.* Tokyo: Kanehara & Co Ltd.

Iyilikci, O., Becker, C., Gunturkun, O., & Amado, S. (2010). Visual processing asymmetries in change detection. *Perception, 39,* 761-769. doi:10.1068/p6623

Izzidien, A., Ramaraju, S., Roula, M. A., & McCarthy, P. W. (2016). Effect of anodal-tDCS on event-related potentials: a controlled study. *BioMed Research International,* 1-8. doi:10.1155/2016/1584947

Jamali, M., Sadeghi, S. J., & Cullen, K. E. (2008). Response of vestibular nerve afferents innervating utricle and saccule during passive and active translations. *Journal of Neurophysiology, 101,* 141–149. doi:10.1152/jn.91066.2008

Jehkonen, M., Loukosalo, M., & Kettunen, J. E. (2006). Impact of neglect on functional outcome after stroke - a review of methodological issues and recent research findings. *Restorative Neurology and Neuroscience, 24,* 209-215.

Jeon, Y. W., & Polich, J. (2001). P3a from a passive visual stimulus task. *Clinical Neurophysiology, 112,* 2202-2208. doi:10.1016/S1388-2457(01)00663-0

Jodo, E., & Inoue, K. (1990). Effects of practice on the P300 in a Go/NoGo task. *Electroencephalography and Clinical Neurophysiology, 76,* 249-257. doi:10.1016/0013-4694(90)90019-G

Jeong-Woo, L., Gi-Eun, L., Ji-Hyang, A., & Se-Won, Y. (2014). Effects of galvanic vestibular stimulation on visual memory recall and EEG. *Journal of Physical Therapy Science, 26,* 1333-1336. doi:10.1589/jpts.26.1333

Kalra, L., Perez, I., Gupta, S., & Witlink, M. (1997). The influence of visual neglect on stroke rehabilitation. *Stroke, 28,* 1386-1391. doi:10.1161/01.STR.28.7.1386

Karnath, H. O., & Dieteric, M. (2006). Spatial neglect—a vestibular disorder? *Brain, 129,* 293–305. doi:10.1093/brain/awh698

Karnath, H. O., & Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia, 50,* 1010-1017. doi:10.1016/j.neuropsychologia.2011.06.027

Katayama, J., & Polich, J. (1998). Stimulus context determines P3a and P3b. *Psychophysiology, 35,* 23-33. doi:10.1111/1469-8986.3510023

Katz, N., Hartman-Maeir, A., Ring, H., & Soroker, N. (1999). Functional disability and rehabilitative outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Archives of Physical Medicine and Rehabilitation, 80,* 379-384. doi: 10.1016/S0003-9993(99)90273-3

Kerkhoff, G., Hildebrandt, H., Reinhart, S., Kardinal, M., Dimova, V., & Utz, K. S. (2011). A long-lasting improvement of tactile extinction after galvanic vestibular stimulation: two Sham-stimulation controlled case studies. *Neuropsychologia, 49,* 186-195. doi: 10.1016/j.neuropsychologia.2010.11.014

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia, 50,* 1072–1079. doi:10.1016/j.neuropsychologia.2012.01.024

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,* 1-10. doi:10.1371/journal.pone.0069055

Kiss, M., Van Velzen, J., & Eimer, M. (2008). The N2pc component and its links to attention shifts and spatially selective visual processing. *Psychophysiology, 45,* 240–249. doi:10.1111/j.1469-8986.2007.00611.x

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology, 38,* 557-577.

Koivisto, M., & Revonsuo, A. (2003). An ERP study of change detection, change blindness, and visual awareness. *Psychophysiology, 40*, 423–429. doi:10.1111/1469-8986.00044

Kranczioch, C., Debener, S., & Engel, A. (2003). Event-related potential correlates of the attentional blink phenomenon. *Cognitive Brain Research, 17,* 177-187. doi:10.1016/S0926-6410(03)00092-2

Làdavas, E., Del Pesce, M., & Provinciali, L. (1989). Unilateral attention deficits and hemispheric asymmetries in the control of visual attention. *Neuropsychologia, 27,* 353-366. doi:10.1016/0028-3932(89)90024-9

Lee, S., Kim, D. J., Svenkeson, D., Parras, G., Mitsuko, M., Oishi, 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*. doi:10.3389/fnsys.2015.00005

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,* 1333–1336. doi:10.1589/jpts.26.1333

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*, 2604–2607. doi:10.1589/jpts.28.2604

Levitt, H. (1970). Transformed up-down methods in psychoacoustics. *The Journal of the Acoustical Society of America, 49,* 467-477. doi:10.1121/1.1912375

Leyland, L. A., Godwin, H. J., & Benson, V. &. (2017). Neglect Patients Exhibit Egocentric or Allocentric Neglect for the Same Stimulus Contingent upon Task Demands. *Nature Scientific Reports, 7,* 1-9. doi:10.1038/s41598-017-02047-x

Li, C., Liu, Q., & Hu, Z. (2017). Further Evidence That N2pc Reflects Target Enhancement Rather Than Distracter Suppression. *Frontiers in Psychology, 8*, 8. doi:10.3389/fpsyg.2017.02275

Lien, M. C., Ruthruff, E., Goodin, Z., & Remington, R. W. (2008). Contingent Attentional Capture by Top-Down Control Settings: Converging Evidence From Event-Related Potentials. *Journal of Experimental Psychology: Human Perception and Performance, 34*, 509-530. doi:10.1037/0096-1523.34.3.509

Linden, D. E., Prvulovic, D., Formisano, E., Völlinger, M., Zanella, F. E., Goebel, R., & Dierks, T. (1999). The Functional Neuroanatomy of Target Detection: An fMRI Study of Visual and Auditory Oddball Tasks. *Cerebral Cortex, 9*, 815–823. doi:10.1093/cercor/9.8.815

Lobel, E., Kleine, J. F., Le Bihan, D., Leroy-Willig, A., & Berthoz, A. (1998). Functional MRI of galvanic vestibular stimulation. *Journal of Neurophysiology, 80*, 2699-2709, doi: 10.1152/jn.1998.80.5.2699.

Lopez, C., Blanke, O., & Mast, F. W. (2012). The human vestibular cortex revealed by co-ordinate based liklihood estimation meta-analysis. *Neuroscience, 212*, 159–179. doi:10.1016/j.neuroscience.2012.03.028

Luck, S. J., & Ford, M. A. (1998). On the role of selective attention in visual perception. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 825-830. doi:10.1073/pnas.95.3.825

Luck, S. J., & Hillyard, S. A. (1994). Spatial filtering during visual search: evidence from human electrophysiology. *Journal of Experimental Psychology: Human Perception and Performance, 20*, 1000-1014. doi:10.1037/0096-1523.20.5.1000

Luck, S. J., Girelli, M., McDermott, M. T., & Ford, M. A. (1997). Bridging the gap between monkey neurophysiology and human perception: an ambiguity resolution theory of

visual selective attention. *Cognitive Psychology, 33*, 64-87. doi:10.1006/cogp.1997.0660

Mallet, N., Pogosyan, A., Márton, L. F., Bolam, J. P., Brown, P., & Magill, P. (2008). Parkinsonian Beta Oscillations in the External Globus Pallidus and Their Relationship with Subthalamic Nucleus Activity. *The Journal of Neuroscience, 28*, 14245-14258. doi:10.1523/JNEUROSCI.4199-08.2008

Marotta, J. J., McKeeff, T. J., & Behrmann, M. (2003). Hemispatial neglect: its effect on visual perception and visually guided grasping. *Neuropsychologia, 41,* 1262-1271. doi:10.101/S0028-3932(03)00038-1

Mars, F., Popov, K., & Vercher, J. L. (2001). Supramodal effects of galvanic vestibular stimulation on the subjective vertical. *Neuroreport, 12*, 2991-2994. doi:10.1097/00001756-200109170-00047

Mazza, V., Turatto, M., & Caramazza, A. (2009). Attention selection, distractor suppression and N2pc. *Cortex, 45*, 879-890. doi:10.1016/j.cortex.2008.10.009

Mazza, V., Turatto, M., Umiltà, C., & Eimer, M. (2007). Attentional selection and identification of visual objects are reflected by distinct electrophysiological responses. *Experimental Brain*

McDonnell, M. D., & Abbott, D. (2009). What Is Stochastic Resonance? Definitions, Misconceptions, Debates, and Its Relevance to Biology. *PLOS Computational Biology, 5*. doi:10.1371/journal.pcbi.1000348

Mercado, R., Constantoyannis, C., Mandat, T., Kumar, A., Schulzer, M., Stoessl, A. J., & Honey, C. R. (2006). Expectation and the placebo effect in Parkinson's disease patients with subthalamic nucleus deep brain stimulation. *Movement Disorders, 21*, 1457-1461. doi:10.1002/mds.20935

Monajemi, S., Jarchi, D., Ong, S. H., & Sanei, S. (2017). Cooperative Particle Filtering for Tracking ERP Subcomponents from Multichannel EEG. *Entropy, 19*, 1-22. doi:10.3390/e19050199

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*, 12–28. doi:10.3988/jcn.2006.2.1.12

Morgan, S. T., Hansen, J. C., & Hillyard, S. A. (1996). Selective attention to stimulus location modulates the steady-state visual evoked potential. *Proceedings of the National Academy of Sciences of the United States of America, 90*, 4770–4774. doi:10.1073/pnas.93.10.4770

Mort, D., J, Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C; Husain, M. (2003). The anatomy of visual neglect. *Brain, 126*, 1986-1997. doi:10.1093/brain/awg200

Moss, F., Ward, L. M., & Sannita, W. G. (2004). Stochastic resonance and sensory information processing: a tutorial and review of application. *Clinical Neurophysiology, 115*, 267-281. doi:10.1016/j.clinph.2003.09.014

Muller, M. M., Picton, T. W., Valdes-Sosa, P., Riera, J., Teder-Salejarvi, W. A., & Hillyard, S. A. (1998). Effects of spatial selective attention on the steady-state visual evoked potential in the 20–28 Hz range. *Cognitive Brain Research, 6*, 249–261. doi:10.1016/S0926-6410(97)00036-0

Nakamura, J., Kita, Y. I., Kojima, K., Okada, Y., & Shomoto, K. (2015). Influence of the stimulus parameters of galvanic vestibular stimulation on unilateral spatial neglect. *Neuroreport, 26*, 462-466. doi:10.1097/WNR.0000000000000369

Norcia, A. M., Appelbaum, L. G., Ales, J. M., Cottereau, B. R., & Rossion, B. (2015). The steady-state visual evoked potential in vision research: A review. *Journal of Vision, 15*, 1-46. doi:10.1167/15.6.4

O'Connell, G, R., Dockree, P. M., & Kelly, S. P. (2012). A supramodal accumulation-to-bound signal that determines perceptual decisions in humans. *Nature Neuroscience, 15*, 1729–1735. doi:10.1038/nn.3248

Oppenländer, K., Keller, I., Karbach, J., Schindler, I., Kerkhoff, G., & Reinhart, S. (2015). Subliminal galvanic-vestibular stimulation influences ego- and object-centred components of visual neglect. *Neuropsychologia, 74*, 170-177. doi: 10.1016/j.neuropsychologia.2014.10.039

Palla, A., & Lenggenhager, B. (2014). Ways to investigate vestibular contributions to cognitive processes. *Frontiers in Integrative Neuroscience, 8*, 1-4. doi:10.3389/fnint.2014.00040

Parton, A., Malhotra, P., & Husain, M. (2004). Hemispatial neglect. *Journal of Neurology, Neurosurgery and Psychiatry, 75*, 13-21. doi:10.1016/S0072-9752(07)88018-3

Patel, S. H., & Azzam, P. N. (2005). Characterization of N200 and P300: Selected Studies of the Event-Related Potential. *International Journal of Medical Sciences, 2*, 147–154. doi:10.7150/ijms.2.147

Patel, M., Roberts, R. E., Arshad, Q., Ahmed, M., Riyaz, M. U., & Bronstein, A. M. (2015). Galvanic Vestibular Stimulation Induces a Spatial Bias in Whole-body Position Estimates. *Brain Stimulation, 8*, 981-983. doi:10.1016/j.brs.2015.07.030

Pavlidou, A., Ferrè, E. R., & Lopez, C. (2017). Vestibular stimulation makes people more egocentric. *Cortex, 101*. doi:10.1016/j.cortex.2017.12.005

Peirce, JW (2007) PsychoPy - Psychophysics software in Python. *Journal of Neuroscience Methods, 162*, 8-13. doi:10.1016/j.jneumeth.2006.11.017.

Pisella, L., & Mattingley, J. B. (2004). The contribution of spatial remapping impairments to unilateral visual neglect. *Neuroscience and Biobehavioural Reviews, 28*, 181-200. doi:10.1016/j.neubiorev.2004.03.003

Pitzalis, S., Spinelli, D., Vallar, G., & Di Russo, F. (2013). Transcutaneous electrical nerve stimulation effects on neglect: a visual-evoked potential study. *Frontiers in Human Neuroscience, 7*(111). doi:10.3389/fnhum.2013.00111

Polich, J. (1988). Bifurcated P300 peaks: P3a and P3b revisited? *Journal of Clinical Neurophysiology, 5*, 287-294.

Polich, J. (1989). Habituation of P300 from auditory stimuli. *Psychobiology, 17*, 19-28.

Polich, J. (1993). Cognitive Brain Potentials. *Current Directions Psychological Science, 2*, 175-179.

Polich, J. (2007). Updating P3: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*, 2128–2148. doi:10.1016/j.clinph.2007.04.019

Polich, J., & Criado, J. R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. *International Journal of Psychophysiology, 60,* 172-185. doi:10.1016/j.ijpsycho.2005.12.012

Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biological Psychology, 41*, 103-146. doi:10.1016/0301-0511(95)05130-9

Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *4*, 1863-1874. doi:10.1523/JNEUROSCI.04-07-01863.1984

Preuss, N., Hasler, G., & Mast, F. W. (2014a). Caloric Vestibular Stimulation Modulates Affective Control and Mood. *Brain Stimulation, 7*, 133-140. doi:10.1016/j.brs.2013.09.003

Preuss, N., Mast, F. W., & Hasler, G. (2014b). Purchase decision-making is modulated by vestibular stimulation. *Frontiers in Behavioral Neuroscience, 8*. doi:10.3389/fnbeh.2014.00051

Ringman, J. M., Saver, J. L., Woolson, R. F., Clarke, W. R., & Adams, H. P. (2004). Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. *Neurology, 63*(3), 468-474. doi:10.1212/01.WNL.0000133011.10689.CE

Reinhart, S., Wagner, P., Schulz, A., Keller, I., & Kerkhoff, G. (2013). Line bisection error predicts the presence and severity of neglect dyslexia in paragraph reading. *Neuropsychologia, 51*, 1-7. doi:10.1016/j.neuropsychologia.2012.10.026

Rode, G., & Perenin, M. (1994). Temporary remission of representational hemineglect through vestibular stimulation. *NeuroReport, 5*, 869–872. doi:10.1097/00001756-199404000-00004

Rorden, C., Karnath, H. O., & Driver, J. (2001). Do neck-proprioceptive and caloric-vestibular stimulation influence covert visual attention in normals, as they influence visual neglect? *Neuropsychologia, 39*, 364-375. doi:10.1016/S0028-3932(00)00126-3

Rorsman, I., Magnusson, M., & Johansson, B. B. (1999). Reduction of visuo-spatial neglect with vestibular galvanic stimulation. *Scandinavian journal of rehabilitation medicine, 31*, 117-124. doi:10.1080/003655099444632.

Rubens, A. B. (1985). Caloric stimulation and unilateral visual neglect. *Neurology, 35*, 1019-1024. doi:10.1212/WNL.35.7.1019

Ruet, A., Jokic, C., Denise, P., Leroy, F., & Azouvi, P. (2014). Does galvanic vestibular stimulation reduce spatial neglect? A negative study. *Annals of Physical and Rehabilitation Medicine, 57*, 570-577. doi:10.1016/j.rehab.2014.09.009

Saevarsson, S., Kristjánsson, A., Bach, M., & Heinrichd, S. P. (2012). P3 in neglect. *Clinical Neurophysiology, 123*, 496-506. doi:10.1016/j.clinph.2011.07.028

Saliasi, E., Geerligs, L., Lorist, M. M., & Maurits, N. M. (2013). The Relationship between P3 Amplitude and Working Memory Performance Differs in Young and Older Adults. *PLOS One, 8*, 1-9. doi:10.1371/journal.pone.0063701

Salti, M., Bar-Haim, Y., & Lamy, D. (2012). The P3 component of the ERP reflects conscious perception, not confidence. *Consciousness and Cognition, 21,* 961–968. doi:10.1016/j.concog.2012.01.012

Saupe, K., Schröger, E., Andersen, S. K., & Müller, M. M. (2009). Neural mechanisms of intermodal sustained selective attention with concurrently presented auditory and visual stimuli. *Frontiers in Human Neuroscience*. doi:10.3389/neuro.09.058.2009

Saj, A., Honore, J., & Rosseaux, M. (2006). Perception of the vertical in patients with right hemispheric lesion: effect of galvanic vestibular stimualtion. *Neuropsychologia, 44*, 1509-1512. doi: 10.1016/j.neuropsychologia.2005.11.018

Schankin, A., Hagemann, D., & Wascher, E. (2009). The N2pc as an electrophysiological correlate of attention in change blindness. *Journal of Psychophysiology, 23*, 43-51. doi:10.1027/0269-8803.23.2.43

Schiff, N., & Pulver, M. (1999). Does vestibular stimulation activate thalamocortical mechanisms that reintegrate impaired cortical regions? *Proceedings of the royal society b: Biological sciences, 266*, 421-423. doi:10.1098/rspb.1999.0654

Schmidt, L., Utz, K., Depper, L., Adams, M., Schaadt, A., Reinhart, S., & Kerkhoff, G. (2013). Now You Feel both: Galvanic Vestibular Stimulation Induces Lasting Improvements in the Rehabilitation of Chronic Tactile Extinction. *Frontiers in Human Neuroscience, 7*(90). doi:10.3389/fnhum.2013.00090

Schmidt-Kassow, M., Heinemann, L. V., Abel, C., & Kaiser, J. (2013). Auditory–motor synchronization facilitates attention allocation. *NeuroImage, 82*, 101–106. doi:10.1016/j.neuroimage.2013.05.111

Schmidt-Kassow, M., Wilkinson, D., Denby, E., & Ferguson, H. (2016). Synchronised vestibular signals increase the P3 event-related potential elicited by auditory oddballs. *Brain Research, 1648*, 224-231. doi:doi.org/10.1016/j.brainres.2016.07.019

Schwarzkopf, D. S., Silvanto, J., & Rees, G. (2011). Stochastic Resonance Effects Reveal the Neural Mechanisms of Transcranial Magnetic Stimulation. *The Journal of Neuroscience, 31*, 3143-3147. doi:10.1523/JNEUROSCI.4863-10.2011

Simons, D. J., & Levin, D. T. (1997). Change blindness. *Trends in cognitive sciences, 1*, 261-267 doi: 10.1016/S1364-6613(97)01080-2

Smith, P. F., Geddes, L. H., Baek, J. H., Darlington, C. L., & Zheng, Y. (2010). Modulation of memory by vestibular lesions and galvanic vestibular stimulation. *Frontiers in Neurology, 1*, 1-8. doi:10.3389/fneur.2010.00141

Soma, R., Kwak, S., & Yamamoto, Y. (2003). 1/f noise outperforms white noise in sensitizing baroreflex function in the human brain. *Physical Review Letters, 91*. doi:10.1103/PhysRevLett.91.078101

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. doi:10.1016/j.neuroimage.2005.02.049

Stephan, T., Hufner, K., & Brandt, T. (2009). Stimulus profile and modeling of continuous galvanic vestibular stimulation in functional magnetic resonance imaging. *Basic and clinical aspects of vertigo and dizziness, 1164*, 472-475. doi:10.1111/j.1749-6632.2008.03715.x

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-Potential Correlates of Stimulus Uncertainty. *Science, 150*, 1187-1188. doi:10.1126/science.150.3700.1187

Suzuki, M., Kitano, H., Ito, R., Kitanishi, T., Yazawa, Y., Ogawa, T., Shiino, A., Kitajima, K. (2001). Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. *Cognitive Brain Research, 12*, 441-449. doi:10.1016/S0926-6410(01)00080-5

Talsma, D., Slagter, H. A., Nieuwenhuis, S., Hage, J., & Kok, A. (2005). The orienting of visuospatial attention: An event-related brain potential study. *Cognitive Brain Research, 25*, 117 – 129. doi:10.1016/j.cogbrainres.2005.04.013

Toffanin, P., Jonga, R., Johnson, A., & Martens, S. (2009). Using frequency tagging to quantify attentional deployment in a visual divided attention task. *International Journal of Psychophysiology, 72*, 289-298. doi:10.1016/j.ijpsycho.2009.01.006

Török, A., Ferrè, E. R., Kokkinara, E., Csépe, V., Swapp, D., & Haggard, P. (2017). Up, Down, Near, Far: An Online Vestibular Contribution to Distance Judgement. *PLOS One, 2017*. doi:10.1371/journal.pone.0169990

Tseng, P., Hsu, T., Chang, C., Tzeng, O., Hung, D., Muggleton, N.G., Walsh, V., Liang, W.K., Cheng, S.K., Juan, C. H. (2012). Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *The Journal of Neuroscience, 32*(31), 10554-1061. doi:10.1523/JNEUROSCI.0362-12.2012

Twomey, D. M., Murphy, P. R., Kelly, S. P., & O'Connell, R. G. (2015). The classic P300 encodes a build-to-threshold decision variable. *Cognitive Neuroscience , 42*(1), 1636-1643. doi:10.1111/ejn.12936

Utz, K., 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*, 2789-2810. doi: 10.1016/j.neuropsychologia.2010.06.002.

Utz, K. S., Keller, I., Kardinal, M., & Kerkhoff, G. (2011). Galvanic vestibular stimulation reduces the pathological rightward line bisection error in neglect - A sham stimulation-controlled study. *Neuropsychologia, 49*, 1219-1225. doi:10.1016/j.neuropsychologia.2011.02.046

Verleger, R., Moller, F., Kuniecki, M., Smigasiewicz, K., Groppa, S., & Siebrier, H. (2010). The left visual-field advantage in rapid visual presentation is amplified rather than reduced by posterior-parietal rTMS. *Experimental Brain Research, 203*(2), 355-365. doi:10.1007/s00221-010-2237-z

Volkening, K., Bergmann, J., Keller, I., Wuehr, M., Müller, F., & Jahn, K. (2014). Verticality perception during and after galvanic vestibular stimulation. *Neuroscience Letters, 581*, 75-79. doi:10.1016/j.neulet.2014.08.028

Volkening, K., Kerkhoff, G., & Keller, I. (2018). Effects of repetitive galvanic vestibular stimulation on spatial neglect and verticality perception-a randomised sham-controlled trial. *Neuropsychological Rehabilitation, 28*, 1179-1196. doi:10.1080/09602011.2016.1248446

Wickens, C., Kramer, A., Vanasse, L., & Donchin, E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science, 221*, 1080-1082. doi:10.1126/science.6879207

Wilkinson, D., Ferguson, H. J., & Worley, A. (2012). Galvanic vestibular stimulation modulate the electrophysiological response during face processing. *Visual Neuroscience, 29*, 255-262. doi:10.1017/S0952523812000235

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, 11, 925-929. doi:10.1017/S1355617705051076

Wilkinson, D., Morris, R., Milberg, W., & Sakel, M. (2013). Caloric vestibular stimulation in aphasic syndrome. *Frontiers in Integrative Neuroscience, 7*, 1-9. doi:10.3389/fnint.2013.00099

Wilkinson, D. T., Nicholls, S., Pattenden, C., Kilduff, P., & Milberg, W. (2008). Galvanic vestibular stimulation speeds visual memory recall. *Experimental Brain Research, 189*, 243-248. doi:10.101/S0952523812000235

Wilkinson, D., Sakel, M., Camp, S., & Hammond, L. (2012). Patients with hemispatial neglect are more prone to limb spasticity, but this does not prolong their hospital stay. *Archives of physical medicine and rehabilitation, 93*, 1191-1195. doi:10.1016/j.apmr.2012.01.010

Wilkinson, D. T., Zubko, O., DeGutis, J., Milberg, W. P., & Potter, J. (2010). Improvement of a figure copying deficit during sub-sensory galvanic vestibular stimulation. *Journal of Neuropsychology, 4*, 107-118. doi:10.1348/174866409X468205

Wilkinson, D., Zubko, O., & Sakel, M. (2009). Safety of repeated measures of galvanic vestibular stimulation following stroke: a single case study. *Brain Injury, 23*, 841-845. doi:10.1080/02699050903232541

Wilkinson, D., Zubko, O., Sakel, M., Coulton, S., Higgins, T., & Pullicino, P. (2014). Galvanic Vestibular Stimulation in hemi-spatial neglect. *Frontiers in Integrative Neuroscience*. doi:10.1007/s00221-008-1463-0

Woodman, G. F., Arita, J. T., & Luck, S. J. (2009). A cuing study of the N2pc component: An index of attentional deployment to objects rather than spatial locations. *Brain Research, 1297*, 101-111. doi:10.1016/j.brainres.2009.08.011

Woodman, G. F., & Luck, S. J. (1999). Electrophysiological measurement of rapid shifts of attention during visual search. *Nature, 400*, 867-869. doi:10.1038/23698

Woodman, G. F., & Luck, S. J. (2003). Serial Deployment of Attention During Visual Search. *Journal of Experimental Psychology: Human Perception and Performance, 29*, 121-138. doi:10.1037/0096-1523.29.1.121

Xie, S., Liu, C., Obermayer, K., Zhu, F., Wang, L., Xie, X., & Wang, W. (2016). Stimulator selection in SSVEP-based spatial selective attention study. *Computational Intelligence and Neuroscience, 2016*, 1-9. doi:10.1155/2016/6410718

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*, 175-181. doi:10.1002/ana.20574

Zerafa, R., Camilleri, T., Falzon, O., & Camilleri, K. P. (2013). Comparison of plain and checkerboard stimuli for brain computer interfaces based on steady state visual evoked potentials. *International IEEE/EMBS Conference on Neural Engineering, NER*, 33-36. doi:10.1109/NER.2013.6695864

Zhou, L., & Thomas, R. D. (2015). Principal component analysis of the memory load effect in a change. *Vision Research, 110*, 1-6. doi:10.1016/j.visres.2015.01.028

Zubko, O., Wilkinson, D., Langston, D., & Sakel, M. (2013). The effect of repeated sessions of galvanic vestibular stimualtion on target cancellation in visuo-spatial neglect: Preliminary evidence from two cases. *Brain Injury, 27*(5), 613-619. doi:10.3109/02699052.2013.767938

Appendix A

Colour Name	**RGB Values**	**CIE1931**
Red	255, 0, 0	X = .656, Y = .317, I = 37.57 cd/m^2
Blue	0, 0, 255	X = .132, Y = .044, I = 11.34 cd/m^2
Violent	0, 128, 0	X = .305, Y = .209, I = 78.31 cd/m^2
Green	255, 255, 0	X = .300, Y = .603, I = 35.44 cd/m^2
Yellow	238, 130, 238	X = .430, Y = .511, I = 170.91 cd/m^2
Black	0, 0, 0	X = .178, Y = .195, I = .047 cd/m^2
White	255, 255, 255	X = .301, Y = .309, I = 181.52 cd/m^2

Appendix B

To investigate whether there was a baseline hemispheric difference between electrodes PO7 and PO8 in the N2pc data of Chapter 3, a 3x2x2x2 ANOVA was conducted comparing stimulation type (sham, neck sham or GVS), target detection (seen or unseen), electrode (PO7 or PO8) and ipsi/contra (ipsilateral or contralateral). There was no significant main effect of electrode, $F(1, 45) = 3.27$, $p = .077$, $\eta_p^2 = .07$. As in the original analysis, contralateral amplitude was more negative than ipsilateral, demonstrated through a main effect of ipsi/contra, $F(1, 45) = 14.143$, $p < .001$, $\eta_p^2 = .24$. Also as in the original analysis, N2pc amplitude was bigger for seen targets versus unseen targets, as demonstrated through a target detection by ipsi/contra interaction, $F(1, 45) = 11.65$, $p = .001$, $\eta_p^2 = .21$. There was also a main effect of target detection, $F(1, 45) = 11.79$, $p = .001$, $\eta_p^2 = .21$. There was an effect involving stimulation, in a stimulation by target-detection by target-side interaction, $F(2, 45) = 3.48$, $p = .039$, $\eta_p^2 = .13$, however since N2pc is the difference between the ipsilateral and contralateral amplitudes, this effect is not meaningful as it does not involve the ipsi/contra variable. No other effects were significant, all Fs < 2.65 and all ps > .111.