Vestibular Stimulation in Post-Stroke Visual Disorders

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Word count: 22782

Abstract

Stroke is one of the leading causes of death and disability worldwide and survivors often suffer from disorders of the visual system, which include both visual neglect and hemianopia. The first section of this work focuses on the former. Several studies have investigated different forms of vestibular stimulation as a potential therapy for neglect. However, this evidence is yet to be systematically reviewed, a gap in the literature which this thesis aims to fill. Nine studies addressing this topic are evaluated, with results revealing mixed evidence of low quality as to the efficacy of the stimulation. Better quality evidence, which more thoughtfully considers the many complexities of neglect and its assessment needs to be conducted. By addressing the inconsistencies found, future research should be able to achieve results in which we can have greater confidence, subsequently advancing the search for a more effective treatment for the condition. A second purpose of the thesis is to present theoretical justification and research methods for a novel intervention for individuals suffering from hemianopia. The treatment is based on the principles of multisensory integration and involves combining visual training with galvanic vestibular stimulation. Unfortunately, no data are available for this experiment due to the COVID-19 outbreak, but anticipated outcomes are provided.

Keywords: stroke, unilateral spatial neglect, hemianopia, vestibular stimulation, systematic review

Acknowledgements

Firstly, I would like to thank my supervisor Professor David Wilkinson for all the incredible opportunities and guidance he has provided me with, not just during my masters but over the past three years. His encouragement of me to reach my full potential has played a huge role in growing my abilities and confidence. I would also like to thank Dr Kristina Dietz for all the hours she gave up to help me, alongside her expertise and reassurances when I wasn't feeling the most enthusiastic about the review process.

Secondly, a mention must be given to the technical team, especially Frank Gasking, for all their help with the setup of my experiment, as well as to Harriet Caesley and Sapna Gupta for putting up with my constant distractions and sarcasm, and to Kamyla Marques for so willingly answering my many GVS-related questions.

Finally, thanks to Mum and Rosie, for always listening to me talk about my work despite it often not making a lot of sense. Your unwavering belief in me means the world and I hope this thesis makes you proud (if not bored). Also thank you to Chloe, whose constant support through the laughs and tears of this year has kept me going and whose friendship I am so grateful for.

Overview

Stroke and Post-Stroke Visual Disorders

Stroke, also known as cerebrovascular accident (CVA), is defined by the World Health Organisation as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Aho, Harmsen, Hatano, Marquardsen, Smirnov, & Strasser, 1980, p. 114). Stroke is one of the leading causes of death and disability worldwide; in 2013, it accounted for 11.8% of global deaths, with only ischemic heart disease posing a greater burden (Feigin, Norrving, & Mensah, 2017). In the UK, more than 100 000 people experience a stroke each year (SSNAP, 2015), resulting in 38 000 deaths in 2016 (Patel, 2017). Of those who survive, almost two thirds are discharged with some form of disability (Adamson, Beswick, & Ebrahim, 2004). The aetiology of stroke can be separated into two main subtypes. 87% of strokes are ischaemic and occur when an artery within the brain becomes blocked by a blood clot, which prevents the flow of blood through this vessel. The remaining 13% of CVAs are haemorrhagic, arising as a result of a burst artery, causing a bleed into the surrounding brain tissue (Haast, Gustafson, & Kiliaan, 2012; Sacco et al., 2013)**.** The risk factors for stroke are numerous, but 80% of cases can be predicted by only five: hypertension, smoking, obesity, diet, and decreased physical exercise (O'Donnell et al., 2010).

The effects of stroke vary hugely between cases as they are dependent upon several factors, including the location and size of the lesion. This means that a large range of deficits can be seen post-stroke which differ in their exact presentation and severity. Common problems include hemiplegia or paresis, aphasia, dysphagia, fatigue, pain or numbness, as well as mood disorders such as anxiety and depression (Lawrence et al., 2001). All of these issues can take intense and prolonged periods of time to rehabilitate, a process which is often complicated by the presence of anosognosia,

a term originally coined in 1914 by Babinski, in which the sufferer denies that they are suffering from any impairment (Prigatano, & Schacter, 1991).

Disorders of the visual system are also common post-stroke, affecting approximately 65% of this population (Hepworth et al., 2016). These conditions include reduced visual acuity, nystagmus, diplopia, and visual hallucinations, as well as perceptual difficulties such as visual agnosia (difficulties with interpreting visual information), achromatopsia (inability to perceive colours), and akinetopsia (inability to perceive moving stimuli; Rowe et al., 2017c).

The most common of these visual perceptual problems is unilateral spatial neglect (Rowe et al., 2017c), an attentional disorder in which individuals fail to respond to contralesional stimuli despite displaying no sensory impairment (Walker, Findlay, Young, & Welch, 1991). Another prevalent post-stroke visual disorder is hemianopia, which has been estimated to affect up to 57% of survivors (Ali, Hazelton, Lyden, Pollock, & Brady, 2013). In contrast to neglect, this condition results from sensory loss in the absence of attentional issues (see Pollock et al., 2011). Despite their differences, both neglect and hemianopia are both debilitating conditions that have been shown to become a barrier to individuals carrying out everyday activities such as driving and reading (Hepworth & Rowe, 2016). They negatively impact quality of life (Rowe, 2017a; Sobrinho et al., 2018) and significantly impede recovery from stroke (Chen, Hreha, Kong, & Barrett, 2015; Jones & Shinton, 2006), making clear the requirement for appropriate treatment. Although many interventions for the disorders have been trialled and several show promising effects, the evidence thus far is insufficient to recommend any particular rehabilitation approach (Bowen, Hazelton, Pollock, & Lincoln, 2013; Pollock et al., 2011), suggesting there is a significant unmet need for more effective methods to be developed. Their prevalence, refractory nature, and subsequent requirement for more efficacious treatment indicate that the conditions necessitate further investigation, and it is for these reasons they are the focus of this thesis. More specifically, the work will consider how neglect and hemianopia might be impacted by vestibular stimulation, a technique discovered over a

century ago (Volta, 1918), which has not only shown benefits in a number of neurological conditions (e.g. Wilkinson et al., 2019) but also activates brain structures implicated in these two disorders.

The Structure of the Current Thesis

This thesis therefore aims to further investigate the potential of vestibular stimulation as an intervention for neglect and hemianopia. Multiple primary studies have been conducted to assess the effects of vestibular stimulation in neglect. However, whilst a Cochrane review has explored cognitive rehabilitation techniques (Bowen et al., 2013), and several other pieces of work have looked at other forms of non-invasive brain stimulation for neglect (Fan, Li, Yang, Qu, & Li, 2018; Müri, Cazzoli, Nef, Mosimann, Hopfner, & Nyffeler, 2013), to our knowledge there has not yet been any systematic appraisal of the specific effects of vestibular stimulation in this population. Therefore, the first section of this work reviews the research conducted so far, taking into consideration the complexities of neglect in terms of its clinical presentation, diagnosis and current management options, with the aim of discovering whether the overall evidence base supports vestibular stimulation as a treatment option. The results of the review highlight the need for further research which addresses the clinical and methodological inconsistencies found, with suggestions on how best to implement this provided.

Treatments for hemianopia are also currently insufficient despite the clear clinical demand for effective rehabilitation. Therefore, the second part of the thesis focuses on hemianopia and provides the background and justification for a novel intervention involving a form of vestibular stimulation, built upon the principles of multisensory integration. The methods for this paradigm are presented, followed by anticipated outcomes (we were unable to collect any data due to COVID) and potential directions for future research.

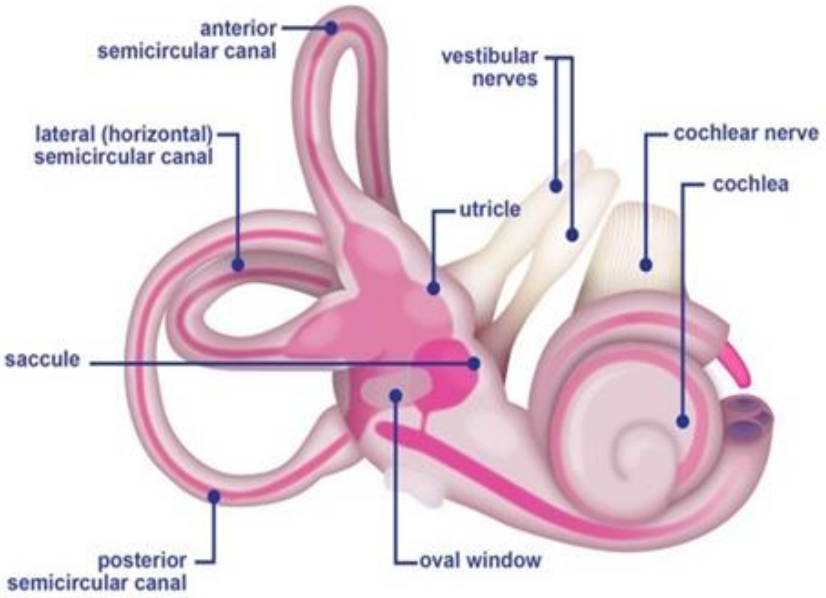
To provide context to these two sections, a brief overview of the anatomy, function, and stimulation of the vestibular system is provided below.

The Vestibular System

The vestibular system is an ancient structure which is critically important for the day-to-day functioning of humans. The significance of vestibular signals is reflected in the fact that they are often referred to as our sixth sense, alongside sight, hearing, touch, taste, and smell (Grabherr, Macauda, & Lenggenhager, 2015). Most commonly known for its role in balance, the peripheral vestibular system can be found within the dense temporal bone of the inner ear (Kingma & Van de Berg, 2016). Its anatomy can be broadly categorised into two types of vestibular end organ: the semicircular canals, and the otoliths, which both continually monitor movements of the head. The three semicircular canals, responsible for the detection of rotational head movements, are positioned perpendicular to one another. The otoliths consist of the saccule and utricle, which detect linear head movements (that is, when the head moves forwards, backwards, up, or down), as well as gravitational pull (Khan & Chang, 2013). Hair cells within these structures bend as the head moves, resulting in the translation of these actions into electrical potentials (Colclasure & Holt, 2007).

Figure 1.

Anatomy of the peripheral vestibular system.



Retrieved from https://www.eyeandear.org.au/

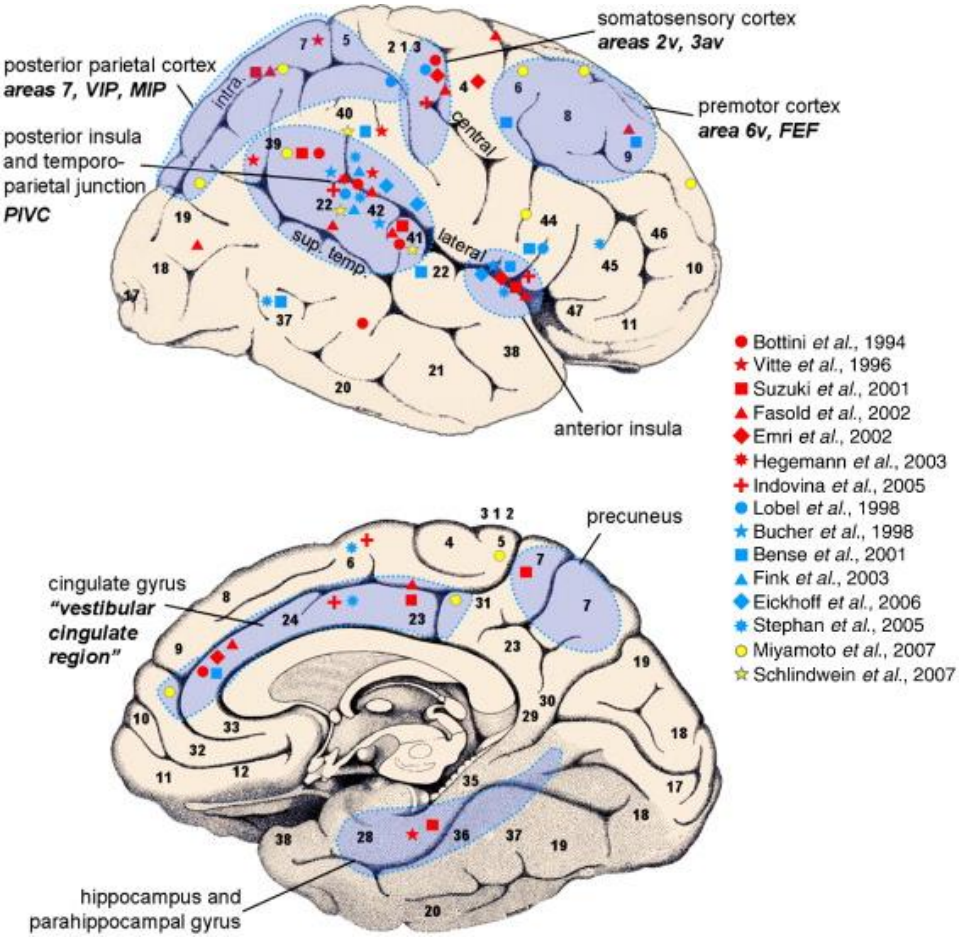
The vestibular organs send signals via the eighth cranial nerves, which themselves project to four vestibular nuclei found in the pons and medulla of the brainstem. Within these nuclei, signals from the visual system, as well as the cerebellum and spinal cord, are integrated with vestibular inputs (Highstein, 2004). From the nuclei, several direct and indirect pathways connect to a number of widespread cortical and subcortical locations including the thalamus, basal ganglia, hippocampus, cerebellum, and multiple areas of cerebral cortex (Hitier, Besnard, & Smith, 2014; see also Figure 2.). This long list of connections highlights the fundamentally multimodal nature of the vestibular system. Inputs from other sensory modalities are constantly being integrated with those of a vestibular nature and, unlike the other senses, there is no primary vestibular cortex. Rather, vestibular signals are processed in regions spread throughout the brain. In non-human primates, a parieto-insular vestibular cortex (PIVC) has been identified (Lopez, Blanke, & Mast, 2012) and in humans, similar activations can be seen in the temporoparietal junction, posterior insula, and posterior parietal cortex (Bense Stephan, Yousry, Brandt, & Dieterich, 2001). These areas are thought to be analogous to the PIVC, the neurons of which are not only responsive to vestibular inputs, but visual and somatosensory ones too (Grüsser, Guldin, Mirring, & Salah-Eldin, 1994).

This close connectivity is necessary for the maintenance of balance and posture. For example, the convergence of visual and vestibular inputs allows for fine-tuned control of oculomotor behaviours such as the vestibulo-ocular reflex, which ensures the stable maintenance of images on the retina when head movements are made (Angelaki, 2004). However, balance-related roles are not the only purpose these associations serve. The vestibular system has also been implicated in a number of other neural, affective, and cognitive functions, such as visuospatial memory, navigation, anxiety, and depression **(**Bigelow & Agrawal, 2015; Hilber, Cendelin, Le Gall, Machado, Tuma, & Besnard, 2019). Uncovering the systems' input in these behaviours has been made possible by investigations involving vestibular stimulation, a process which can be achieved through several different methodological approaches.

One such stimulation method is vestibular rehabilitation (VR), which prescribes specific head exercises alongside balance and gait activities designed to stimulate the system (Herdman, 2013). Alternatively, this activation can also be accomplished in an artificial manner, usually through caloric (CVS) or galvanic (GVS) vestibular stimulation. CVS involves irrigation of the outer eardrum with warm or cold water. This changes the density of the endolymphatic fluid in the semi-circular canals, creating convection currents which lead to a change in the firing rate of the vestibular nerves (Black, Rogers, Ade, Nicoletto, Adkins, & Laskowitz, 2016). GVS makes use of mild electrical, rather than thermal, currents, which are applied to the mastoid (Palla & Lenggenhager, 2014). These currents again alter the firing rate of the nerves, which, due to their extensive connections with other brain areas, causes widespread patterns of activation in both cortical and subcortical regions (Fitzpatrick & Day, 2004). To employ bipolar GVS, an anode is attached to one mastoid, and a cathode to another. Whilst imaging data has shown that a cathode to either ear results in vestibular activation in that hemisphere, the spread of the activation is not equal in both cases. Fink et al. (2003) showed using fMRI that right-cathodal, left-anodal GVS (CR-GVS; excitation of the right and inhibition of the left vestibular nerves) results in activation of cortical areas in the right hemisphere only, whilst left-cathodal, right-anodal GVS (CL-GVS; vice versa) leads to activity in the same areas, but in both hemispheres.

Figure 2.

Activations in the human brain as a result of vestibular stimulation.



Red symbols indicate areas activated during CVS; blue, GVS; and yellow, auditory. Taken from Lopez & Blanke (2011).

A wide range of settings can be implemented when using GVS. These include differing waveforms (direct current, alternating current, noisy current, and pulse; Dlugaiczyk, Gensberger, & Straka, 2019). The timing and intensity of the current can also be modified within pre-determined safety limits. The stimulation technique has been shown to be safe and tolerable in stroke populations, although when applied at higher intensities, can lead to itching or tingling behind the ears (Utz et al., 2011). GVS possesses several methodological advantages which make it particularly valuable for experimental work. Firstly, its intensity can be modified so that it is subsensory, a tool especially useful when blinding participants, as, if completed correctly, it makes active and sham stimulation indistinguishable. Concealing condition is much more difficult to achieve when using CVS or VR. Secondly, unlike other non-invasive brain stimulation techniques (such as transcranial

direct current or magnetic stimulation), which are only able to target localised areas of the cortex (Bikson & Rahman, 2013), GVS activates a pre-existing neural network and is consequently able to reach a wide range of both cortical and subcortical structures. Finally, the technique is inexpensive, portable, and requires relatively little technical expertise to apply, making it ideal for therapeutic home use.

Vestibular stimulation has been trialled as an intervention for many neurological and psychiatric conditions, with numerous studies finding improvement with the application of the technique. This includes Parkinson's disease (Wilkinson et al., 2019), minimally conscious state (Vanzan, Wilkinson, Ferguson, Pullicino, & Sakel, 2017), PTSD (Carrick, McLellan, Brock, Randall, & Oggero, 2015), anxiety (Pasquier, Denise, Gauthier, Bessot, & Quarck, 2019), and episodic migraine (Wilkinson et al., 2017), to name but a few. These findings further confirm that the vestibular system contributes to far more than just balance (Gurvich, Maller, Lithgow, Haghgooie, & Kulkarni, 2013), and that it may also possess the potential to help treat both neglect and hemianopia.

Indeed, GVS has been shown to improve visual and spatial representation impairments such as post-stroke figure copying deficits (Wilkinson, Zubko, DeGutis, Milberg, & Potter, 2010) and the neglect-related phenomenon of extinction (Schmidt et al., 2013). In healthy individuals, vestibular stimulation alters line bisection performance (an assessment commonly used in the diagnosis of neglect; Ferrè, Longo, Fiori, & Haggard, 2013), a result which has also generalised to several studies involving neglect samples (e.g. Oppenländer et al., 2015).

Regarding hemianopia, multiple studies have shown improvements using multisensory integration techniques (e.g. Bolognini, Rasi, Coccia, & Làdavas, 2005). This research area has generally made use of audiovisual paradigms, which build upon the standard visual training used for the condition by augmenting it with auditory tones. Despite the multisensory nature of the vestibular

system, no studies to date have utilised vestibular signals in this way, an oversight in the research rectified here.

To summarise, neglect and hemianopia are enduring and debilitating conditions which warrant further study in order to uncover more appropriate interventions for the conditions, of which vestibular stimulation may be one. This work aims to achieve this firstly, by reviewing the evidence for the efficacy of vestibular stimulation in neglect, and secondly, by describing a potential new intervention involving GVS for hemianopia.

A Systematic Review of Vestibular Stimulation in Post-Stroke Visual Neglect

Clinical Presentation of Neglect

Unilateral spatial neglect (more simply known as neglect) is an attentional disorder which causes affected individuals to struggle to report or respond to stimuli in the contralesional side of space (Walker et al., 1991). Unlike some other visual disorders that are experienced post-stroke, neglect occurs in the absence of any sensory or motor loss (Heilman, Valenstein, & Watson, 1994). Although individuals with neglect may struggle to automatically orient their attention towards their contralesional side (Bartolomeo & Chokron, 2002), their conscious adaptation is not impaired (i.e. if their attention is drawn to the neglected side of space, they are able to perceive whatever is being presented there; Driver & Mattingley, 1998). However, whilst neglect is not synonymous with sensory impairment, it is possible for the disorder to occur alongside sensory loss conditions such as visual field defects (VFDs). When these two deficits co-occur, they lead to severe functional impairment, due not only to the individual's inability to perceive stimuli in one hemifield, but also their unawareness of their condition, which results in a lack of compensatory behaviour (Müller-Oehring, Kasten, Poggel, Schulte, Strasburger, & Sabel, 2003).

Even when presenting alone, the behavioural effects of neglect are devastating and all-encompassing. Individuals living with the syndrome may have difficulties with personal care, such as a failure to dress one side of their body or shave half of their face. Anyone sat to the affected side of the sufferer will often be ignored in conversation, as will food on the left side of the plate. Difficulties with reading and writing are common and getting lost or bumping into people in public places often occurs (Halligan, & Robertson, 2014). Understandably, these difficulties can severely limit autonomy: neglect sufferers report lower levels of functional independence both whilst in hospital and also in the later stages of recovery (Jehkonen et al., 2000). As a consequence, their quality of life (QoL) is significantly decreased, with correlations as large as -0.97 found between

QoL and neglect assessments (Sobrinho et al., 2018). Not only this, but stroke survivors with neglect have a poorer long-term prognosis than those without; in fact, neglect is a major predictor of rehabilitation outcome. Individuals with neglect have an increased risk of falls, experience longer hospital admissions (regardless of the severity of the neglect; Katz, Hartman-Maeir, Ring, Soroker, 1999) and are less responsive to rehabilitation for other post-stroke problems (Chen et al., 2015; Wilkinson, Sakel, Camp, & Hammond, 2012). This evidence highlights the huge burden that neglect can exert, not only on sufferers, but their caregivers too (Chen, Fyffe, & Hreha, 2017).

Whilst the negative impact of neglect is clear, the precise prevalence of the disorder has proven difficult to determine for a number of reasons. To start, the frequency of the condition varies widely according to which hemisphere has been affected by stroke, with almost all studies reporting that the condition comes about more frequently as a result of right brain damage (Bowen, McKenna, & Tallis, 1999). It was initially thought that this hemispheric asymmetry could be a result of sampling bias, due to the fact that individuals who have suffered a left-sided lesion are at greater risk of developing aphasia and consequently, are often excluded from studies of other post-stroke impairments (Beis et al., 2004). However, a large-scale analysis has shown that skewed samples are not sufficient to explain this imbalance in presentation and that the higher incidence of neglect as a result of right lesions reflects a true disparity in the population (Behrmann, Ebert, & Black 2004). This could be a result of the hemispheric organisation of the attentional system. The right side of the brain orients attention to both sides of space but the left hemisphere attends to contralateral areas only. Subsequently, when the left hemisphere is damaged, the right is able to compensate for this, but the same is not true when right brain damage occurs, resulting in the classic lateralised pattern of neglect (Heilman, Watson, & Valenstein, 1997).

However, even when considering only left-sided neglect (as a result of right-sided stroke, which the rest of this work will focus on), prevalence estimates still display significant variation (e.g. Evald, Wilms, & Nordfang, 2020), with a review of the topic finding values which ranged from 12%

to 100% of stroke survivors (Bowen, McKenna, & Tallis, 1999). This is likely due to the complexity of the condition. Large heterogeneity has been shown both within and between individuals suffering from the disorder, to the extent that some have argued that it cannot be classed as single entity (Halligan & Marshall, 1992). This may be a result of differing aetiologies. Whilst neglect is most commonly a product of middle cerebral artery (MCA) infarction, more rarely it can also be caused by anterior or posterior cerebral artery stroke (Parton, Malhotra, & Husain, 2004). Even if neglect cases are caused by damage of the same blood vessel, large enough infarcts (particularly of the MCA) can affect a wide range of brain locations, meaning lesion sites tend to vary between individuals. Indeed, there is no single neural correlate which can explain all cases of neglect (Vallar, 1998). Lesions can be cortical or subcortical in nature, and if they impact the cortex, can manifest in many different locations, including areas of the parietal, temporal, and frontal lobes (Vallar, 2001).

This range of lesion sites results in dissociable behavioural patterns, which can primarily be classified in two ways: by modality, or spatial distribution (Heilman, Valenstein, & Watson, 1994). Regarding the former, neglect can be motor, representational, or sensory in nature. Motor neglect occurs when a person fails to initiate a movement in response to a stimulus, despite having an awareness of it and no motor deficit (Heilman, Watson, & Valenstein, 1993). Representational neglect relates to internally generated images. For example, if a person is asked to imagine a room in their house, they would fail to describe any items that should have been pictured on the contralesional side of space (Bisiach & Luzzatti, 1978). Finally, sensory neglect is the form most widely considered in the literature and refers to an unawareness of stimuli received from the senses. This form can itself be further classified into visual, auditory, tactile, and even buccal modalities (André, Beis, Morin, & Paysant, 2000; Bowen et al., 1999). This review will focus on visual neglect (although it is recognised that it can be difficult to fully disentangle the different forms of neglect and that participants may be suffering from a more complex presentation than visual neglect alone),

given that the majority of standardised outcomes are primarily designed to assess neglect in this modality and it is consequently the most common focus of research.

Even when contemplating only the visual form of neglect, the condition can be further divided in terms of its spatial distribution, which can be egocentric, object-centric, or a combination of the two. The frame of reference for egocentric neglect is the individuals' body; that is, any stimulus presented to one side of the body midline is ignored. In contrast, allocentric neglect is manifested in the ignorance of one side of an external object itself, no matter its spatial relation to the individual's frame (Kerkhoff, 2001). Again, the clinical picture is additionally complicated by the fact that these subtypes of neglect can occur in personal space (i.e. part of the person's body), peripersonal space, (the area within reaching distance), and extrapersonal space (any area beyond this; Beschin & Robertson, 1997). What makes a precise diagnosis all the more complex is that it is possible for individuals to simultaneously suffer from numerous forms of neglect, which can interact to form a multitude of unique presentations (Plummer, Morris, & Dunai, 2003).

Diagnosis of Neglect

In order to fully encapsulate this wide range of deficits, there exist a correspondingly large number of neglect assessments. Some, such as the Catherine Bergego Scale (CBS), are functional in their approach, attempting to understand the impact the disorder has on everyday behaviours. However, many others rely solely upon pen-and-paper assessments. One of the most commonly employed is the Behavioral Inattention Test (BIT), which aims to measure the overall severity of neglect. A summary score is created to give an indication of whether an individual is suffering from the condition, according to a clinical cut-off. This broader overview can also be further broken down, as the test consists of six subtests which separately, are able to tap more directly into these individual aspects of neglect (Wilson, Cockburn, & Halligan, 1987). Many separate versions of these more specific tests are available, a few of which are detailed below.

Cancellation tasks involve presenting individuals with a display of stimuli and directing them to cross out targets, with a failure to cancel stimuli on only one side taken as a sign of neglect. Within this category itself there are differences between tests, with some tasks presenting only targets (e.g. Albert's test; Albert, 1973), and others including distractors (e.g. Bells test; Gauthier, Dehaut, & Joanette, 1989). Despite relying upon the same principles, these differences in display can lead to dissociations in behavioural performance e.g. tests which use distractors show greater sensitivity to the presence of neglect than those without (Halligan, Marshall, & Wade, 1989). Another often-used test is line bisection, in which participants are instructed to mark the middle of several horizontal lines. Individuals suffering from left-sided neglect tend to deviate to the right of the true midline in this task (although there are some conditions under which this is not the case; see Halligan & Marshall, 1988). Finally, figure copying tests involve the presentation of a picture of a simple symmetrical object such as a butterfly or a clock. Lateralised omissions in an individual's copy are used to determine the presence or absence of neglect (e.g. Friedman, 1991).

The reason that there exists such an array of outcome measures for the classification of neglect is that each displays a different level of sensitivity regarding ego- and object-centred neglect. Cancellation tasks are used to assess egocentric neglect. When the stimulus array is placed directly in front of the participant, the body midline becomes the frame of reference. Therefore, any individuals suffering from egocentric neglect will perform poorly on the task. In contrast, those with object-centred neglect should not show the same deficit because little attention needs to be paid to the details of the objects themselves, only their position on the page (Marsh & Hillis, 2008). Figure copying reveals the opposite pattern of impairment due to omissions being made regarding the left of the object, no matter where the picture is placed in relation to the body (Halligan & Marshall, 1993). Line bisection can be considered to test both ego- and object-centric neglect, given that the relative position of each line on the page differs in respect to the body midline, but also that aspects of the

line itself also affect performance (Harvey, Milner, & Roberts, 1995). This diversity in performance brings to light that multiple considerations need to be made when diagnosing neglect.

Hopefully this brief overview makes clear the extent of the heterogeneity which surrounds the neglect syndrome, both in its presentation and assessment. Taking this variation into account makes clearer the reasons for the wide range of prevalence estimates previously mentioned. Although these differences may make precise approximation of the overall incidence of neglect cases seem unattainable, what is evident from the evidence thus far is that neglect is a considerable problem in the stroke population, one that deserves further study. This is a particularly significant point, given that for many, the condition will persist for many years after their stroke.

Recovery from Neglect and Current Interventions

Spontaneous recovery from neglect can, and does, occur. However, this is not the case for all, and the timeframe within which most recovery happens is generally confined to the acute and subacute stages. After this, the rate of improvement significantly slows or often completely stops, meaning that any recovery is frequently only partial. The quickest rate of recuperation takes place in the first 10 days post-stroke (Stone et al., 1992), but gains continue to be made up until 12-14 weeks. One study found that at 12 weeks post-stroke, 46% of a neglect sample were still displaying symptoms. At the one-year milestone, this number had only decreased by a further 6% (Nijboer, Kollen, & Kwakkel, 2013). This reflects not only that a large proportion of those with neglect will suffer from the condition long-term, but also that there is very little change past a three-month timepoint if individuals are left without appropriate treatment.

This highlights the need for effective interventions for the disorder, as time alone seems insufficient to heal every individual suffering from neglect. Many different forms of therapy (including limb activation, visual imagery tasks, theta burst stimulation, and eye patching, to name a few; for reviews see Kerkhoff & Schenk, 2012; Yang, Zhou, Chung, Li, & Fong, 2013) have been

trialled for people with neglect, all revealing differing levels of effectiveness. These various treatments build on a wide range of theoretical rationales and are all distinct in their implementation. However, one way in which they can be broadly categorised is into top-down and bottom-up methods.

Top-down methods require individuals who are suffering from neglect to voluntarily compensate for their deficit (Azouvi, Jacquin-Courtois, & Luauté, 2017). An example is visual scanning, in which individuals are encouraged to explore their neglected side of space, a task often accompanied by alerting cues or feedback from an experimenter (e.g**.** Diller & Weinberg, 1977). Whilst studies have shown that top-down approaches can positively impact neglect, these gains tend to be short-lived and only generalise to tests with similar characteristics to the training method itself (Wagenaar, Van Wieringen, Netelenbos, Meijer, & Kuik, 1992). Perhaps a more serious issue is that an awareness of the neglect deficit is required for these types of therapy to be implemented. As many individuals do not possess this level of insight, top-down interventions are of limited utility in neglect (Parton et al., 2004). Despite this, top-down therapies are commonly used in clinical practice and are one of the interventions recommended by the National Institute for Health and Care Excellence (NICE, 2013), further emphasising that current treatments are not as effective as they should be and that more efficacious methods need to be found.

Bottom-up methods do not require a great deal of attentional input, as they aim to modify the underlying cause of neglect by changing maladaptive spatial representations through automatic mechanisms (Bowen et al., 2013). One such therapy is prism adaption, first investigated by Rossetti et al. (1998). During treatment, patients wear prism glasses which deviate their field of view to the right (usually by 10 degrees). Whilst wearing the prisms, individuals are asked to point towards a target. Initially, their aim is deviated rightwards. However, with multiple trials, they begin to adapt for this deflection, bringing their pointing leftwards and towards the target. The therapeutic benefit of this technique lies in the fact that it produces a persisting aftereffect, with the seminal work

demonstrating that this lasted for up to two hours. Since then, it has been established that the consequences of the intervention can be maintained for even longer, up to five weeks in one case (albeit with an extended training programme rather than a single session; Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Serino, Barbiani, Rinaldesi, & Ladavas, 2009). The technique not only alters pointing performance, but improvements also generalise to other tests of neglect (Jacquin-Courtois et al., 2013b), both with and without visuomotor components (Rode, Pisella, Rossetti, Farnè, & Boisson, 2003). This suggests that prism adaption causes a recalibration of sensory and spatial mechanisms. However, evidence from randomised trials has shown that this technique generates a strong placebo effect and that when properly controlled, beneficial results are only short-lived (Nys, De Haan, Kunneman, De Kort, & Dijkerman, 2008), or even eliminated completely (Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). It therefore seems as though a differing method of spatial recalibration may be required.

Creating and altering internal representations of space is a complex process, influenced by contributions from multiple sensory and cognitive systems, including the integration of vestibular inputs (Brandt, 2003). The vestibular system is responsible for updating information regarding the head’s acceleration and movement in space and forms a widespread network throughout the brain (Day & Fitzpatrick, 2005). Through the combination of vestibular, visual, and somatosensory signals, humans are able to keep a constant body position in relation to external space (Highstein, 2004). Given that higher-level spatial representations are disrupted in neglect, alongside the fact that activation of the vestibular nerves sends signals to brain regions implicated in the disorder (Bense, et al., 2001; Miller & Ngo, 2007), it seems plausible that vestibular stimulation may be a potential method for the amelioration of neglect.

The Current Review

As previously detailed, vestibular stimulation can be administered in many different forms. These include vestibular rehabilitation (VR), which involves head movement exercises, caloric vestibular stimulation (CVS), in which the outer ear canal is irrigated with water, and galvanic vestibular stimulation (GVS), where mild electrical currents are applied to the mastoid. When using CVS for neglect, the contralesional ear is usually irrigated with cold water, as this leads to activation of the affected hemisphere (e.g. Bottini et al., 2001). Although the effects of GVS are also lateralized (with right-cathodal, left-anodal GVS (CR-GVS) leading to activation of the right hemisphere, and left-cathodal, right-anodal GVS (CL-GVS) activating both hemispheres), both polarities have been utilised in the investigation of neglect.

Several studies have assessed whether vestibular stimulation is a feasible treatment for neglect. However, despite some promising outcomes, the evidence thus far appears to be mixed in its quality and conclusions, making it difficult to know whether the intervention is suitable for purpose. Given that GVS in particular is becoming a more widespread technique, it is important that we understand, to as great an extent as possible, any potential effects of the stimulation. Neglect is a common and debilitating issue from which many do not fully recover and for which there is currently no wholly effective treatment. Therefore, any potential rehabilitation options need to be carefully evaluated to assess their benefits and shortcomings, in order to advance the treatment of neglect. To this end, this review aims to consolidate the existing evidence, with the intention of gaining a broader and more objective overview of the topic.

Method

Criteria for Considering Studies for this Review

Types of studies.

It was anticipated that there would be few randomized controlled trials (RCTs) addressing this topic. Consequently, studies of any design were included.

Types of participants.

Studies were deemed eligible if the included participants were adults (over 18 years old) who had suffered a stroke as defined by WHO guidelines (or a clinical definition if not specifically stated i.e. signs and symptoms lasting longer than 24 hours), confirmed by neurological examination or brain scan. Participants who had suffered any type of stroke (i.e. haemorrhagic or ischaemic) at any anatomical location (i.e. cortical or subcortical) were included, as well as those in both the acute and chronic phases of the disease. Participants with both egocentric and allocentric neglect (or a combination of the two) were deemed eligible.

Given the ongoing debate about whether extinction can be classified as a subtype of neglect or whether it constitutes a separate disorder, studies involving participants suffering from extinction were not included unless they formed part of a mixed population. Individuals suffering from neglect as a result of a different neurological cause (such as tumours or traumatic brain injury) were not included. If studies included mixed populations, individuals who had suffered a stroke were included if their data had been analysed separately from those with differing aetiology. If stroke survivors had been analysed together with these other individuals, the study was included if they made up more than 50% of this group. The same criterion was applied for studies which pooled groups of stroke survivors both with and without neglect, or with different types of neglect. If individual participants were identified who were suffering from both visual neglect and another form of the disorder (e.g. tactile), or if the type of neglect they were suffering from was not clearly identified, the decision of whether or not to include the study was discussed and a decision made amongst the review team.

Types of interventions.

We included any form of vestibular stimulation which was used in an interventional context (as opposed to diagnostic), including (but not restricted to) galvanic vestibular stimulation, caloric vestibular stimulation, or vestibular rehabilitation therapy. If vestibular stimulation was used as part

of a combined treatment, the study was included if the adjunctive therapy was kept constant across all experimental groups.

Types of comparator/control.

Any form of vestibular stimulation was compared to any control, including alternative interventions for the condition, usual care, or no treatment. Controls could also be vestibular stimulation: either in a different form, or of the same type but with different parameters e.g. intensity, duration, number of sessions, frequency (including sham stimulation).

Types of outcome measures.

Primary outcomes.

Any clinically validated tests of visual neglect, including cancellation tasks and line bisection. The Behavioural Inattention Test (Halligan, Marshall, & Wade, 1989), was also considered, along with its component subtests (if administered separately).

Secondary outcomes.

Any test used to assess visual neglect which has not been clinically validated in this population.

Search Methods for Identification of Studies

Cochrane Controlled Register of Trials (CENTRAL), PubMed, the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP), PsychINFO, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) were searched for relevant records. OpenGrey was used to search for grey literature, whilst Latin American and Carribbean Health Science Literature (LILACS) and the African Index Medicus (AIM) were searched for non-English sources. Search strategies for each of these databases are detailed in Appendix A**.** Due to time constraints, other methods of searching were not completed (e.g. reference lists of studies were not manually searched).

Data Collection and Analysis

Records retrieved from the above searches were exported into reference management software (EndNote X9) and any duplicates removed. One member of the review team (CW) screened the titles and abstracts of the remaining records. Another review team member (KD) independently screened a stratified sample of 10% of these records in order to ensure agreement between raters was 80% or greater.

Selection of studies.

Full-text articles (if available) of any relevant studies were retrieved and independently screened according to our participant, intervention, comparator, and outcome (PICO) criteria, recording studies which were not deemed eligible and the primary reason for their exclusion. Due to time constraints, any studies which were not readily accessible were not included.

Data extraction and management.

A Cochrane data extraction form was edited and used to extract data from the included studies.

The following information was extracted:

- Study methods (including aim, design, unit of allocation, duration, funding sources, and any conflicts of interest)
- Participant information (including setting, inclusion and exclusion criteria, method of neglect diagnosis, age, sex, race, time since stroke, type and location of lesion, and the presence of visual field defects or hemiplegia/paresis)
- Description of the intervention (including number of intervention groups, the specific intervention used (i.e. type of vestibular stimulation or control intervention), and details of parameters such as stimulation frequency, intensity, and duration)
- Outcomes (including definitions, time points, upper and lower limits of any scales used and whether a high or low score is favourable)

- Results (including means and standard deviations/errors at all available timepoints alongside any other reported results such as mean differences and *p* values).

Assessment of risk of bias in included studies.

Studies were identified as low, high, or unclear risk of bias regarding each of the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias
- Carryover effects
- Period effects

The appropriate Cochrane risk of bias tool for each study type was used.

The quality of the evidence was assessed according to GRADE criteria (Guyatt, 2008). This approach allows a judgement to be made about the confidence that can be placed in an effect estimate, alongside whether further evidence is likely to change this. The quality of the evidence was downgraded by one or two levels according to four criteria: overall risk of bias, inconsistency, indirectness, and imprecision. Evidence could also be upgraded according to four criteria: publication bias, dose response, large effect, and plausible confounding.

Measures of treatment effect.

Review Manager 5.4 software (RevMan 2014) was used to carry out statistical analyses to determine the treatment effect of:

- Left-cathodal/right-anodal GVS (CL-GVS) compared to sham GVS on line bisection scores

- Right-cathodal/left-anodal (CR-GVS) compared to sham GVS on line bisection scores

Comparisons were made at the end of the treatment period. A random-effects model was used for both analyses to adjust for heterogeneity in stimulation protocols between studies. As all the extracted data were continuous and used the same outcome measurement, mean differences (MDs) and 95% confidence intervals (CIs) were calculated.

All other data were synthesised narratively.

Unit of analysis issues.

Many of the studies had a repeated crossover design in which each participant received CL-GVS, CR-GVS, and sham GVS. As CL- and CR-GVS have been shown to differentially activate the vestibular system, alongside the fact that all included participants were suffering from right-hemisphere lesions, we split these studies and included the data from each stimulation condition in separate analyses. This also addressed the potential issue of double counting participants within the same analysis. For crossover studies, the unit of analysis was identified as the order in which participants received each stimulation condition, rather than participants themselves.

Dealing with missing data.

We accepted studies which used a per-protocol analysis rather than intention-to-treat. Again, due to the limited timescale of the project, we did not contact authors to collect any missing values.

Assessment of heterogeneity.

For the meta-analyses, heterogeneity was visually assessed by looking at the forest plots and considering the extent to which the 95% CIs overlapped. The I^2 statistic was also considered.

Assessment of reporting biases.

An attempt was made to reduce reporting bias as much as possible by searching grey literature alongside databases of published studies. It was (correctly) anticipated that there would not be enough studies included in the review to formally assess for publication bias using a funnel plot.

Data synthesis.

Any data that were considered similar enough to group were pooled and analysed in a meta-analysis using RevMan 5.4 software. Any data that would not produce clinically meaningful results if combined were described in a narrative synthesis.

Subgroup analysis and investigation of heterogeneity.

It was originally considered that subgroup analysis might be conducted, splitting studies by variable such as time since stroke. However, not enough studies were identified to complete this type of analysis.

Sensitivity analysis.

Similarly, too few studies were retrieved for sensitivity analysis to be carried out.

Results

Description of Studies

Results of the search.

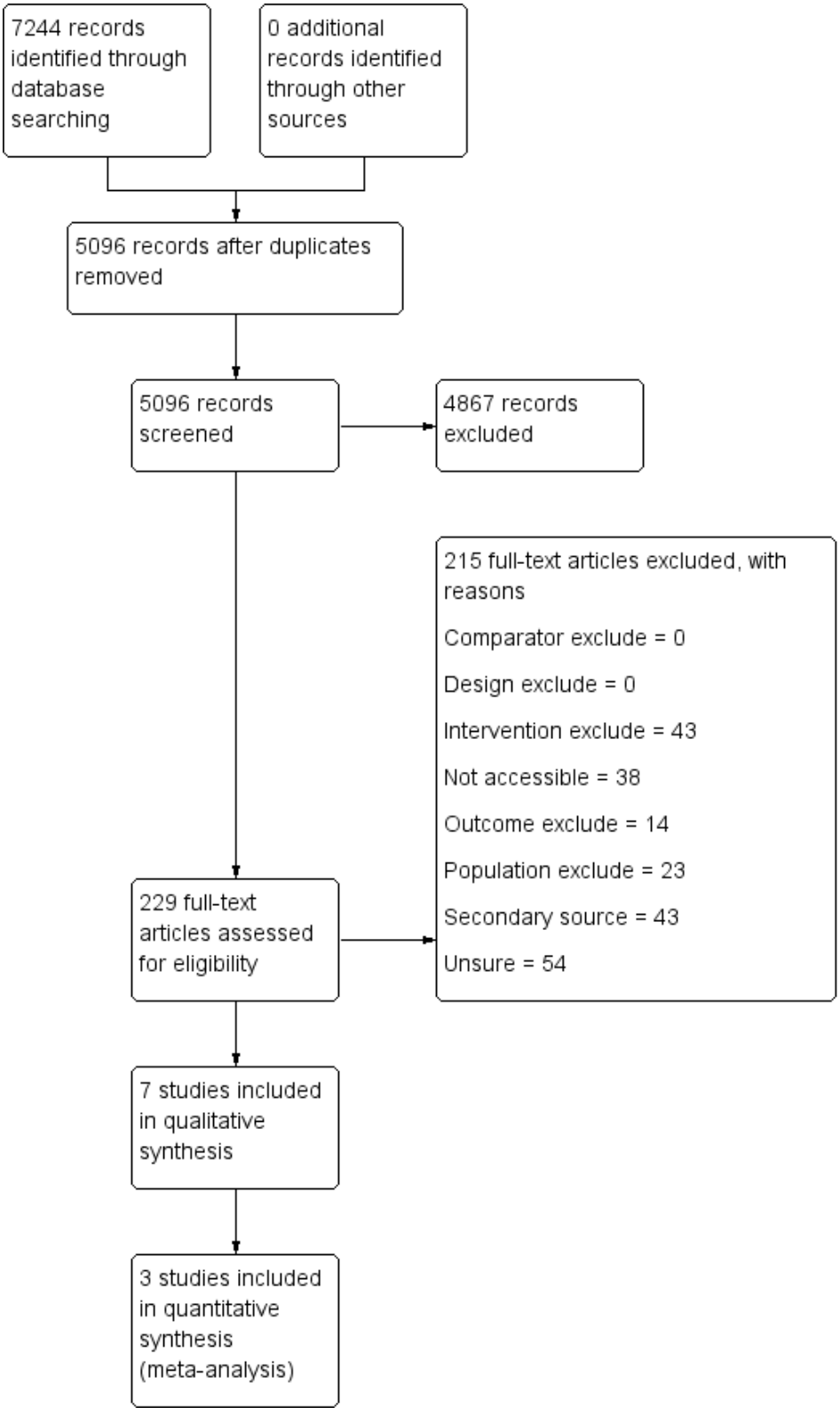
For results of the search see Figure 1. The search strategy returned 7244 records, which, after deduplication, was reduced to 5096. The titles and abstracts of these were screened, leaving 229 full texts to be assessed, from which 13 records were identified as eligible. Of these, three were trial registrations (IDs: JPRN-UMIN000037152; NCT00271388; JPRN-UMIN000012437), none of which linked to any data or publications. Data from Matjačić, Hesse, and Sinkjaer (2003) are also not included here, as the reported results were very brief and unclear. Due to the limited timescale of the

project, we were unable to contact authors to request the required information to include in the review.

It should also be noted that a number of records were found which utilised prism adaption, neck muscle vibration, and optokinetic stimulation. These records are classed as ‘Unsure’ in the PRISMA flow diagram (Figure 1). Whilst these interventions do affect the vestibular system as a result of its complex interplay with visual inputs (e.g. Dieterich, Bucher, Seelos, & Brandt, 1998; Karnath, 1994), due to the limited scope of the review, the fact that their effects are not directly vestibular in nature meant they were excluded from this particular piece of work.

Figure 3.

PRISMA flow diagram displaying the results of the search.



Included studies.

The data from 129 participants from nine studies were included in this review (Cappa, Sterzi, Vallar, & Bisiach, 1987; Dai et al., 2013; Nakamura et al., 2015; Oppenländer et al., 2015; Ruet, Jokic, Denise, Leroy, & Azouvi, 2014; Sturt & Punt, 2013; Utz, Keller, Kardinal, & Kerkhoff, 2011; Volkening, Kerkhoff, & Keller, 2018; Wilkinson et al., 2014). This number of participants is very small, due to the small sample sizes in individual studies. Only one study (Wilkinson et al., 2014) conducted a power analysis to determine how many participants would be needed to find an effect.

A brief overview of these studies is provided below. The heterogeneity between studies means it was difficult to succinctly summarise their characteristics. Therefore, the details of the three studies included in the meta-analyses (Oppenländer et al., 2015; Ruet et al., 2014; Utz et al., 2011) are the primary focus of each section. Full descriptions of all included studies can be found in the Characteristics of included studies tables (Appendix B).

Study design.

The meta-analysis studies used a crossover design, comparing three treatment conditions (CL-GVS, CR-GVS, and sham GVS) to one another (Oppenländer et al., 2015; Ruet et al., 2014; Utz et al., 2011). The order of the conditions was pseudorandomised or counterbalanced. The exact method of randomisation is not reported for two studies, but it is assumed that, as per convention, a Latin square was used. Oppenländer et al.'s participants all received sham as their first condition and the order of the two subsequent GVS conditions was counterbalanced. Although not included in the meta-analyses, Nakamura et al. (2015) also used the same design.

Three studies were parallel arm RCTs, two of which consisted of three GVS treatment groups (Volkening et al., 2018; Wilkinson et al., 2014), and one of an experimental (VR) group and a control (Dai et al., 2013). The two remaining studies (Cappa et al., 1987; Sturt & Punt, 2013) used non-randomised designs in which participants all received the same intervention (CVS).

Interventions studied.

The studies varied not only in the type of vestibular stimulation used (due to the broad scope of the review), but also in the implementation of each type of stimulation (e.g. the intensity and duration of GVS).

The three studies included in the meta-analyses all used direct-current CL-GVS, CR-GVS, and sham GVS. Whilst Ruet et al. (2014) and Utz et al. (2011) administered GVS at 1.5mA for 20 minutes in active conditions, Oppenländer et al. (2015) tailored stimulation to each participant's sensory threshold (mean intensity = 0.7mA) and stimulated for approximately an hour in each condition. In an attempt to blind participants, all studies turned on the current for a few seconds at the beginning and end of sham stimulation to mimic the tingling that can be felt during active sessions.

Three other studies also used GVS (Nakamura et al., 2014; Volkening et al., 2018; Wilkinson et al., 2014), two of which also utilised direct-current CL-GVS, CR-GVS and sham GVS. The remaining study looked at the effects of noisy CR-GVS only, comparing the effects of differing numbers of active and sham stimulation sessions (Wilkinson et al.). Two studies assessed the effects of CVS (Cappa et al., 1987; Sturt & Punt, 2013). Whilst Cappa et al. looked at the effects of contralesional CVS only, Sturt and Punt also made a comparison with ipsilesional stimulation. One study compared the effects of vestibular rehabilitation to standard occupational and physical therapy (Dai et al., 2013).

Populations studied.

All studies included participants with neglect as a consequence of right hemisphere stroke. Several studies also included control groups who were not suffering from neglect, but data from these groups were not included in the review. Many studies recorded specific lesion locations but due to the differing classification systems used, this information is not reported here. All studies' samples

apart from Ruet et al. (2014; who only recruited males), were mixed regarding gender. They were all roughly comparable regarding age. Participants in all studies but two had suffered their first-ever stroke (Cappa et al., 1987 and Wilkinson et al., 2014 did not report this information). Two studies recruited participants who were all suffering from hemianopia (Cappa et al.; Ruet et al.), three studies' samples had participants both with and without visual field defects (Oppenländer et al., 2015; Utz et al, 2011.; Volkening et al., 2018) and the remaining four studies did not report this information. Length of time since stroke differed widely both within and between studies, the smallest mean being less than two days (Cappa et al.) and the longest more than five months (Nakamura et al, 2015). Many studies recruited participants in differing stages of stroke recovery.

The three studies included in the meta-analyses used different methods to diagnose neglect. Utz et al. (2011) used six conventional tests. Participants were considered to have neglect if they scored below a cut-off on at least three. The cut-offs were either decided by the researchers or determined using data from healthy age-matched controls. Oppenländer et al. (2015) also used healthy controls to determine cut-off scores. However, they grouped individuals differently according to their performance on each task. Individuals classed as having neglect on one task (e.g. line bisection) may not have been included in this group based on their score on another task (e.g. cancellation). Ruet et al. used a line bisection cut-off score (determined by the researchers).

Outcome measures.

The three main studies all used line bisection as an outcome. Oppenländer et al. (2015) used the BIT version, in which participants bisect three 200mm x 1m lines. Ruet et al. (2014) used the batterie d'évaluation de la négligence (BEN) version, which uses the same length line. However, each participant bisected a different number of lines. Utz et al. (2011) used the Schenkenberg line bisection test (Schenkenberg, Bradford, & Ajax, 1980), which consists of 17 lines of differing

lengths (ranging from 100-200mm). All studies measured deviation from midline in millimetres, with a smaller score (closer to zero) indicating improvement.

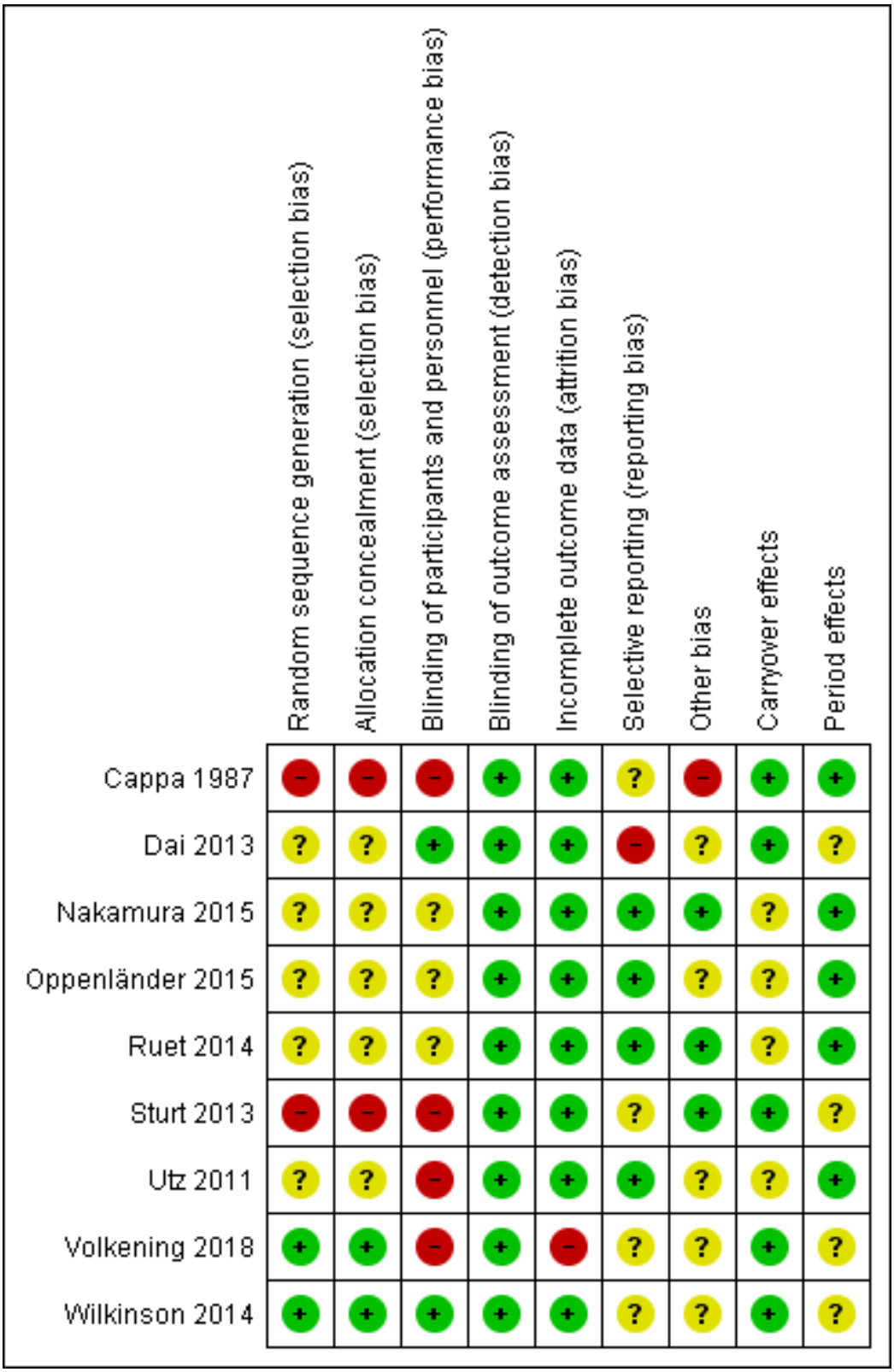
All other studies used clinically validated tests of visual neglect. Two studies used the conventional subtest of the BIT (Dai et al., 2013; Wilkinson et al, 2014.), and one used a German adaptation of this called the neglect test battery (NET; Volkening et al., 2018). Five studies used cancellation tasks (Cappa et al., 1987; Nakamura et al., 2015; Oppenländer et al., 2015; Ruet et al., 2014; Sturt & Punt, 2013).

Risk of Bias in Included Studies

The risk of bias assessments for individual studies can be found in the Characteristics of included studies table. A summary can be found in Figure 2, the details of which are reported by domain below.

Figure 4.

Risk of bias summary for all included studies.



Green circles indicate a study was judged to be at low risk of bias for that domain, yellow, unclear risk of bias, and red, high risk of bias.

Random sequence generation (selection bias).

Four of the studies classed as unclear risk used a crossover design, in which the order of stimulation was pseudorandomised or counterbalanced. Although this method is not classed as 'true' randomisation, given the small sample sizes of the studies and that the randomisation method did not appear to lead to any large imbalances, it was decided that it was adequate and that the risk of bias was unlikely to be unduly large. The two studies judged to be at high risk were non-randomised.

Allocation (selection bias).

Many of the studies did not provide any information regarding this domain and were accordingly rated as unclear risk.

Blinding of participants and personnel (performance bias).

Several of the studies which utilised GVS claimed that participants were blinded to whether they were receiving active or sham stimulation. However, they did not determine the sensory threshold for each individual, rather administering stimulation of the same intensity (generally 1.5mA) to all, meaning it cannot be known for certain if blinding was successful.

Blinding of outcome assessment (detection bias).

Only three studies (Dai et al., 2013; Sturt & Punt, 2013; Volkening et al., 2018) stated that their outcome assessors were blinded to participants' condition. However, given that the outcomes used to assess neglect in these studies are unlikely to be assessed in a subjective way, unblinded outcome assessors were not judged to increase the risk of bias.

Incomplete outcome data (attrition bias).

All studies but one (Volkening et al., 2018) were judged to be at low risk of bias in this domain as the attrition rate was small. Volkening et al. had a higher rate of attrition than the other

studies, the rate of dropout was imbalanced across treatment groups, and was this not adjusted for using an appropriate analysis.

Selective reporting (reporting bias).

It was difficult to evaluate this domain due to the fact that only one study provided information regarding pre-registration (Wilkinson et al., 2014), and this did not include an analysis plan. Therefore, this bias was judged on whether all stated outcomes were reported at all timepoints in the article itself, alongside whether appropriate analyses were used. The study that was classed as high risk of bias (Dai et al., 2013) reported analyses showing conflicting results, of which only the significant result, which favoured the intervention, was elaborated upon.

Other potential sources of bias.

A wide range of potential sources of bias were considered for this domain, which included plausible confounding regarding intervention, amongst others.

Carryover effects.

This domain was included to consider the effect of carryover in the studies which used a crossover design and therefore did not apply to several of the studies (which were accordingly judged as low risk). All crossover studies all incorporated a washout period of at least 24 hours to account for carryover. However, given that the exact longevity of GVS effects is not currently known, these were classed as unclear risk as it is not known if this is a lengthy enough period to achieve its intended purpose.

Period effects.

This domain was judged primarily on the length of time since stroke (alongside the duration of the study) and whether participants were past the point at which they were likely to experience spontaneous recovery (three months).

Effects of Interventions

See below for a summary of findings table, which collates the results of the analyses below, including the quality of the evidence (according to GRADE criteria; further details in Appendix C).

Table 1.

Summary of findings.

Outcome	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Line bisection (CR-GVS vs. sham). Smaller deviation from midline indicates improvement. Assessed post-intervention	-4.00mm [-14.72, 6.73] Reduction of 4.00mm (favours GVS)	22 (3 studies)	⨁⨁⨀⨀ **low**	Downgraded 1 for risk of bias, 2 for inconsistency (due to differences in length of time since stroke, presence of visual field defects, method of neglect diagnosis, line bisection tests and stimulation parameters), and 2 for imprecision (due to very small sample size and wide 95% CIs). Upgraded 1 for plausible confounding (sham stimulation was not truly inert in one study).
Line bisection (CL-GVS vs sham). Smaller deviation from midline indicates improvement. Assessed post-intervention.	-8.68mm [-18.37 – 1.01] Reduction of 8.68mm (favours GVS)	22 (3 studies)	⨁⨁⨀⨀ **low**	Downgraded 1 for risk of bias, 2 for inconsistency (due to differences in length of time since stroke, presence of visual field defects, method of neglect diagnosis, line bisection tests and stimulation parameters), and 2 for imprecision (due to very small sample size and wide 95% CIs). Upgraded 1 for confounding (sham stimulation was not truly inert in one study).
Cancellation tasks (CL- and CR-GVS vs. sham). Assessed post-intervention.	CL-GVS: 3 studies showed no difference	23 (3 studies)	⨁⨁⨀⨀ **low**	Downgraded 1 for risk of bias, 2 for inconsistency (due to differences in length of time since stroke, method of neglect diagnosis, cancellation tests, and stimulation parameters), and 2 for imprecision (due to very small sample size and large SDs). Upgraded 1 for dose response.

	CR-GVS: 2 studies showed no difference and favoured GVS			
BIT (CL-GVS and CR-GVS pre- vs. post-stimulation).	CL-GVS: 1 study showed no difference CR-GVS: 1 study showed no difference and 1 favoured GVS	CL-GVS: 8 (1 study) CR-GVS: 24 (2 studies)	⨁⨁⊖⊖ **low**	Downgraded 1 for risk of bias, 2 for inconsistency (due to differences in length of time since stroke, presence of VFDs, and stimulation parameters), and 1 for imprecision (due to small sample size). Upgraded 1 for plausible confounding (concurrent therapies may have reduced the effectiveness of GVS).
Cancellation tasks (Contralesional and ipsilesional CVS pre- vs. post-stimulation).	Contralesional: 1 study showed no difference and 1 favoured CVS Ipsilesional: 1 study showed no difference	Contralesional: 10 (2 studies) Ipsilesional: 6 (1 study)	⨁⊖⊖⊖ **very low**	Downgraded 2 for risk of bias, 2 for inconsistency (due to differences in length of time since stroke and stimulation administration), and 2 for imprecision (due to very small sample size and large SDs).
BIT (VR vs. control). Assessed post-intervention.	1 study showed no difference	48 (1 study)	⨁⨁⊖⊖ **low**	Downgraded 1 for risk of bias, 1 for inconsistency (no information provided regarding presence of visual field defects), and 2 for imprecision (due to very small sample size and large SDs). Upgraded one for plausible confounding (control group intervention was similar to experimental).

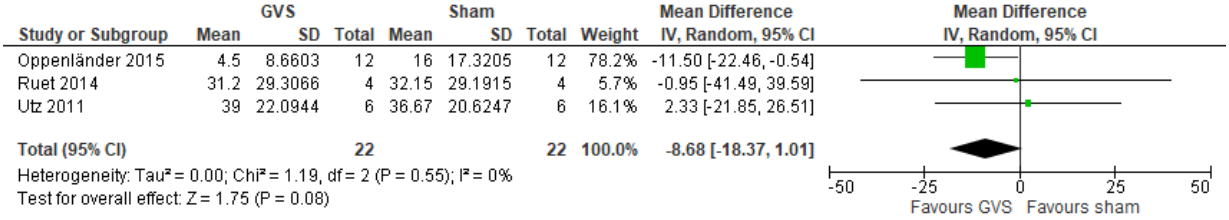
According to GRADE criteria, low quality evidence: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality evidence: We are very uncertain about the estimate.

Due to the heterogeneity between studies, it was only possible to pool the data from three (Oppenländer et al., 2015; Ruet et al., 2014; Utz et al., 2011), in two meta-analyses (which both included 22 participants). These studies all used a crossover design comparing the effects of CL-GVS, CR-GVS, and sham. The data were pooled and random effects meta-analyses conducted regarding line bisection results (measured in millimetre deviation from the midline), looking separately at the effects of CL-GVS vs. sham and CR-GVS vs sham.

Effects of CL-GVS vs. sham on line bisection.

Figure 5.

Forest plot displaying the statistical analysis of CL-GVS vs. sham on line bisection.



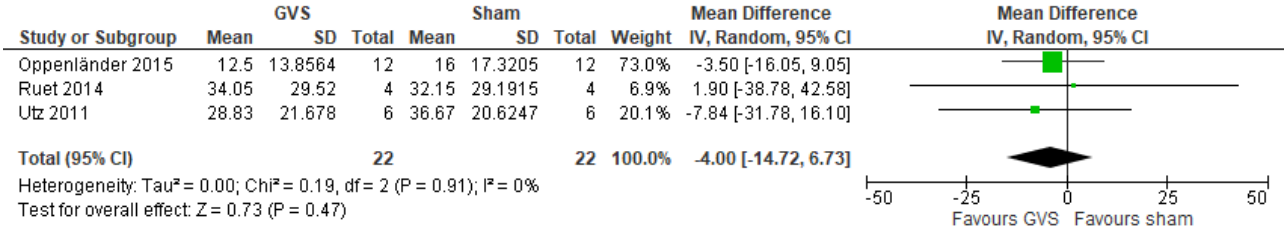
The green boxes and horizontal lines depict the effect estimate and 95% CIs, respectively for each study, whilst the black diamond represents the overall effect estimate and 95% CIs. Negative numbers indicate that CL-GVS was more effective than sham and positive values, vice versa (0 = no effect).

The analysis, displayed in Figure 5, shows a mean difference of -8.68mm (reflecting a reduction in the deviation from midline which favours GVS over sham), with 95% CIs spanning from -18.37 to 1.01. However, this result is not statistically significant (p = .08), suggesting that there is no significant difference between the two conditions. This evidence was judged to be of low quality.

Effects of CR-GVS vs. sham on line bisection.

Figure 6.

Statistical analysis of the effects of CR-GVS vs. sham on line bisection.



The green boxes and horizontal lines depict the effect estimate and 95% CIs, respectively for each study, whilst the black diamond represents the overall effect estimate and 95% CIs. Negative numbers indicate that CR-GVS was more effective than sham and positive values, vice versa (0 = no effect).

The analysis, displayed in Figure 6, shows a mean difference of -4.00mm and 95% CIs which range from -14.72 to 6.73. Although this effect estimate favours GVS, the wide range of the CIs means there is high uncertainty as to where the true effect may lie, and the non-significant *p* value (0.47) suggests that there is no difference between the two conditions. This evidence was judged to be of low quality**.**

Heterogeneity.

Although the I^2 value for both analyses (0%), when taken alone, suggests there is no heterogeneity between studies, this is unlikely to reflect the true extent of their statistical differences. The 95% CIs are wide and imprecise, and it is for this reason that they overlap, rather than because the effect estimates for all studies are similar. That statistical heterogeneity is higher than this value initially indicates is supported by the fact that there is significant clinical and methodological heterogeneity between the studies (see GRADE tables [Appendix C] for details).

Narrative Synthesis

The remaining data found from the studies were not included in a meta-analysis but rather, summarised in the narrative synthesis below, pooled together by intervention and outcome. The data were combined in this way because the scope of the PICO criteria meant that a wide range of

vestibular interventions and neglect assessments were captured. Due to this high level of heterogeneity, it would not be appropriate to pool data from all studies, as the results would not be clinically meaningful. For example, whilst many of the studies we found utilised GVS, some used other methods of vestibular activation such as CVS and VR. Whilst it is known that these methods all stimulate the vestibular system, the mechanism through which this is achieved, and the subsequent patterns of activation and effect are unlikely to be identical. This could potentially lead to differing effects on neglect between interventions which the research surrounding this area is yet to investigate and therefore remains unknown.

Similarly, neglect assessments range hugely in their scope. Whilst some are more focused and aim to assess specific facets of neglect, others, such as the BIT, combine multiple different subtests in order to gain a more holistic view of neglect. Therefore, studies are also grouped according to the outcome utilised, with outcomes that are considered to tap into the same ability assessed together. As in the meta-analyses, when data are available, comparisons involving CL-GVS and CR-GVS are considered separately.

The results are presented as effect direction plots, in which an upward pointing arrow (↑) indicates that GVS led to a significantly greater improvement than the comparator, a downwards pointing arrow (↓) indicates comparative deterioration, and a sideways arrow (↔), no difference.

Effect of GVS vs. sham on cancellation score post-intervention.

Three studies were found which compared the effects of CL-GVS and CR-GVS to sham on cancellation task performance (Nakamura et al., 2015; Oppenländer et al., 2015; & Ruet et al., 2014).

Table 2.

Effect directions for GVS vs. sham on cancellation scores.

Study	Direction of effect (CL-GVS)	Direction of effect (CR-GVS)
Nakamura	↔	↔
Oppenländer	↔	↑
Ruet	↔	↔

All three studies found no significant difference between CL-GVS and sham, whilst for the comparison of CR-GVS vs sham, two studies found no significant difference and one found an improvement in cancellation score after GVS. This evidence was of low quality.

Effect of GVS on pre- and post-stimulation BIT/NET score.

Two studies were found for this comparison (Volkening et al., 2018; Wilkinson et al., 2014), both of which were parallel-arm RCTs. Given the design of Wilkinson's study (in which sham stimulation was incorporated into the active treatment regimen and not analysed as a separate arm), comparisons were made pre- and post-intervention, rather than comparing two post-intervention groups. Wilkinson et al. also only looked at the effects of CR-GVS, so for pre- and post-CL-GVS scores, data was only available from Volkening et al., who assessed this difference using the NET.

Table 3.

Effect directions for pre- and post-GVS BIT/NET scores.

Study	Direction of effect (CL-GVS)	Direction of effect (CR-GVS)
Volkening	↔	↔
Wilkinson	n/a	↑

One study showed no significant difference between pre- and post CL-GVS. For CR-GVS, one study again demonstrated no difference, whilst the other shows a significant improvement post-stimulation. This evidence was of low quality.

Effect of CVS on pre- and post-stimulation cancellation score.

Two studies assessed performance on cancellation tasks pre- and post-CVS (Cappa et al., 1987; contralesional CVS only; Sturt & Punt 2013; contralesional and ipsilesional CVS).

Table 4.

Effect directions for pre- and post-CVS cancellation scores.

Study	Direction of effect (contralesional CVS)	Direction of effect (ipsilesional CVS)
Cappa et al., 1987	↑	n/a
Sturt & Punt, 2013	↔	↔

One study showed a positive effect of contralesional CVS post-stimulation, whilst the other showed no significant difference. The study which assessed the effects of ipsilesional CVS also found no difference between pre- and post-intervention scores**.** This evidence was of very low quality.

Effect of VR vs control on BIT score.

One study was found for this comparison: Dai et al. (2013) compared the effects of VR plus conventional rehabilitation to the effects of conventional rehabilitation alone on the BIT. No significant difference was found between the groups. This evidence was of low quality.

Discussion

In this review, nine studies with 129 participants were found. Given the heterogeneity of the findings, only two meta-analyses were conducted, whilst the rest of the data were summarised narratively. Both meta-analyses provided low-quality evidence to suggest that there is no difference between CL-GVS and sham GVS, or CR-GVS and sham GVS, in reducing the deviation from midline seen in line bisection scores of participants with visual neglect. The narrative syntheses, which assessed the effects of GVS, CVS, and VR on a number of relevant neglect outcomes, provided mixed results regarding the effectiveness of these interventions. Again, these comparisons were of low or very low-quality, making it difficult to come to any conclusions concerning the true efficacy of the interventions.

As previously mentioned, time constraints meant that study authors could not be contacted to clarify any ambiguities or to request missing data. It was also not feasible to use manual search methods to identify studies which the original search strategy may have overlooked, meaning there is a possibility that the evidence base is not entirely complete. However, it is hoped that this review provides a robust foundation on which future reviews can expand. What can be taken from the work is that studies in this area show substantial heterogeneity within and between several domains, making it difficult to synthesise the evidence, an issue that needs to be addressed when moving forward. Although the results of both meta-analyses favoured the null hypothesis, these are preliminary findings which display considerable heterogeneity and therefore warrant further investigation. However, several variables need to be considered to ensure that future studies provide a valuable contribution and further our knowledge on this topic. Key issues which need to be addressed to ensure this is the case are discussed below.

A problem that was common to almost all studies was small sample size, often due to lack of power analyses to determine appropriate participant numbers. Due to heterogeneity between studies, the number of participants included in each meta-analysis was only 22, limiting the conclusions that can be drawn from these analyses. Future studies should therefore use power analysis to ensure that sample sizes are adequately large, as only one study in the review used this technique.

The outcomes used in any future research need to be carefully considered. It was decided to only include assessments which directly measured visual neglect in this review. Therefore neglect-related measures of activities of daily living (such as the Catherine Bergego Scale; CBS) were not included as they did not meet this criterion. Although these types of test can be considered more ecologically valid than those which solely measure visual neglect, they are more likely to be affected by other cognitive and physical impairments (Azouvi, 1996) and therefore provide a less focused view, making them unsuitable when trying to answer the review question. Because of this exclusion, none of the measures in the review directly assess change in quality of life or functional ability,

limiting the applicability of the evidence somewhat. Unfortunately, no studies to date have determined what can be classed as clinically meaningful change in the outcomes which *were* used. However, the assessments highly correlate with measures of functional ability. BIT score at 10 days post-stroke has been shown to account for 73%, 64% and 61% of variance in the Frenchay Activities Index (a measure of functional outcome) at 3, 6, and 12 months post-stroke (Jehkonen et al., 2000). The measure also has a correlation of .64 with the Barthel Index (BI; Halligan, Cockburn, & Wilson, 1991), whilst the star cancellation test has a correlation of .55 with the BI (Marsh & Kersel, 1993). Line bisection error is a significant predictor of gait recovery after hemiplegic stroke (Friedman, 1990), and also significantly correlates with scores on the CBS (Azouvi, 1996). These relationships suggest that although tests of visual neglect are unable to directly measure functional outcome, the changes they are designed to assess are likely to be reflected in similar variations in participants' day-to-day functioning, therefore providing a valuable insight into relevant, real-life situations.

However, although the information that these tests provide appears to be meaningful, there was a general lack of recognition regarding the complexity of neglect and subsequent assessment choice in the included studies. Research has shown that ego- and object-centred neglect are separable and that this is reflected in performance on different tasks. For example, several studies have demonstrated that there is a double dissociation between performance on cancellation tasks and line bisection (Ferber & Karnath, 2001; Halligan & Marshall, 1992; Marshall & Halligan, 1995), with other research further supporting this by establishing that there are only weak correlations between scores on the two (Binder, Marshall, Lazar, Benjamin, & Mohr, 1992). These results suggest that the tests may reflect different underlying processes, reinforcing the notion that neglect is a highly heterogenous disorder, the subcomponents of which can be categorised accordingly by these differing assessments. However, this specificity is not one that is reflected in many studies' choices of test, with few considering that different tests do not measure precisely the same aspects of neglect. This led to a wide range of likely unintended heterogeneity which could, to some extent, explain why

such different results were found between studies**.** That there is heterogeneity within a neglect diagnosis itself, and that this affects scores differently on individual tests, is something that needs to be considered more closely when outcomes are chosen.

Creating better designed studies which more carefully choose and measure outcomes should help to provide valuable information about the treatment of neglect, potentially helping to discover which individuals, if any, are most likely to benefit from the intervention. For example, it may be found that GVS is more efficient at treating ego- than object-centred neglect, but because this detail is often not considered when designing studies and interpreting scores, it has not yet been discovered. Not only this, but the distinction between the two may have important connotations for experimental methods and design regarding vestibular stimulation and may help us to better understand the mechanisms of the intervention, as well as neglect, (both of which not yet fully understood), and how they might interact.

This is only one small example of the heterogeneity that was found between outcomes, meaning that an important note going forward is to ensure that outcomes (alongside other study characteristics) are standardised in other ways too. Studies made use of different methods when it came to categorising participants as having neglect or not, with some using normative samples to create cut-offs, and some using pre-defined values. For the sake of consistency, the same methods and numbers should be used to ensure participants are comparable in the severity of their neglect. Another issue is the standardisation of the tests themselves. For example, the three studies used in the meta-analyses all utilised line bisection as an experimental outcome. However, whilst the studies coincided in the metric used to score performance (millimetre deviation from the mean), the test versions, and subsequently, the length of the lines, differed. Line length has been shown to affect performance in bisection, wherein the extent of the rightwards deviation is proportional to the total length of the line (i.e. a longer line results in a greater exaggeration of the ipsilesional error seen in neglect; Halligan & Marshall, 1988; Harvey et al., 1995). Another example of how test

characteristics can affect performance is seen in cancellation tasks, in which the number of distractors (Halligan et al., 1989) and organisation of the stimulus array (Weintraub & Mesulam, 1988) have been shown to alter the sensitivity of the measure. Therefore, if results are to be combined to provide a clinically meaningful result, it is important that test characteristics are carefully controlled.

Methodological heterogeneity was not only a consequence of unstandardized outcomes. Stimulation parameters also differed widely (again, it is recognised that this is partly due to the broad PICO criteria used, which led to many different forms of vestibular stimulation being included in the review. However, differences were found even between studies which used the same type of stimulation, namely GVS). Variations were found in the intensity of the current used, as well as the length and number of stimulation sessions. The data did not allow for subgroup analysis according to these factors, therefore this review is unable to comment on whether these divergent parameters are likely to have affected results. However, individual studies within this work seem to provide differing perspectives as to whether there is a dose response of GVS in the rehabilitation of neglect (with Nakamura et al. discovering a significant correlation between total charge applied and neglect improvement, in contrast to Wilkinson et al.'s finding that one session of GVS was just as effective as 10 in ameliorating symptoms). Until a clearer consensus is reached on this issue, standardising a GVS regimen to control for any confounding effects of dose would be a helpful contribution to the literature.

Alternatively, studies which focus more clearly on dose response may provide invaluable insights into this contradiction. Currently, there is scant evidence to indicate whether a dose response occurs with the application of GVS, not only in the realm of stroke rehabilitation, but also further afield. Preliminary findings have shown that in healthy participants, the velocity of GVS-induced eye movements increases as greater stimulus intensity is applied (Cauquil, Faldon, Popov, Day, & Bronstein, 2003). However, it is important to note that this study relates only to autonomic reflexes

and therefore, caution must be exercised when extending these findings to more complex processes such as the amelioration of neglect. It must also be considered that other research has shown that GVS signals of a lower intensity can, in certain cases, be effective in a way that higher amplitudes are not (Mulavara et al., 2011; who showed that the optimum GVS parameters for improving balance performance predominantly range from 100 to 400 μA). Again, further research is required in order to assess how these findings might be applicable in the context of the current thesis, but this is nevertheless evidence that is important to consider.

When considering the effects of GVS on neglect, the findings of the above debate may have both clinical and methodological repercussions. If a dose response does exist when utilising GVS for neglect, from a clinical perspective, a higher intensity of stimulation should be given so that the greatest therapeutic effect can be achieved. However, this clinical optimisation potentially comes at a cost to methodological integrity. A higher current intensity is likely to make the stimulation suprathreshold, meaning participants are able to perceive when they are being stimulated. This effectively unblinds them to their condition.

It is possible to carry out a procedure in which stimulation intensity is tailored to each participants' sensory threshold, a process which ensures that stimulation is delivered at a level which is truly subliminal. However, this technique was utilised in very few studies, with the majority choosing to apply stimulation at a current intensity of 1.5mA. Whilst two studies cited evidence (Gandiga, Hummel, & Cohen, 2006) that this is a subsensory level in a stroke population, the technique used (transcranical direct current stimulation), whilst related to GVS, is not identical. Additionally, the stimulation in Gandiga's study was in fact only applied at an intensity of 1mA. This, coupled with the fact that the mean current in the studies which *did* individually modify the stimulation threshold was lower than 1.5mA, suggests that at least some participants in the former studies are likely to have felt some kind of sensation. Whilst these studies used a ramp-up and -down phase during sham to imitate any itching or tingling that may occur during the same phase of active

stimulation, there is the possibility that participants may have perceived some kind of sensation during any point of the active stimulation, which may have led to them becoming unblinded. Given that thresholding is a relatively quick and easy procedure, if studies intend for their stimulation to be delivered at a subthreshold level, it would be valuable for them to implement this simple step in order to increase the quality of their evidence. If it can be known for certain whether blinding procedures in individual studies were successful, it paves the way for future investigation to address the aforementioned tension that arises between the methodological motivation to blind participants and the search for the most efficacious stimulation parameters. In other words, if methodological flaws are first addressed, it should allow future reviews to focus on independently assessing the presence or absence of a dose response and whether stimulation would be most effectively applied at higher intensities. This would subsequently help to answer the question of whether sub- and supra-threshold stimulation exert differing effects.

Another factor to contemplate when considering stimulation parameters is waveform. GVS can be applied using a number of different wave shapes and frequencies, each of which can lead to differing results. Whilst many of studies included in this review used direct current stimulation, other waveforms may also be suitable contenders for neuromodulation in a neglect population**.** Research suggests that many neurological conditions are caused by dysfunctional brain oscillators (Assenza et al., 2017). As sinusoidal currents have been shown to have the potential to restore normal oscillatory rhythm by entraining neural responses, they therefore may be a valuable asset when searching for an intervention for neurological conditions such as neglect (Black & Rogers, 2020). These results further highlight the requirement to consider the complexity of stimulation parameters and, subsequently, the need to carefully consider methodological details when investigating the most efficacious implementation of GVS for people with neglect.

The heterogeneity explored thus far has primarily been methodological in nature. However, the review also revealed significant discrepancies in relation to clinical characteristics, both within

and between study samples. An important consideration when testing interventions in people with stroke is how long ago the brain injury was acquired. This is a critical concern due to the likelihood of spontaneous improvement occurring in the early stages of recovery. Studies have consistently shown that a range of impairments display the majority of spontaneous recovery in the first weeks and months post-stroke (e.g. hemianopia; Zhang, Kedar, Lynn, Newman, & Biousse, 2006; upper extremity function; Nakayama, Jørgensen, Raaschou, & Olsen, 1994), and that after this point, any improvement generally plateaus (Bernhardt et al., 2017). Neglect is no exception to this pattern; time alone is enough to predict recovery up until 12 weeks, after which this rate of change stabilises (Nijboer et al., 2013; Stone et al., 1992). However, only one study in the current review considered the potential effects of spontaneous recovery when recruiting participants, meaning the majority of samples were widely mixed regarding this demographic. In many, the mean time since stroke was less than three months. For the studies which took place over a matter of hours or days, this lack of consideration is unlikely to hugely confound results (although Stone et al. did find that the greatest rate of recovery occurs within the first 10 days post-stroke, so any participants in this subacute stage may have been accordingly affected by this). However, for the studies which took place over longer periods, there is a considerable possibility that spontaneous improvement may have become confused with the results of the intervention. By only recruiting participants once they have progressed past this three-month milestone, it should be possible to rule natural recovery out as a contributing factor, leading to greater confidence that any improvement seen is due to vestibular stimulation alone.

Of course, there is also the possibility that vestibular stimulation may have the most beneficial effect on post-stroke difficulties during the acute phase of recovery, due to the stimulation strengthening naturally occurring mechanisms (e.g. Adeyemo, Simis, Macea, & Fregni, 2012). If this is the case, any improvements seen past this three-month cut-off may be diminished in comparison to those observed as a result of earlier intervention and consequently, will be harder to demonstrate.

Therefore, there is also an argument to suggest that it may be beneficial to recruit participants closer to their stroke event.

Theoretically, this would be an interesting avenue to investigate. However, practical considerations should also be accounted for. As has previously been discussed, neglect can be a hugely demanding and fatiguing disorder for stroke survivors to live with. Neglect is often particularly debilitating during the acute and sub-acute stages, during which time, many individuals may also be afflicted with other cognitive and physical problems (Katz et al., 1999)**.** Consequently, recruiting participants so soon after their stroke may cause participation to become too burdensome or distressing for these people. Given the lowered quality of life that many of these individuals will be experiencing (Xie et al., 2006), it is also important that wellbeing is considered alongside other needs, and that no stress is unnecessarily added to what is already a difficult period. Therefore, integrating brain stimulation into these peoples' routine so early on may prove too challenging for some, or potentially could even be detrimental to their overall recovery.

It should also be considered that non-invasive brain stimulation has been shown to induce long-term plastic change in the brain after stroke (Bolognini, Pascual-Leone, & Fregni, 2009; Sandrini & Cohen, 2013). If any improvement in neglect symptoms after the application of vestibular stimulation comes about as a result of this more enduring mechanism of action, the stage of stroke recovery during which we intervene becomes much less significant. Positive effects should be seen at any point, not just in the first days and weeks after the event, and should persist as time passes, meaning there is greater potential to treat individuals later on.

Nevertheless, whether studies choose to recruit in the acute or chronic phase, careful consideration needs to be made about the length of time since participants' strokes, ensuring populations are not mixed in regard to this demographic. By implementing this change, individuals in the chronic phase post-stroke (who will be experiencing the effects of stimulation alone), will not

be assimilated with those in more acute stages, who may be benefitting from improvements due to both spontaneous recovery and the intervention itself. To achieve this homogeneity, studies need to more clearly define their criteria regarding this characteristic. It would also be beneficial to conduct these investigations in tandem with studies investigating more closely the mechanisms of effect of vestibular stimulation i.e., whether the technique bolsters existing mechanisms of recovery or works by another means. This, in turn, would increase our understanding of the timepoint at which it might be most beneficial to intervene.

Another confounding participant characteristic observed in the current review was the presence of visual field defects (VFDs). Many studies failed to report the incidence of VFDs in their cohorts, and of the studies that did note this information, none cited VFDs as an exclusion criterion and consequently had a sample free from this comorbidity. This may not be a problem when evaluating some outcomes, but will almost certainly impact line bisection, the assessment evaluated in the meta-analyses (which is also a subtest of the BIT). Whilst individuals suffering from neglect bisect a horizontal line to the right of the midline, those with hemianopia show the opposite pattern of impairment (Barton & Black, 1998; Kerkhoff, 1993). However, when hemianopia occurs alongside neglect, as is the case for some participants here, this pattern is abolished. Rather, the effects of neglect are exaggerated, and a greater rightwards deviation occurs (Doricchi & Angelelli, 1999). Given that VFDs amplify the effects of neglect, and that the participants included in the review are not homogenous regarding this trait, the effects of GVS on neglect alone are difficult to disentangle from the simultaneous impact of VFDs. Future research should consider this and attempt to recruit samples unconfounded by co-occurring VFDs, especially if line bisection is to be used as an outcome.

One domain in which the sample was homogenous is the side of the stroke: all studies included participants who had suffered a right hemisphere CVA. Although neglect can also occur as a consequence of left-sided stroke, this is a rarer occurrence than right (Ten Brink, Verwer,

Biesbroek, Visser-Meily, & Nijboer, 2017), likely because spatial attention is thought to be lateralised, with the right hemisphere attending to both sides of space and the left hemisphere only the to the right (Mesulam, 1981). Although this means that the results of the review can only be generalised to individuals with left-sided neglect, this may be an advantage in terms of data interpretation, given that those who are suffering from right-sided neglect often present with other complications such as aphasia (Bowen, McKenna, & Tallis, 1999). Therefore, not recruiting these participants means there is one less confounding variable to contend with, making for a simpler and more easily interpretable view. However, it may be interesting for future research to separately investigate whether the effects of GVS are the same in those with right-sided neglect as a result of left brain damage, especially given the dominance of the right vestibular system (Brandt, 2003).

Although homogeneity was achieved regarding the affected hemisphere, the more specific brain lesion site was not a factor which was systematically investigated in this review. This is since a) the data were unsuitable for subgroup analysis and b) not all studies recorded information regarding precise lesion location. The way in which studies that did report this information categorised it would have been difficult to group in an analysis (some categorised according to aetiology, whilst others listed the lesion site itself). Anatomical lesion location would, however, be an interesting topic to investigate, especially given that other studies have raised the possibility that ego- and object-centred neglect may be related to differing neural correlates (e.g. Hillis et al., 2005; Karnath, & Rorden, 2012). If a standardised method could be decided upon and universally employed to classify data according to this variable, it may help us to understand not only the mechanisms of neglect, but also vestibular stimulation, to a greater extent.

On another note, it would also be useful for future research to more thoroughly investigate and report adverse events. Although research has shown that GVS is generally tolerable for individuals who have suffered a stroke, people do report mild adverse events such as itching under the electrodes, which is more noticeable at higher intensities, as often used in these studies (Utz et

al., 2011). Collecting this information regarding these events is an important step in discovering whether GVS is likely to be a more widely accepted treatment. Concerning CVS, adverse events such as nystagmus and vertigo are a common consequence of the intervention (Lidvall, 1962). Although the presence of nystagmus was recorded in the studies which used this technique, it was not reported as an adverse event as such. In order for a treatment to be feasible, side effects must not outweigh benefits and therefore this needs to be investigated more thoroughly to ensure the stimulation is tolerable. On a related note, studies tended to use per-protocol analyses. Although attrition rates were generally low, it was sometimes difficult to determine whether the reasons for dropout were related to the stimulation protocol. Further research needs to make this information more transparent and use intention-to-treat analyses where possible in order to gain a better idea of the viability of the intervention in a less tightly controlled context.

Conclusion

Although this review is unable to provide conclusive evidence regarding the effects of vestibular stimulation on post-stroke visual neglect, it has highlighted that there is a significant need for better quality evidence to be conducted in order to adequately answer the review question. Future research would provide more useful evidence if, alongside increasing sample size, it addressed the substantial heterogeneity found here, both methodological and clinical. More specifically, outcomes should be carefully chosen, considering the exact process that is intended to be measured, and stimulation protocols should be standardised, ensuring that sham stimulation is subsensory to guarantee participant blinding. Inclusion criteria need to be thoughtfully selected to avoid heterogenous samples, considering factors such length of time since stroke (ideally recruiting participants who suffered a stroke long enough ago to not be at risk of spontaneous recovery from neglect) and ensuring participants are free from co-occurring VFDs. By implementing these recommendations, future inquiries into this topic should be able to untangle some of the conflicting

results found in the review and add a clear and valuable contribution to the literature as to whether vestibular stimulation is effective in treating post-stroke neglect.

Visual Training and Galvanic Vestibular Stimulation in Hemianopia

Whilst the results of the above review do not, per se, provide concrete evidence that GVS is a suitable treatment for neglect, they do suggest that there may be therapeutic potential within the technique, albeit one that requires further investigation to be confirmed. Based on this, the current section focuses on the use of vestibular stimulation in another post-stroke visual disorder: hemianopia. This condition commonly co-occurs with neglect (37% of those with neglect also suffer from hemianopia; Wilkinson et al., 2012) and worsens the prognosis of these individuals (Müller-Oehring et al., 2003). Whilst many treatments for the condition have sadly proven ineffective, there seems to be promise in those based upon the principles of multisensory integration. This, combined with the multisensory nature of the vestibular system and the promising results of the review, suggest that GVS may be an appropriate method to consider for the treatment of hemianopia. Therefore, here we present the theoretical rationale and experimental methods for a novel intervention which draws up these principles, administering GVS alongside visual training. There are no data presented in this section due to the COVID-19 outbreak, because of which the project had to be stopped before data collection had begun.

Aetiology and Clinical Presentation of Hemianopia

In contrast to neglect, in which primary visual processing is intact but mechanisms of attention abnormal, hemianopia arises from sensory, rather than attentional, loss. Hemianopia is a defect in which the same half of space in each visual field is rendered cortically blind. This absence of sight responds retinotopically to the area of brain which has sustained injury (Zihl & Kennard, 1996). Hemianopia is most commonly a consequence of stroke, but can also come about as a result of traumatic brain injury, tumours, or as a comorbid symptom of diseases such as posterior cortical atrophy (Delaj, D'Alessandro, Stracciari, Fonti, Cretella, & Lodi, 2010; Trobe, Lorber, & Schlezinger, 1973; Zhang, Kedar, Lynn, Newman, & Biousse, 2006). Although there is currently not

a strong consensus as to the exact prevalence of the condition, the literature makes it clear that hemianopia affects a large proportion of those who have experienced a stroke, with estimates ranging from 20 to 57% (Ali et al., 2013). The deficit is caused by damage to the retino-geniculate-striate pathway, with lesions occurring between the optic chiasm and primary visual cortex. This can include the optic radiations, primary visual, and extrastriate cortices (Zhang et al., 2006), meaning that the precise location of the lesion is highly heterogeneous. Indeed, Fujino, Kigazawa, and Yamada (1986) found that 40% of those with hemianopia had sustained a lesion to the occipital lobe; 30% to the parietal lobe; 25% to the temporal lobe; and 5% to the lateral geniculate nucleus or optic tract. Given the primarily posterior locations of these structures, it logically follows that the condition is most likely to be caused by a stroke involving the posterior cerebral artery, with 70% of CVAs involving this blood vessel leading to hemianopia (Pambakian & Kennard, 1997).

Given that vision is a highly relied upon sensory function, hemianopia can hugely impact the functional ability of those living with the condition, often constituting a major obstacle for them. Individuals with hemianopia report feeling unsafe and panicked when asked to navigate both familiar and unfamiliar environments, with almost 90% expressing a tendency to bump into other people and objects (Warren, 2009). This in turn increases the risk of falls and subsequent injuries (Ramrattan et al., 2001). The emotional consequences of the condition also take their toll, with many reporting that they feel a burden to others or embarrassed about being out in public, alongside a loss of confidence (Rowe, 2017a), which may in turn exacerbate the previously mentioned issues. Many are required to give up driving, reducing their autonomy and decreasing quality of life. Reading ability is often affected, as individuals can struggle with locating the beginning or end of lines of text, as well as processing words as a whole (Zihl, 2010). This may prevent individuals from returning to work, creating another obstacle on the path to independence (Rowe, 2017a). Hemianopia can also have a negative impact on healing itself, with multiple studies finding that the condition is a negative predictor of recovery and slows down the rehabilitative process (Jones & Shinton, 2006). In some

cases, hemianopia may be misdiagnosed as neglect or agnosia, delaying appropriate treatment (Serino et al., 2014). Even when correctly identified, many individuals report that their rehabilitation was focused on other post-stroke issues such as dysphagia and aphasia, with little consideration given to their VFD (Rowe, 2017a).

The recovery pattern of hemianopia is similar to neglect. Spontaneous recovery can occur, with the majority of this progress confined to the first three months post-stroke (Zhang et al., 2006). However, improvement only occurs in 20-30% of cases (Zihl & von Cramon, 1985) and is rarely complete, meaning that difficulties in everyday activities still persist (de Haan, Heutink, Melis-Dankers, Brouwer, & Tucha, 2015), and that individuals are unlikely to return to the level of functionality they displayed pre-stroke (Machner et al., 2009). Once individuals are in the chronic phase, it is unlikely that any further improvement will occur without intervention of some kind. This research highlights the overwhelming impact of hemianopia and subsequently, the clear need for an effective therapy for the condition. Current treatment options are limited, and primarily focus on visual training. This is the only intervention currently recommended by NICE (2013), one which can be broadly categorised into substitutive, restitutive, and compensatory forms.

Interventions for Hemianopia

Substitutive techniques.

The aim of substitutive techniques is to replace the lost area of vision via artificial strategies. This involves making changes to the individual's environment so that it is optimally structured to meet their needs and to assist them in activities that may be difficult or compromised as a result of their VFD. Examples of this type of intervention include aids such as magnifying glasses, eye patches and adapted lighting (Beis, André, Baumgarten, & Challier, 1999; Plow, Maguire, Obretenova, Pascual-Leone, & Merabet, 2009). Prism glasses, which project the blind area of vision onto the seeing field, can also be worn (Peli, 2000). Although the rapid effects of these substitutive

aids may initially paint them as an attractive choice, evidence has suggested they may not be as beneficial as they first may seem. An early study found improved scores on clinical tests following the use of prisms, but these results did not generalise to activities of daily living (Rossi, Kheyfets, & Reding, 1990). Other studies showing similar improvements also indicate that long-term use of the glasses is uncommon, with the majority of participants discontinuing wear at follow-up (Bowers, Keeney, & Peli, 2008; Giorgi, Woods, & Peli, 2009). These results imply that prisms may not be a viable longstanding treatment; Rowe et al. (2017b) not only found no significant change in visual field area, but also that adverse events occurred in 69% of the sample. This assessment is supported by a Cochrane review, which suggests that the evidence thus far is insufficient to recommend prisms as a treatment for hemianopia (Pollock et al., 2011). It therefore seems that other forms of therapy may be better suited to remedying the condition.

Restorative techniques.

In contrast to the artificial strategies used in the substitutive approach, restorative therapies aim to alter brain activity and consequently improve visual function. This is achieved by stimulating areas of partial injury. This technique, known as visual restitution therapy (VRT) was pioneered by Zihl and von Cramon in 1979 and is achieved by repeatedly presenting stimuli in the area bordering the scotoma, known as the transition zone. A key assumption of the technique is that some residual vision still exists in this region. This remaining sight is thought to correspond to neurons associated with damaged visual areas which have retained some functionality (Grunda, Marsalek, & Sykorova, 2013). Stimulating these cells is believed to increase the sensitivity of residual tissue, leading to plasticity-like changes which result in expansion of the visual field and partial restoration of the blind side of space. Several studies have shown an increase in the ability to detect stimuli in the blind hemifield using VRT (e.g. Julkunen, Tenovuo, Jääskeläinen, & Hämäläinen, 2003; Mueller, Mast, & Sabel, 2007; Poggel, Kasten, Müller-Oehring, Sabel, & Brandt, 2001) with average gains of around five degrees (Kasten, Wüst, Behrens-Baumann, & Sabel, 1998), an improvement suggested to be

enough to restore the perceptual window for reading (Bergsma & Van der Wildt, 2010). Given that the technique can be practised at home without the supervision of a clinician (see novavision.com), it was initially believed that it could have valuable potential as a therapeutic intervention.

However, protocols using this approach tend to be extensive and intensive, with an average regimen consisting of six months of daily sessions. Poggel et al. (2001) found that training intensity (and an uninterrupted schedule) was a significant predictor of outcome, suggesting that the therapy must be completed for this extended period of time in order to have the optimum effect. Given the comorbid complaints stroke survivors often suffer from, this may be too burdensome for all to achieve. Results also showed that not all individuals suffering from hemianopia benefitted. Kasten et al. (1998) proposed that VRT is more effective in those suffering from optic nerve injury (as opposed to cortical lesions), suggesting that this is due to the more diffuse nature of their brain damage and their subsequently larger transition zones. Poggel, Mueller, Kasten, and Sabel (2008) agreed with the view that size of the remaining intact visual field was an important predictor of success but found that lesion site had little impact on therapeutic gains. Zihl & von Cramon imply that the intervention is only effective in those who do not display a sharp demarcation between their blind and seeing fields, a characteristic suggestive of a partially reversible damage. There therefore seems to be little consensus as to which clinical factors best predict improvement with VRT, making it difficult to decide who might most benefit from the treatment.

It has also been argued that the above results cannot be taken at face value due to significant methodological weaknesses, one of which is a failure to employ an active control group (e.g. Kasten, Bunzenthal, & Sabel, 2006; Mueller et al., 2007). More importantly, due to fixation instability, studies may not have truly been measuring an effect of visual restitution as such. An essential feature of VRT is that central fixation is maintained whilst stimuli are presented, as any eye movements will bring previously unseen stimuli into view, utilising undamaged areas of sight rather than the transition zone. Many studies fail to adequately control for this – in fact, one of the foremost studies

conducted by Sabel and Kasten (2000) did not record eye movements at all. Studies which report that they have controlled for fixation often do not use appropriate methods to do so, using procedures which are insensitive to potential compensatory eye movements. For example, Jobke, Kasten, & Sabel (2009) used subjective patient reports to ensure the maintenance of fixation. To do this, a fixation cross periodically changed colour and the patient was instructed to press a button in response. Any missed changes or false alarms indicated that the cross was not being centrally fixated. However, it is possible to monitor these alterations using peripheral vision, meaning that small saccades can be made into the blind field and central changes still correctly identified. Given that the improvement in performance is on average less than five degrees, a value not notably larger than the error rate of perimetry (the method used to assess the effects of VRT), it is clear to see why the prevention of these saccades is necessary. When fixation is effectively controlled for using scanning laser ophthalmoscopy (regarded as the gold standard for this purpose), the gains observed become non-significant (Balliet, Blood, & Bach-y-Rita, 1985; Reinhard et al., 2005. See also Horton, 2005; Plant, 2005). This suggests that the positive effects of VRT are unlikely to be legitimately due to restitution. A more plausible explanation for the improvement would be compensatory oculomotor strategies, in which patients make brief saccades into the blind side of space in order to bring the stimuli presented there into their intact visual field. This theory is supported by evidence from Nelles, Esser, Eckstein, Tiede, Gerhard, and Diener (2001), who compared conditions in which participants were required to maintain fixation and in which they were allowed to make exploratory eye movements. Higher rates of detection and faster reaction times were observed after eye movement training, whilst no improvements occurred in the fixation condition. When measured, the size of patients' scotomata remained unchanged. These studies have together led to considerable controversy about whether restoration of vision in hemianopia is possible at all.

Compensatory techniques.

Although these results seem reason enough to cast doubt upon (if not entirely discount) restitution as an intervention for VFDs, they do provide valuable information about the mechanisms that *are* being drawn upon during rehabilitative efforts. Clearly compensatory eye movements play a role in the gains observed during VRT, a fact not disregarded in the search for an effective treatment. In fact, many studies, including a Cochrane review, suggest that compensatory interventions may be the most viable form of therapy for this population (Pollock et al., 2011). The objective of compensatory therapy is to alter abnormal eye movements, which occur in 60% of patients with hemianopia (Zihl, 1995). These irregular oculomotor strategies can be characterised by shorter, slower, and less accurate saccades, alongside a greater number of fixations, resulting in disorganised scanpaths and consequently, difficulties with target location (Passamonti, Bertini, & Làdavas, 2009). In general, compensatory therapies use visual exploration to encourage individuals to search their blind hemifield more efficiently and to expand the area into which their eyes explore. Behavioural evidence has demonstrated that these techniques result in better performance on visual search tasks (Aimola, Lane, Smith, Kerkhoff, Ford, & Schenk, 2014; Pambakian, Mannan, Hodgson, & Kennard, 2004; Sahraie, Smania, & Zihl, 2016). Eye tracking studies have also shown that oculomotor strategies change with training. These improvements include a greater number of fixations in the blind hemifield, alongside quicker saccades into this side of space. Patients also require fewer saccades overall to locate the target, beneficial adaptations which have been shown to persist for at least a month post-intervention (Mannan, Pambakian, & Kennard, 2010). These results suggest that individuals who undertake compensatory training learn to adjust for their VFD and that functional reorganisation of eye movement control occurs as a result of this.

However, the ecological validity of these studies needs to be considered. The tightly controlled nature of experimental paradigms makes it difficult to generalise these results to more routine scenarios, meaning any improvement in tested scores may not be a true reflection of recovery when measured outside the laboratory. For example, many studies examine reaction times and

accuracy scores, which may give little indication of any adaption to the condition in everyday life. One way to tackle this problem is to use subjective questionnaires to specifically assess activities of daily living (ADLs) and provide a more realistic view of how an individual's recovery is progressing. Several studies have found that improvement in ADLs often accompanies objective recovery, suggesting that experimental results do reflect a more generalised improvement (Lévy-Bencheton et al., 2016; Mödden, Behrens, Damke, Eilers, Kastrup, & Hildebrandt, 2012; Nelles et al., 2001).

Other studies have addressed this issue by quantifying objective gains in a more ecologically valid manner. Pambakian et al. (2004) had participants complete tasks such as bead threading, whilst Jacquin-Courtois et al. (2013a) used a search task in which participants were required to find an everyday object (e.g. a pair of scissors), amongst other items in a crowded desk scene. It was found that the positive results seen in conventional tests were also observed when using these more innovative measures, demonstrating that results have not only good internal, but also external validity. de Haan, Melis-Dankers, Brouwer, Tucha, and Heutink (2015) expanded upon this concept and asked participants to complete an obstacle course in which they had to avoid common household objects such as chairs and bins. They found that after compensatory training, participants were faster at completing the course and less likely to bump into obstacles. This improvement was seen even in dual task situations when attentional capacity was limited due to additional cognitive load. Given that these tasks are highly reminiscent of activities that may be completed as part of an individuals' daily routine, these improvements provide good evidence that compensatory training can provide rehabilitation which reveals itself not only in precisely manipulated experimental tasks, but also in those relevant to ordinary life. It is also important to note that these studies make use of different experimental tests to those that participants were trained with, limiting learning effects and showing that results are not simply due to participants gaining the specific skills needed to perform well on that particular task.

These studies demonstrate the efficacy of compensatory therapy but leaves the question of effectiveness somewhat unanswered. Certain forms of this intervention require the use of specialist equipment, making it necessary for patients to come into a clinic, rendering the therapy inaccessible to those unable to do so. Other therapies require a clinician to travel to participants' homes in order to supervise sessions, making it a costly process (e.g. Pambakian et al., 2004). However, recent results have demonstrated that this may be an unnecessary expense, as unsupervised web-based therapies have been shown to have positive therapeutic effects (e.g. Read-Right [Ong, Brown, Robinson, Plant, Husain, & Leff, 2012]; Eye-Search [Ong, Jacquin-Courtois, Gorgoraptis, Bays, Husain, & Leff, 2015]; Aimola et al., 2014). Web-based interventions not only make compensatory therapy more accessible to individuals with hemianopia, but also reduce the experimenter's influence on results, making it more certain that positive gains are due to the effects of the intervention alone.

Another benefit of compensatory strategies is that they require relatively little training for therapeutic effects to be seen. A good example of the speed at which gains can be made is revealed by Jacquin-Courtois, Bays, Salemme, Leff, & Husain (2013a), who found significant improvements in visual search in the blind hemifield following only 300 trials of a novel compensatory strategy. Although this study did not follow up participants past the experimental session, the fact that benefits could be seen using only 30 minutes of training suggests that there lies great promise within this method.

Although compensatory methods of training clearly have their advantages, it should be considered that they are primarily reliant on top-down mechanisms, requiring patients to voluntarily shift their attention to the stimuli presented to them. The brain damage that causes hemianopia can be widespread, often leaving individuals with other deficits alongside their VFD. As such, problems with viewing stimuli on the affected side of space may not be solely due to problems with the visual system but may also be impacted by concurrent attentional deficits. Nevertheless, search task performance is comparable for those with simulated and acquired hemianopia (Nowakowska, Clarke,

Sahraie, & Hunt, 2016), and healthy individuals with simulated hemianopia display search strategies which are similarly inefficient to those suffering from the condition as a result of acquired brain injury (Tant, Cornelissen, Kooijman, & Brouwer, 2002). Considering that neurologically healthy individuals are unlikely to be experiencing attentional deficits, this suggests that impairment is due to the visual defect itself, rather than issues stemming from damage to other functional areas of the brain. However, one study showed that in patients, attention training led to the same level of improvement as visual search tasks (Lane, Smith, Ellison, & Schenk, 2010), suggesting that attention may play a key role in the condition's rehabilitation. This may be problematic for stroke patients if their lesion site is diffuse, as damage may have occurred to brain regions involved in attentional processing, making top-down procedures too demanding to complete. Consequently, therapies which utilise bottom-up techniques may be more suitable, as these processes are more implicit and therefore less effortful.

Multisensory integration.

One way of implementing bottom-up mechanisms is by using multisensory stimulation. Multisensory integration allows the simultaneous processing of information from several different modalities. It is a technique that humans constantly rely on in the navigation of day-to-day life, as it allows several sensory inputs to be integrated into a single comprehensive awareness of our environment (Stein & Stanford, 2008). A function of multisensory integration is to facilitate more accurate detection of stimuli. When signals from more than one sensory modality are presented concurrently, they can be detected at a lower threshold than when they are presented alone (Stein, London, Wilkinson, & Price, 1996).

Multisensory integration is governed by three key principles, which must be met in order for the process to occur. These are spatial concordance, temporal concordance, and inverse effectiveness. The first two rules state that stimuli must be presented in a spatially and temporally

coincident manner; that is, they should be displayed in the same place at the same time. When this occurs, the two signals can be processed by the same receptive field of a neuron and subsequently integrated into a single entity (Stein, Meredith, & Wallace, 1993). The combined influence of these two inputs is not only greater than the effect observed when the stimuli are presented separately, but larger still due to the multiplicative nature of this enhancement (Stein, Meredith, & Wallace, 1994). However, one caveat of this principle is that a lack of spatial and temporal agreement can negatively impact integration; the further apart two events occur, the less likely it is that the process will ensue. In fact, if too disparate in their timing and location, stimuli that previously produced an enhancement of response can cause a diminution due to the brain processing them as discrete events (Meredith, Nemitz, & Stein, 1987). The third and final principle of multisensory integration is inverse effectiveness. This states that combining weak stimuli results in a greater level of enhancement than combining strong, which makes logical sense given that inputs that are unlikely to produce a response alone are those that are most in need of augmentation (Stein & Meredith, 1993). This principle is particularly pertinent to hemianopia, given that any input from the visual system will be weakened as a result of the condition. This means the gains that could potentially be achieved by making stimuli multisensory in nature would likely be even more salient in this group than in those with fully functional vision (Leo, Bolognini, Passamonti, Stein, & Làdavas, 2008).

Many studies have investigated whether this is the case, usually enhancing visual training with concurrent auditory stimuli. Bolognini et al. (2005) recruited eight participants with visual field defects, who were trained with audiovisual stimulation for four hours a day, for a total of two weeks. During training, visual stimuli (LEDs) appeared at different eccentricities in the visual field, accompanied by an auditory tone from the same location. Post-training visual search tasks revealed an improvement in oculomotor exploration, resulting in significantly faster and more accurate visual search and detection at the end of the treatment period. Perhaps more importantly, this improvement was also shown in participants' responses on a questionnaire assessing ADLs, with these effects

remaining stable one month after cessation of the training. It is also interesting to note that these effects were only seen in conditions where eye movements were allowed. In tasks where participants were required to fixate a central point, no improvement was seen. This suggests that the gains observed were due to compensatory mechanisms rather than restorative ones, facilitated by an increased sensitivity of the oculomotor system.

Other studies have reported similar findings. Jiang, Stein, and McHaffie (2015) found that audiovisual stimulation was able to restore visuomotor abilities in cats who had an induced hemianopia due to ablation of the visual cortex, whilst Keller and Lefin-Rank (2010) discovered that audiovisual training was more effective (in humans) at improving object search, reading ability, and activities of daily living than visual training alone. These results are further supported by Passamonti et al. (2009), who showed that oculomotor strategies became more adaptive with a similar training programme, leading to quicker overall exploration and enhanced reading performance. Leo et al. (2008) demonstrated that this relationship holds when reversed and that, even in the blind hemifield, presenting visual stimuli at the same time as auditory helps participants to localise the auditory signal. Several of these studies have demonstrated that their effects are long-lasting, with one finding an improvement which persisted at eight months (Grasso, Làdavas, & Bertini, 2016). Given that the behavioural differences seen were also accompanied by changes in EEG activity, the authors suggest that these results may be the result of neuroplastic change, further validating multisensory therapy as a treatment for the enduring condition that is hemianopia.

Although the above studies all make use of audiovisual training, audition and vision are not the only senses between which integration can occur. For example, tactile stimuli can also be incorporated into these paradigms (Diederich & Colonius, 2004). However, one avenue that is yet to be explored is that of vestibular stimulation. Vestibular signals may in fact be better suited to these kinds of paradigms than auditory stimuli, due to the potential for them to be made subsensory. Being

unable to perceive this input would not only make it more tolerable in a therapeutic context but may also increase the stimulation's salience and strength of processing due to its non-distracting nature.

Whilst the vestibular system is most commonly known for its role in balance, it also plays a crucial part in multiple other processes, including cognition and mental health. Studies have shown that individuals with damage to their vestibular system also display memory impairments and commonly suffer from anxiety and depression (Smith, Wilkinson, Bodani, Bicknell, & Surenthiran, 2019). Another relevant characteristic of the vestibular system is its close interplay with the other sensory systems, an interdependency necessary in order for balance to be maintained (Highstein, 2004). The vestibular nuclei receive signals from all the primary senses, both from the sensory organs and also their corresponding thalamic nuclei (Kotchabhakdi, Rinvik, Walberg, & Yingchareon, 1980; Leong et al., 2019), highlighting its inherently multisensory nature. The system has close connections with visual structures, playing a crucial role in oculomotor behaviour and the control of gaze (Robinson, 1968). This relationship can perhaps be most clearly seen when studying the vestibulo-ocular reflex, which allows the eyes to maintain fixation when head movements occur, by the use of compensatory eye movements. This function can only take place if the vestibular and visual systems are in constant communication, a process achieved through the activation of multiple direct and indirect neural pathways (Miles & Lisberger, 1981; Precht & Strata, 1980).

One such pathway projects from the vestibular afferents to the superior colliculus (SC; Maeda, Shibazaki, & Yoshida, 1979) a midbrain structure which plays a vital role in multisensory integration. The neurons of the SC are able to respond to and integrate signals from more than one sensory modality (Meredith & Stein, 1986), as well as playing a vital role in saccadic eye movements (Wurtz & Goldberg, 1971). Studies have shown that neurons of the SC demonstrate plasticity and can become responsive to visual stimuli when repeatedly exposed to cross-modal inputs (Yu, Stein, & Rowland, 2009). For these reasons, it is thought to be a structure crucial to the improvements seen in previous studies (Dakos, Walker, Jiang, Stein, & Rowland, 2019). It is also likely to be

particularly important for individuals suffering from VFDs, as their deficits most commonly arise from damage sustained to their retino-geniculate-striate pathway (Bertini, Grasso, & Làdavas, 2016), requiring them to instead utilise the spared retino-colliculo-dorsal pathway, which projects from the SC to the visual cortex (Milner & Goodale, 2006).

The integration that occurs in the SC is also mediated by other brain regions, including parts of the posterior parietal cortex. Evidence has demonstrated that inhibition of this area using non-invasive brain stimulation leads to a reduction in multisensory integration (Bertini, Leo, Avenanti, & Làdavas, 2010). This brain area not only supports the SC in combining sensory signals but is also able to perform the process itself. The region is of particular interest to this work due to the fact that it is strongly activated by vestibular stimulation. Although there is no primary vestibular cortex per se (with vestibular processing occurring throughout multiple brain regions; Della-Justina et al., 2015), there are numerous pathways between the vestibular nuclei and the parieto-insular vestibular cortex (Kirsch et al., 2016), the neurons of which respond not only to vestibular, but also visual inputs (Grüsser, Pause, & Schreiter, 1990; Lopez & Blanke, 2011). This evidence strongly suggests, due to its many relevant neural connections and multisensory nature, that vestibular system may be a prime target for multisensory integration. As such, we decided to use a combination of visual and vestibular stimulation in the current study.

As previously discussed, a common method of activating the vestibular system is GVS, which would seem to be an appropriate technique in this instance. Whilst the studies included in the review portion generally used direct-current GVS, another widely used waveform is pulse, in which stimulation is briefly administered via a boxcar wave. The current immediately jumps from zero to a pre-specified intensity with no ramp-up or -down phase (Dlugaiczyk et al., 2019). It was decided that this would be the most appropriate waveform to use in the current experiment, as it would allow for stimulation to occur only with the simultaneous appearance of visual stimuli, therefore satisfying the temporal concordance principle and allowing the integration of the two inputs.

We therefore planned to conduct a multiple single-case study to investigate whether the addition of GVS to visual training would be a more efficacious treatment of hemianopia than visual training alone. Participants were to complete two blocks of training: both would have included visual training but in one, concurrent GVS would have been administered, and the other, placebo stimulation. These blocks were to be counterbalanced across participants, and washout periods would have been introduced in between to prevent carryover effects. During and after each phase, computerised visual tasks, designed to assess detection, discrimination, and search ability, were to be administered. We hypothesised that accuracy would be higher and reaction times faster in these tasks in the GVS condition than placebo. A secondary prediction was that this improvement would also transfer to activities of daily living, measured using the Visual Functioning Questionnaire-25 (Mangione, Lee, Gutierrez, Spritzer, Berry, & Hays, 2001).

Method

Ethics

Ethical approval for the study was granted by the East of England-Essex Research Ethics Committee (REC reference: 19/EE/0378, IRAS ID: 274231) and by the School of Psychology at the University of Kent (ethics ID: D2020157971762079). The study was pre-registered on the Open Science Framework prior to the collection of any data.

Participants

Participants were to be recruited through East Kent Hospital University Foundation Trust**.** Planned inclusion criteria for the study included a diagnosis of homonymous hemianopia as a result of stroke at least three months prior to screening, visual acuity of at least 6/12, and the ability and means to travel to testing sessions at the university. Participants would also have had to be 18 years of age or older. Exclusion criteria included unilateral spatial neglect (score of ≥129 on the BIT), contra-indications to GVS, pregnancy, relevant visual processing deficits (assessed using the length,

size, and orientation match, position of gap, minimal feature and foreshortened view, and the easy and hard object decision subtests of the Birmingham Object Recognition Battery; Riddoch & Humphreys, 1993), or a score ≥26 on the Montreal Cognitive Assessment. During their screening visit, it was planned that participants would also be tested to ensure they could discriminate between the shapes used in the visual tasks in their normal field of vision.

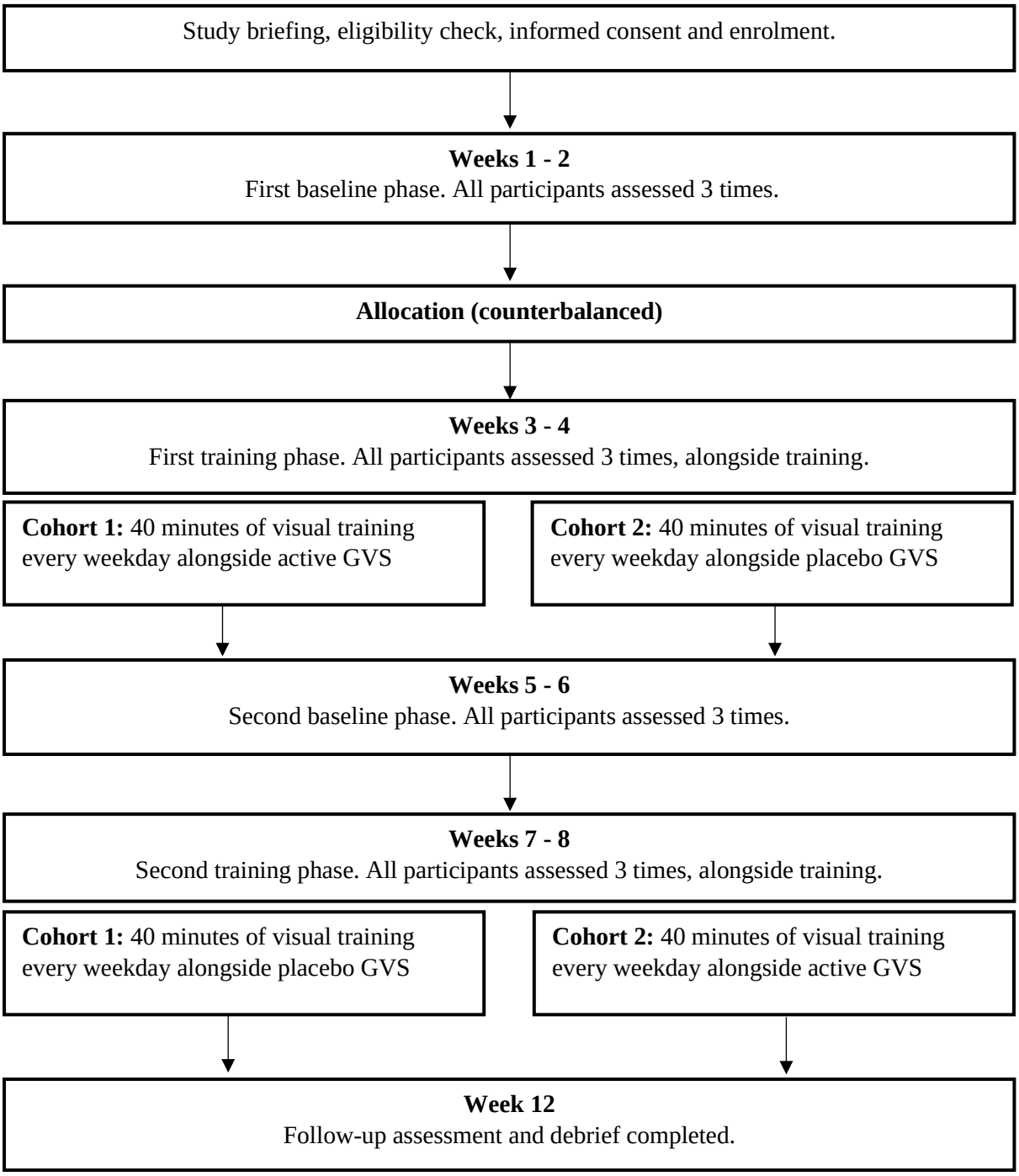
Procedure

Schedule.

The study would have consisted of four two-week blocks. During each block, participants would have been assessed 3 times, using the measures described below. Multiple assessments were planned within each block so that any trends within each phase could be visually analysed. Initially, participants would have completed a baseline phase. This was to be included to gauge their initial level of ability on each task, and to identify any learning effects. They would then move on to their first training phase, in which they were to complete training every weekday for two weeks, alongside either active or placebo GVS (the order of which was to be counterbalanced across participants). Then a second baseline phase was to be administered. Given that this was to be the first study to assess the effects of GVS on hemianopia, we were not sure how long any potential improvement might last for. Therefore, a second baseline was to be included to act as a washout phase or to measure and account for any intervention effects that might last longer than the first training phase and subsequently affect the second. The second baseline phase was to be followed by this second training phase, in which participants were to receive the type of GVS (placebo or active) they had not already had. Finally, the plan was for participants to return four weeks after their final training session to complete a follow-up assessment to measure any longer-lasting benefit.

Figure 7.

Participant Test Schedule.



GVS preparation and thresholding.

GVS would have been bipolar and binaural. In all sessions, the anode was to be placed on the contralesional side of the head, and the cathode on the ipsilesional side, to activate the vestibular

system on the same side that the brain injury had occurred (Fink et al., 2003), mimicking a head turn towards the blind hemifield (Fitzpatrick & Day, 2004). The electrodes were to be 5.1 x 10.2 cm, self-adhesive, and attached to a NeuroConn DC stimulator. It was planned that before the electrodes were applied, the skin behind the ears would be abraded using an exfoliating gel to reduce impedance, and then cleaned with an alcohol wipe. To ensure participants were blinded to their condition, this same process was to be carried out before the placebo training sessions (but with the device turned off).

Although there is a possibility that using subthreshold GVS may not have resulted in such large effects as suprathreshold stimulation, the need to blind participants to their condition and consequently eliminate the possibility of a placebo effect was considered to be more important at this early stage of study than determining the optimum stimulation parameters.

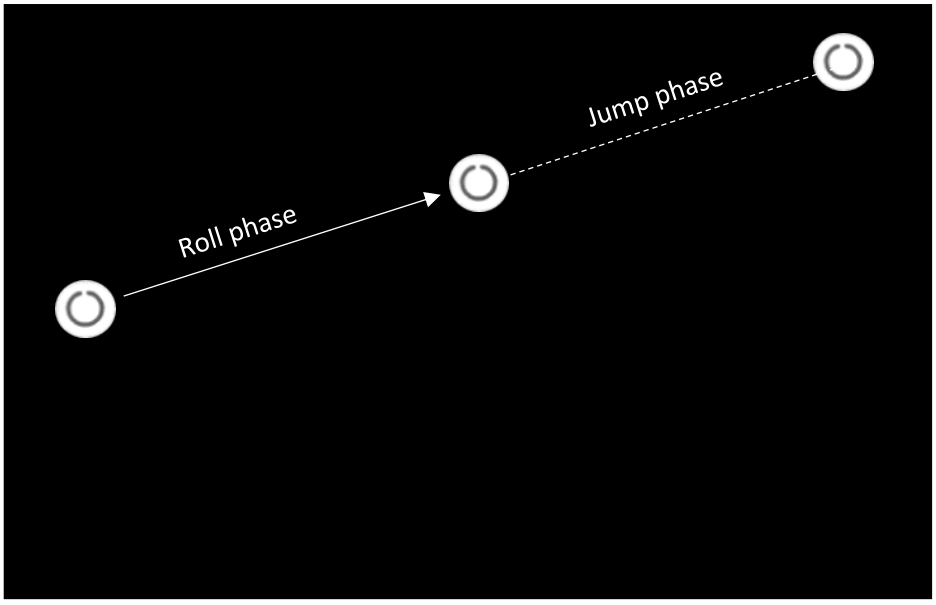
At their final baseline assessment, before participants began visual training, they would have completed a stepwise thresholding procedure to determine at what current intensity they were no longer able to detect GVS. Initially, stimulation would have been applied for 200ms at 300μA. Five pulses of GVS, spaced 10 seconds apart, would be delivered at this intensity. If the participant reported feeling any sensation, the current would be lowered to 250μA and the procedure repeated. If the participant could still feel the effects of stimulation at this level, they would be excluded as it would not be possible to blind them to their condition. If the participant could not feel anything at 300μA, the current would be upped to 350μA. This would continue in 50μA steps up to a ceiling of 600μA – if the participant could still feel no sensation at this level, they would be excluded. The threshold of each participant would be determined by setting the current intensity to 50μA below the current at which they reported any sensation with stimulation. They would be tested five times at this level to ensure no sensation was felt, then this current would be used for the experimental portion of the study.

Training Programme.

The planned training programme was adapted from Jacquin-Courtois et al. (2013a) and would have made use of a ramp-step paradigm. A white circle, containing a smaller, incomplete black ring would appear on either the left or right half of the black computer screen, at either 17.5 or 35˚ from the vertical midline. The side of the screen was to be randomised but chosen with equal probability throughout the task. To begin the trial, the participant would use the mouse to click the circle, which would then began to move smoothly across the screen (ramp phase), at a speed of $15˚s^{-1}$, and at a trajectory randomly chosen between 20˚ above or below the horizontal midline. When the circle reached the vertical midline, it would make a jump of 17.5 or 35˚into the opposite side of the screen (step phase), along the same trajectory as the ramp phase.

Figure 8.

Example of a single trial of the training programme.



The solid arrow indicates that the ball was visible during this movement phase. The dotted line indicates that the ball disappeared then reappeared in the marked locations.

GVS was to be time-locked to the re-appearance of the stimulus on the opposite side of the screen, with participants receiving a 200ms pulse when this occurred. However, GVS was to only be applied when the stimulus moved from the seeing hemifield to the blind one (when participants were in the active block; when in the placebo block, no stimulation would be applied at all). This way,

participants would have received a pulse of GVS whenever the target 'jumped' into the blind half of space. When the circle re-appeared, the gap in the black ring inside was to be randomly positioned either at the top or the bottom of the circle (with equal probability). Half the participants would be asked to click the left mouse button if the gap was at the top, and the right if the gap was at the bottom, the other half vice versa. Left and right button clicks were to be counterbalanced across participants. We planned to attach a picture of the circles to each mouse button to remind participants of which button corresponded to each orientation. This task was to be included to ensure that participants had fixated the target when it re-appeared. The target would remain on screen until participants had made a choice, after which a new trial would begin. Accuracy would have been recorded for each trial to see if participants had completed the training successfully.

We planned to include a ramp phase to encourage participants to follow the initial trajectory of the circle using smooth pursuit, with the idea that this stage would make it easier for them to locate the stimulus once it had moved into the opposite visual field. Although this phase would require a saccade, the target would have continued along the same trajectory and therefore would re-appear at a predictable location.

When completing training, participants would have sat approximately 40cm away from the computer screen. Participants were to complete 400 trials per training session, with a break after every 100 trials, which in total would have taken around 40 minutes to complete. They were to place their head in a headrest so that no head movements were made during training and would have been instructed to explore the visual field with their eyes only.

Assessments

Visual Tasks.

Participants would have completed three different visual tasks: detection, discrimination, and search. Three types of test were chosen to assess various levels of visual processing and to

investigate if training would differentially affect any of these. Each task would have consisted of two separate blocks of 96 trials each: one with stationary, and one with dynamic stimuli. We decided we would include these two types of stimuli because moving stimuli are processed in the extrastriate cortex (Dubner & Zeki, 1971), an area less commonly affected in hemianopia than the striate cortex, the site of processing for stationary stimuli (Zhang et al., 2006). Therefore, we wanted to assess whether performance with moving stimuli was preserved in the blind side of space and whether stimulation would lead to any improvement. All stimuli would have been black, subtended 3 degrees of the visual field, and presented on a white background to prevent after-effects. Stimuli could have appeared in 24 possible locations, evenly distributed in a 6x4 arrangement across the screen. The target would have had an equal probability of appearing in any of the 24 locations of the screen in all tasks. Participants were to use a headrest, placed 40cm away from the screen, to prevent head movements. We planned to record accuracy and response times for all tasks. The order of tasks was to be counterbalanced across participants using a Latin square. Participants would have been able to complete 8 practice trials before beginning the actual task and would have been instructed to make responses using their dominant hand (determined using Edinburgh Handedness Inventory). The length of time between the training session and assessments was going to be standardised to 15 minutes to ensure that any variance in performance seen in the visual tasks was due to genuine change, rather than a difference in carryover effects from the training.

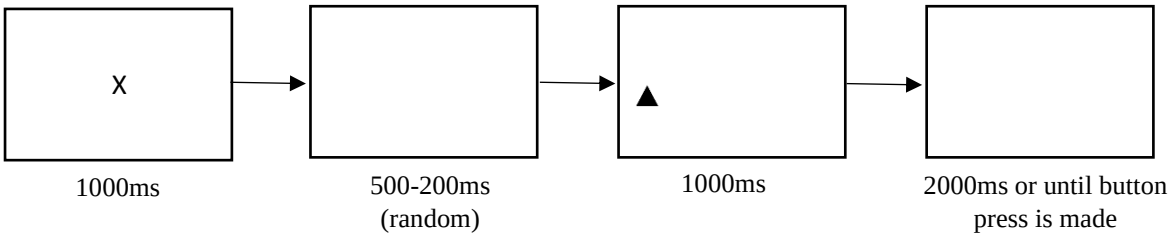
Detection.

In the stationary detection block, it was planned that the target would be one of four different shapes: a triangle, square, pentagon, or hexagon. In the dynamic block, the intention was for the target to be a random dot kinematogram (RDK) with an invisible square border containing 100 dots, which would have been 3 pixels in size and moving in an upward, downward, leftward, or rightward direction with 100% coherence and a speed of 9 degrees per second. It has been demonstrated that the neurons of the SC do not exhibit selectivity regarding direction or speed of movement (Krauzlis,

2004), therefore this speed was chosen so the direction could most easily be distinguished, given the relatively short presentation time of targets**.** The order in which shapes or RDKs appeared would have been randomised, but each would have appeared an equal number of times overall. This was planned to prevent priming of a particular shape or direction if participants were to complete the detection task first, so that performance on the later search task would not be affected.

Figure 9.

Example of a detection trial.



At the beginning of each trial, a black fixation cross, 2 degrees in size, would have appeared in the centre of the screen for 1000 milliseconds, followed by a blank screen for a length of time which was to be randomised between 500 and 2000 milliseconds. The purpose of the fixation cross was to draw participants' eyes back to the midline after each trial, to ensure their gaze would commence from the centre of the screen. The length of time between the offset of the fixation cross and the onset of the stimulus was to be randomised so that the appearance of the stimulus would be unpredictable, meaning that participants could not methodically press the response button even if they had not seen the target.

The target would have then randomly appeared in one of the 24 possible locations for a duration of 1000 milliseconds. We predict that any improvement in these tasks will come about as a result of compensatory mechanisms; that is, participants will saccade into their blind hemifield more frequently to make up for their deficit. Therefore, a duration of 1000 milliseconds was chosen so that the target would be visible long enough for participants to move their eyes into the blind half of space to locate it. Participants were to be instructed to make a button press as quickly as possible whenever they saw a target. Half would be instructed to press 'B', and the remainder to press 'H'.

The B and H keys were chosen to reduce spatial biasing, as they are located in the middle of the keyboard. The allocation of keys was to be counterbalanced across participants. They would have been given 3000 milliseconds from the onset of the target to respond, after which the fixation cross would appear again, and the next trial begin. We planned for the trial to be recorded as inaccurate if no response was made.

Discrimination.

2 versions of the stationary and dynamic discrimination tasks were to be used. Half of participants would have been asked to discriminate between a triangle and a hexagon in the stationary block, the other half to distinguish a square from a pentagon. Similarly, in the dynamic block, half were to discriminate upwards from downwards movement, and half left from right.

The pairs of stimuli and the allocation of B and H keys would have been counterbalanced across participants. All other task parameters were to be kept the same as in the detection task. Responses for this task would have been classed as accurate, inaccurate, or missing.

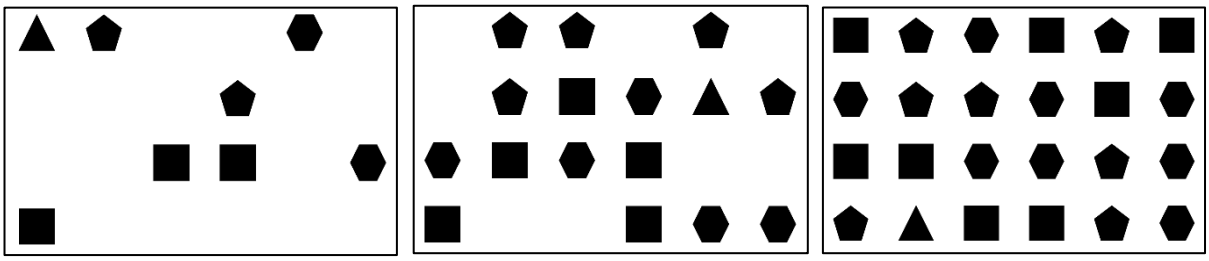
Search.

The aim of the stationary search task would have been to locate a shape amongst distractors. Half of participants would have been asked to locate a triangle amongst the 3 other distractor shapes, the other half a square. The target was to be counterbalanced according to which shapes the participant had seen in the discrimination task, again to prevent priming effects. If the participant had discriminated between a triangle and hexagon, their target in the search task would have been a square. Similarly, if they had discriminated between a square and a pentagon, the target in this task would have been a triangle, as they had not seen this shape previously. We decided not to use pentagons and hexagons as targets in the search task as they were too similar, making the target harder to pick out from the distractors and subsequently making the task harder than when squares or triangles were used as the target.

Half the trials (48) would have been target-present and half target-absent. There were to be 3 different levels comprising 32 trials each, which were to be randomly distributed throughout the task. The levels would have differed in the number of distractors: the easiest level would have displayed the target amongst 7 distractors, the next among 15, then 23. Each quadrant of the display would have featured the same number of stimuli, but within each quadrant, the position of the distractors would have been randomised. The target would have also appeared randomly but would have had the same probability of appearing in any of the 24 coordinates in the target-present levels**.** In the 48 target-absent trials, the position where the target would normally be would have been filled with an extra distractor. Half the participants would have been instructed to press B if and when they found the target, or H if they thought that no target was present. Again, the allocation of keys was to be counterbalanced across participants.

Figure 10.

Example search displays.



The displays are examples of the three levels of target present trials, with a triangle as the target.

In the dynamic stimuli block, the target would have been an RDK containing upwards, downwards, leftwards or rightwards movement, and distractors would have contained the directions of movement not being used as the target.

As in the other tasks, each trial would have begun with a fixation cross, shown for 1000ms. Each search display would have then been presented on the screen for a maximum of 10000ms. If participants made a response before this time had elapsed, the stimuli would have disappeared, and a blank screen would be shown for 2000ms before the fixation cross appeared again. The inter-

stimulus interval would have been the same if participants did not provide a response within 10000ms, and their response would have been recorded as missing. We planned to give participants a short break after every 32 trials. Responses for this task could have been recorded as accurate, inaccurate, or missing.

Visual Functioning Questionnaire-25 (VFQ-25).

The VFQ-25 is a pen and paper test that measures the effect of vision problems on activities of daily living. This outcome has been shown to significantly correlate with other measures used to assess the disorder (George, Hayes, Chen, & Crotty, 2011).

Anticipated Outcomes

Whilst it was not possible to collect any data regarding this study, presented here are the anticipated outcomes if the above hypotheses had proved to be correct. We would have expected accuracy to increase and reaction times shorten to a greater degree in the block in which participants received active GVS than placebo. Given the overwhelming evidence to support compensatory training for hemianopia, it would be anticipated that an improvement would have also be seen in the placebo phase, albeit to a smaller degree. Due to the highly exploratory nature of this work, we cannot be sure in exactly which tasks the greatest improvement would be seen. Previous work using multisensory stimulation has shown improvement in both detection and search (e.g. Bolognini et al., 2005). Consequently, we would have expected to see similar gains in our results. Although no studies to our knowledge have yet investigated the effects of multisensory interventions on discrimination performance, given that we predict that any improvement will be result of enhanced oculomotor strategies, we would have also expected to see an improvement in this type of task. However, if different levels of enhancement were found in detection, discrimination, and search, it may help to uncover which underlying processes are being modified by the training. For example, shortened reaction times or greater accuracy in the detection task might indicate that stimuli are

being more readily processed in early visual areas, whereas similar results in the search paradigm may be more reflective of better organised oculomotor patterns, or the ability to appropriately orient attention to each hemifield.

We are also unaware of any studies which have used moving stimuli as an assessment alongside this type of intervention. Whilst studies have shown that participants with hemianopia are more responsive to moving stimuli than stationary in the blind hemifield (due to the fact that the extrastriate cortex area, V5, is specialised to respond to motion and is less likely to be damaged in this population; Dubner & Zeki, 1971), other work has shown that whilst detection of moving stimuli is often intact, discrimination of direction is still impaired (Azzopardi & Cowey, 2001). Therefore, we would have expected participants to have had a better baseline score in the dynamic detection task than the stationary, one which may not have shown improvement with training as compensatory eye movements would not have been needed to process these stimuli. However, we would have expected to see a similar level of improvement in the dynamic and stationary discrimination and search tasks as the extrastriate cortex is not able to complete these processes in the same way as detection. Obviously, these particular outcomes would be contingent upon V5 being left unaffected by the participants' strokes. We planned to collect information regarding lesion site wherever possible and hopefully therefore would have been able to assess whether these behavioural and anatomical patterns were consistent with one another.

Considering that previous studies have demonstrated that experimental gains transfer to ADLs, we would have also expected a higher score to be found on the VFQ-25 post-GVS. We would have expected these gains to occur as a result of neuroplastic change, which has been shown to occur in other studies (Grasso et al., 2016). Therefore, we would have expected any improvements to be maintained at the one-month follow-up assessment point.

Due to the single-case design of the above study, it would not have been possible to fully generalise any results to a wider hemianopia population. However, if these anticipated outcomes were shown to occur, it would provide proof-of-principle that the above regimen may be a plausible treatment option for these individuals and would therefore justify further study. This should take the form of a powered, parallel-arm RCT, conducted according to CONSORT guidelines, in which one group receives a control (such as visual training with placebo GVS) and the other the active treatment. Using a between-participant design such as this should prevent any carryover effects and make for clearer interpretation of the data. As well as including outcomes related to efficacy (such as the visual tasks used here), another important factor to consider is safety. Therefore, detailed records of any adverse events should be kept alongside attrition rates and reasons for these dropouts (as they also would have been in this study). If the intervention is to be successful as a 'real-world' treatment, tolerability is also a crucial issue to consider and participants' opinions of how acceptable they believe the regimen to be should also be taken into account.

It would also be interesting to investigate further the potential mechanism of effect of any positive results. Whilst it is assumed that any gains will be a consequence of enhanced oculomotor control, improvements on the visual tasks described above could also be a result of attentional gains or expansion of the visual field. By employing measures such as perimetry (which rules out the role of any eye movements) pre- and post-intervention, we may be able to better understand the fundamental mechanisms of any behavioural improvements.

Another way of investigating the mechanisms underlying any potential improvement would be to study whether the length of time since stroke impacts upon results. For the current work, it was planned that participants would only be recruited if their stroke had occurred at least three months prior to screening. As previously discussed, this was to ensure that any spontaneous recovery was no longer occurring, as this may have confounded the effects of training. Although earlier study of multisensory integration has shown that the technique can be effective in participants who suffered

their stroke more than three months previously (e.g. Bolognini et al., 2005), there is a possibility that administering the training past this point in time may result in a lessened intervention effect, the true potential of which may only be observed when applied earlier on in recovery. If the results of the current study prove promising, perhaps future research could examine this further and explore whether time since stroke has a significant influence upon the current training paradigm.

Manipulating dose may also result in noteworthy findings. Gains for hemianopic participants have been seen after very few trials of compensatory therapy (Jacquin-Courtois et al., 2013a) but multisensory treatments thus far have been much more extensive, with Bolognini et al. (2005) requiring participants to complete training for four hours a day. If similar benefits could be achieved with less burdensome protocols it would make treatment more accessible. Investigating a dose response, perhaps by having one group completing one session, another one week's worth of sessions, and another two weeks' worth, may be a helpful way of gaining this information. Another potential way of controlling dose would be to alter the intensity of GVS. If training with subthreshold GVS proves to be an effective intervention, it would be interesting to investigate whether these gains could be amplified even further by increasing the current of the GVS.

Given the portability of GVS and the ease with which it can be administered, alongside the fact that the visual training paradigm can be run on any computer, if a larger, more rigorous study is able to show positive results of the intervention, it could be that it becomes a much needed and viable therapeutic option for individuals suffering from hemianopia.

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Appendix A.

Search strategies.

CENTRAL:

#1 MeSH descriptor: [Stroke] explode all trees
#2 ((stroke or poststroke or "post-stroke" or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplexy* or SAH)):ti,ab,kw
#3 ((brain* or cerebral* or cerebell* or intracran* or intracerebral) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus*)):ti,ab,kw
#4 (brain* or cerebral* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Visual Perception] explode all trees
#7 MeSH descriptor: [Perceptual Disorders] explode all trees
#8 (hemineglect or hemi-neglect)
#9 ((unilateral or spatial or hemispatial or hemi-spatial or visual) near/5 neglect)
#10 (inattention or hemi-inattention or extinction)
#11 ((perceptual or perception or visual or visuospatial or visuo-spatial or visuoperceptual or visuo-perceptual or attention*) near/5 (disorder* or deficit* or impairment* or abilit* or problem*))
#12 #6 or #7 or #8 or #9 or #10 or #11
#13 #5 and #12

PubMed:
("brain injuries/complications"[Mesh] OR stroke[Mesh]) AND (“perceptual disorders”[Mesh] OR “visual perception”[Mesh] OR “vision disorders”[Mesh]) NOT (teen*[TIAB] OR youth*[TIAB] OR adolescen*[TIAB] OR juvenile*[TIAB] OR young adult*[TIAB] OR young person*[TIAB] OR young individual*[TIAB] OR young people*[TIAB] OR young population*[TIAB] OR young man[TIAB] OR young men[TIAB] OR young woman[TIAB] OR young women[TIAB] OR youngster*[TIAB] OR first-grader*[TIAB] OR second-grader*[TIAB] OR third-grader*[TIAB] OR fourth-grader*[TIAB] OR fifth-grader*[TIAB] OR sixth-grader*[TIAB] OR seventh-grader*[TIAB] OR highschool* OR college* OR secondary school*[TIAB] OR secondary education*[TIAB] OR high school*[TIAB] OR high education[TIAB] OR adolescent[MH] OR young adult[MH])

WHO ICTRP:
stroke AND vision OR stroke AND visual perception OR stroke AND neglect OR stroke AND perceptual disorders

PsychINFO:
(DE "Cerebrovascular Accidents") AND ((DE "Perceptual Disturbances" OR DE "Agnosia" OR DE "Hallucinations" OR DE "Misophonia" OR DE "Psychedelic Experiences" OR DE "Sensory Neglect") OR (DE "Vision Disorders" OR DE "Balint's Syndrome" OR DE "Blind" OR DE "Blindsight" OR DE "Eye Disorders" OR DE "Hemianopia" OR DE "Partially Sighted"))

CINAHL:
(MH "Stroke+" OR MH "Brain Injuries+/CO") AND (MH "Visual Perception+" OR MH "Perceptual Disorders+" OR MH "Vision Disorders+")

OpenGrey:
((stroke OR poststroke OR "post-stroke" OR cerebrovasc* OR brain next vasc* OR cerebral next vasc* OR cva* OR apoplexy*) AND (perceptual OR perception OR visual OR visuospatial OR visuo-spatial OR visuoperceptual OR visuo-perceptual OR attention*) AND (disorder* OR deficit* OR impairment* OR abilit* OR problem*)) OR “spatial neglect”

LILACS:
(stroke OR poststroke OR "cerebrovascular accident" OR CVA) AND (perceptual OR perception OR visual OR visuospatial OR visuo-spatial OR visuoperceptual OR visuo-perceptual OR attention) AND (disorder OR deficit OR problem OR impairment OR neglect)

AIM:
Title field: stroke poststroke "cerebrovascular accident" CVA

Appendix B.

Characteristics of included studies and risk of bias tables.

Cappa et al. (1987) - study characteristics.

Methods	**Design:** Non-randomised.
Participants	**Description**: 4 case reports of individuals suffering from neglect and anosognosia **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported **Method of neglect diagnosis:** line and circle crossing tests used as experimental tasks. "In the baseline condition, all four cases showed very severe extrapersonal neglect, being able to cross only the more extreme right-sided items." **Number included:** 4 **Mean age:** 61.25 **Sex (proportion male):** 2 of 4 **Type of stroke:** Not reported **Lesion location:** Right hemisphere **First ever stroke?:** Not reported **Time since stroke:** All participants assessed within 2 days of their stroke **Presence of hemiparesis/plegia:** All participants displayed left hemiplegia **Presence of comorbid visual field defects:** All participants displayed left homonymous hemianopia
Interventions	**Description:** "In cases 1, 2 and 4 the left external ear canal was irrigated with 20 cc of iced water for I min. In case 3 the right ear was irrigated with 20 cc of warm water, due to the presence of a great amount of cerumen in the left ear." **Duration:** 1 minute **Timing:** Administered once **Co-interventions:** None reported
Outcomes	**Description:** "Extrapersonal neglect was evaluated by a circle crossing test in cases 2,3 and 4 and by a line crossing test in case 1." **Unit of measurement:** Percentage of omissions **Upper/lower limits:** Lower = 0%, upper = 100%. Low score is good.

	The outcome was measured pre-stimulation, immediately post-stimulation, and 15 minutes post-stimulation.

Cappa et al. (1987) - risk of bias

Bias	**Judgement**	**Support for judgment**
Random sequence generation (selection bias)	High risk	Non-randomised study. Bias due to confounding = moderate risk.
Allocation concealment (selection bias)	High risk	Non-randomised study.
Blinding of participants and personnel (performance bias)	High risk	No mention of participants or personnel being blinded.
Blinding of outcome assessment (detection bias)	Low risk	No mention of outcome assessors being blinded. However cancellation task results unlikely to be subjectively reported.
Incomplete outcome data (attrition bias)	Low risk	No missing data.
Selective reporting (reporting bias)	Unclear risk	No analysis plan available but all stated outcomes were reported at all timepoints and analysis was appropriate (however, not comparable to an RCT).
Other bias	High risk	Intervention not clearly defined - 3 participants received contralesional stimulation with ice water and one received ipsilesional stimulation with warm water.
Carryover effects	Low risk	n/a to study design.
Period effects	Low risk	Study carried out over a single day.

Dai et al. (2013) - study characteristics

Methods	**Design:** Cluster-parallel RCT, vestibular rehabilitation (VR) + conventional therapy vs. conventional therapy alone
Participants	**Description**: Stroke patients with neglect **Inclusion criteria:** (1) being diagnosed by physicians, computed tomography, or magnetic resonance imaging scan of the brain as having experienced a right hemispheric stroke, including hemorrhagic or ischemic strokes, and first-time stroke with a duration of less than 6 months from the stroke onset; (2) meeting the conditions for neglect on any of the two scales within the Behavioral Inattention Test Conventional (BITC) subtest; and (3) capable of communicating in Mandarin Chinese or Taiwanese, and understanding instructions. **Method of neglect diagnosis:** Below a cutoff on at least two scales of the BITC **Exclusion criteria:** Recurrent stroke with duration of more than 6 months from stroke onset, less than two subtests (BITC) of diagnosed neglect, incapability to communicate, and lack of primary caregivers. **Number randomised:** 55 **Mean age (SD):** VR: 57.21 years (12.23), Control: 64.54 (14.67) **Sex (proportion male):** VR: 16 of 24, control: 12 of 24 **Type of stroke:** Ischaemic or haemorrhagic (proportion of each not reported) **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Mean time since stroke (SD):** VR: 56.88 days (38.93), Control: 73.88 days (37.86) **Presence of hemiparesis/plegia:** Not reported **Presence of comorbid visual field defects:** Not reported
Interventions	**Vestibular Rehabilitation (VR)** **Description:** Participants completed portions of the Cawthorne–Cooksey exercises, including side-to-side head turns, up-and-down head movements, and gaze movements. Patients were seated in a wheelchair and their heads and bodies were in the middle position (verbally reminded to keep this constant if head/neck began to tilt). The gaze target was pasted on a 60 cm long and 20 cm wide white polypropylene corrugated board. The target size was determined by the patients' vision. In most cases, a 2 cm colored dot was used as the target. The VR training procedure is described as follows: (1) with their eyes open, the patients moved their head up and down for 20 times or for 1 minute. They also moved their head from side to side for 20 times or for 1 minute. (2) With their eyes closed, the patients

	moved their head up and down for 20 times or for 1 minute. They also moved their head from side to side for 20 times or for 1 minute. (3) The polypropylene corrugated board was placed on the trainers' thighs. The target was at the same height as the patients' eyes. The patients gazed at the target while moving their head up and down and from side to side for 20 times. (4) The patients rested as necessary. The patients performed steps one to three repeatedly, and the entire process took approximately 30 minutes. **Duration:** A total of 4 weeks **Timing:** During the first and second weeks, a registered nurse (RN) trained the patients in VR. The training was provided once per day for 30 minutes, for a total of ten sessions over 2 weeks. During the third and fourth weeks, the patients were supervised and guided in VR by their primary caregivers. During the first week, the RN also taught the primary caregivers how to supervise and guide the patients' VR. Each session lasted for approximately 5 minutes to 10 minutes, with the primary caregivers requiring two to four sessions (approximately 20 minutes to 40 minutes in total) before being able to supervise and guide the patients' VR correctly **Co-interventions:** During all 4 weeks of VR, participants also completed 2 hours of conventional rehabilitation, 5 days a week. This included one hour of physical and 1 hour of occupational therapy (see below for description). **Control** **Description: P**hysical therapy included passive exercises, active exercises, resistive exercises, ambulation training, and so on. The occupational therapy included maintaining or improving physiological functions such as endurance, balance, and training, to improve ADL, such as dressing, using the toilet, sanitation, home care, and others." **Duration:** 4 weeks **Timing:** The patients were required to spend 2 hours on conventional rehabilitation – specifically, 1 hour for physical therapy and 1 hour for occupational therapy – for a total of 5 days a week. **Co-interventions:** n/a
Outcomes	**Description:** Conventional subtest of the BIT (representation drawing, figure and shape copying, line bisection, line crossing, star cancellation, and letter cancellation). **Unit of measurement:** n/a **Upper/lower limits:** Lower limit = 0, upper limit = 146. High score is good. Cutoff of <129 indicates the presence of neglect. The outcome was measured at baseline (day 0), day 14, and day 28.

Dai et al. (2013) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	No information about the likelihood of allocation sequence being subverted.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias)	Low risk	Study is only single-blind (outcome assessors), however, there appear to be no deviations from the intervention and clusters and participants were analysed according to the group to which they were assigned.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were blinded to participants' conditions.
Incomplete outcome data (attrition bias)	Low risk	Data only available for 87% of participants, however, the rate of missing data is very similar for each experimental group.
Selective reporting (reporting bias)	High risk	No analysis plan available. However, several different tests are conducted and provide differing results, and the one that favours an effect of stimulation is taken and expanded upon.
Other bias	Unclear risk	The control group completed conventional therapy (which consisted of physical and occupational therapy). Given that some of the control exercises are stated to work specifically on participants' balance, it is likely that the vestibular system was also activated during these, therefore reducing the difference between the experimental and control group as vestibular activation is what the experimental group also aimed to achieve.
Carryover effects	Low risk	n/a to this study design
Period effects	Unclear risk	Mean time since stroke in the VR group was 56.88 days and for the control group was 73.88 days. Participants not yet in chronic phase of stroke and study takes place over a period of a month so there is the potential for some spontaneous recovery to occur.

Nakamura et al. (2015) - study characteristics

Methods	**Design:** repeated measures crossover (CL-GVS, CR-GVS, sham GVS)
Participants	**Description**: Individuals with left-sided unilateral spatial neglect **Inclusion criteria:** First ever hemiparetic stroke, right hemisphere damage, right handedness, aged 30-89 years, USN diagnosed with the Japanese version of the conventional BIT **Exclusion criteria:** Bilateral or left sided lesions, aphasia, inability to sit in a wheelchair, extremely impaired eyesight, MMSE score <16, inability to understand study, vestibular disorders, GVS contra-indications **Method of neglect diagnosis:** Below cutoff (131/146) on Japanese version of the BIT **Number included:** 7 **Mean age (SD):** 75.4 (9.0) **Sex (proportion male):** 3 of 7 **Type of stroke:** 2 ischaemic, 5 haemorrhagic **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Mean time since stroke (SD):** 154.8 (53.8) days **Presence of hemiparesis/plegia:** Yes (all participants had hemiparesis) **Presence of comorbid visual field defects:** Not reported
Interventions	**Description:** "We applied bipolar GVS using an electrical stimulation system (Chattanooga Intelect Advanced Combo; DJO Global, Vista, California, USA). Two surface self-adhesive electrodes (32mm× 32 mm) were put on the patient's skin over each mastoid – the cathode on the left, and the anode on the right. The intensity was set below the sensory threshold so that the patient was not aware of any electrical stimulation. The threshold was determined by increasing the current intensity slowly in steps of 0.1 mA until the patient indicated feeling a tingling sensation. The current was then reduced until the patient indicated that the feeling had disappeared. This threshold level differed between patients at a range of 0.4–2.0 mA. In the sham condition, the two electrodes were positioned as in the R-GVS, except that no electric current was applied." **Duration:** 20 minutes **Timing:** "A 48-h interval was established between sessions (each stimulation condition) to avoid carryover effects." **Co-interventions:** None reported

Outcomes	**Description:** Line cancellation from the BIT **Unit of measurement:** Number of cancelled lines **Upper/lower limits:** Lower limit = 0, upper limit = 36 High score is good The authors also investigated the correlation between change in line cancellation score and GVS total charge (current density x duration). For each session, the patient performed the line cancellation test before, at 10 min, and at 20 min after the start of the GVS

Nakamura et al. (2015) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	**Was the allocation sequence random?** stimulation order (unit of analysis in this case) was pseudorandomised - probably yes **Were there baseline imbalances that suggest a problem with the randomization process?** Unit of analysis = intervention allocation sequence, not participants. If a Latin square was used to randomize, there are 6 possible combinations. There were 7 participants in the study so not exactly equal but the imbalance is fairly small and unlikely to affect results - probably no **Is a roughly equal proportion of participants allocated to each of the two groups?** Probably yes
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias)	Unclear risk	**Were participants aware of their allocated intervention during each period of the trial?** Sensory threshold for stimulation found for each individual. However no ramp-up current applied during sham stimulation so participants may ahve noticed a difference between this and the active condition - probably no. **Were carers and trial personnel aware of participants' allocated intervention during each period of the trial?** Single blind (participants) - yes
Blinding of outcome assessment (detection bias)	Low risk	**Were outcome assessors aware of the intervention received by study participants?** Single blind (participants) - yes **Was the assessment of the outcome likely to be influenced by knowledge of intervention received?** Counting number of lines crossed is unlikely to be subjectively interpreted - probably no
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	No analysis plan available but all stated outcomes were reported at all timepoints and appropriate analysis was used.
Other bias	Low risk	n/a
Carryover effects	Unclear risk	"A 48-h interval was established between sessions (each stimulation condition) to avoid carryover effects." However, research is yet to establish exactly how long the effects of GVS last, therefore we can't be sure if this period of time is truly long enough to rule out carryover effects.
Period effects	Low risk	The mean time since stroke was 154.8 days and all participants were at least 3 months post-stroke. making any spontaneous recovery unlikely.

Oppenländer et al. (2015) - study characteristics

Methods	**Design**: repeated measures, crossover trial (3 conditions)
Participants	**Description**: 24 patients with unilateral right-sided stroke. For each of the four neglect tasks described below the patients were – depending on their performance in the sham-baseline condition – allocated to a patient group with neglect (RBD+) in a specific task or a patient group without neglect (RBD-) in that task. **Inclusion criteria:** right-handedness and a single right hemisphere infarction or haemorrhage. **Exclusion criteria:** other neurological or psychiatric diseases, epilepsy, sensitive skin on the scalp, metallic brain implants and medications altering the level of cortical excitability. **Method of neglect diagnosis:** Participants were grouped differently according to their score on the individual experimental tests. A healthy control group was used to create cut off scores for each of the four neglect tasks and stroke participants were grouped as having neglect/no neglect according to these scores. This means that some participants who were classed as having neglect on one task may not be grouped in the same way for a different task. **Number randomised:** 23. **Number allocated to RBD+ and RBD- groups changes according to outcome.** **Mean age:** 63.3 **Sex (proportion male):** 15 of 24 **Type of stroke:** 19 ischaemic, 4 haemorrhagic **Lesion location:** right hemisphere **First ever stroke?:** yes **Median time since stroke:** 2 months **Presence of hemiparesis/plegia:** 20 with hemiparesis, 4 without **Presence of comorbid visual field defects:** 17 without, 3 quadrantanopia, 3 homonymous hemianopia
Interventions	Sham, Cathode-left/anode-right GVS (CL/AR GVS), Anode-left/cathode-right GVS (AL/CR GVS) **Description:** In the first session all participants performed the four tasks while the electrodes of the stimulation device were fixed over the mastoids but not active (Sham=Baseline condition). To this purpose, after fixing the electrodes, the current was initially turned on until the participant perceived a tingling sensation, after which the current was smoothly turned off within 30 s, without the patient being aware of this (due to the subthreshold stimulation, see below). The stimulator was always invisible for the participant. This created an effective sham-stimulation since the individuals were not

	able to discriminate between the conditions where real current was applied and those where the current was turned off due to the imperceptible, sub-threshold intensity of the stimulus. In sessions 2 and 3, the patients repeated all experimental tasks, but received subliminal GVS (CL/AR or AL/CR GVS). The sequence of these 2 experimental conditions was counterbalanced within each group, with one half of the participants receiving CL/AR GVS in session 2 and AL/CR GVS in session 3, and the other half receiving the opposite sequence. Galvanic bipolar stimulation was delivered by a constant direct current (DC) stimulator (9 voltage battery, Type: ED 2011, manufacturer: DKI GmbH, DE-01277 Dresden). The carbon-rubber electrodes (50 mm×35 mm) were mounted on the skin over each mastoid (binaural stimulation), in order to activate the peripheral vestibular organs. Similar to Rorsman et al. (1999) we stimulated below the sensation threshold (subliminal) in order to prevent awareness of any electrical stimulation in the 3 experimental conditions. A switch on the stimulation device delivered current at individually adjusted levels for each patient. This threshold was individually determined in the Sham/Baseline condition by slowly increasing current intensity in steps of 0.1 mA until the participant indicated a tingling sensation. The current was subsequently reduced until the participant reported that the sensation had disappeared. This procedure was repeated a second time and the median of these 4 threshold values was defined as the sensory threshold. The thresholding procedure was always performed in the beginning of session 1 and lasted 30–60 s. **Duration:** Approximately one hour. GVS-stimulation started a few seconds before the task instruction by the experimenter and terminated immediately after completion of the four tests. **Timing:** The three sessions were performed on three separate days. The total experiment was completed within 5 days. Session 1 was always on day 1, session 2 on day 3 and session 3 on day 5, to control for carry-over effects. **Co-interventions:** none reported
Outcomes	**Number cancellation:** 200 digits (ranging from 0-9) were presented on a white sheet of paper, with each number appearing 10 times on the left of the sheet and 10 on the right. Participants were asked to cross out all occurrences of one number (e.g. all the 7s on the page). The centre of cancellation (CoC) was calculated. This score ranges from -1 to +1, with a score of +1 indicating that only right-sided targets were cancelled (indicating a left-sided neglect; v.v. for a score of -1). This test was included to assess egocentric neglect. Given that all participants had left-sided neglect, a lower score (closer to zero) is good. **Copy of symmetrical figures:** six different figures (two for each session) were given to participants and they were asked to copy them below. Missing details of the reproduced figures were counted. This test was included to assess object-centred neglect. Low score is good. **Horizontal line bisection:** the line bisection from the German version of the BIT was used. Three horizontal lines (200mm long) were presented to participants and they were instructed to mark the middle. Deviation from the midline (in mm) was measured. A negative score indicates a deviation to the left, and a positive score a deviation to the right. This test was included to assess both egocentric and object-centred neglect. GIven

that all participants had left-sided neglect, a lower score (closer to zero) is good as it indicates less of a rightwards deviation.

Text copying: six different sentences (two for each session) were shown to participants and they were asked to copy them. Omissions of letters and words were counted. Low score is good.

Outcomes were measured at baseline and during the three GVS conditions.

Oppenländer et al. (2015) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Unclear	**1.1 Was the allocation sequence random?** stimulation order (unit of analysis in this case) was counterbalanced - probably yes **1.3 Were there baseline imbalances that suggest a problem with the randomization process?** Unit of analysis = intervention allocation sequence, not participants. If a Latin square was used to randomize, an imbalance is unlikely given that there are 12 participants and therefore should be an equal number allocated to each intervention sequence - probably no **1.4 Is a roughly equal proportion of participants allocated to each of the two groups?** Probably yes.
Allocation concealment (selection bias)	Unclear	No information
Blinding of participants and personnel (performance bias)	Unclear	**2.1. Were participants aware of their allocated intervention during each period of the trial?** current turned on for a short period of time during sham to mimic any tingling or itchiness felt during true stimulation. True stimulation given at a subsensory level - probably no. **2.2. Were carers and trial personnel aware of participants' allocated intervention during each period of the trial?** Doesn't directly state that experimenters were blinded - probably yes
Blinding of outcome assessment (detection bias)	Low	**4.1 Were outcome assessors aware of the intervention received by study participants?** Not directly stated that assessors were blinded to participants' condition - probably yes **4.2 Was the assessment of the outcome likely to be influenced by knowledge of intervention received?** Measurement of deviation from midline hard to interpret subjectively - probably no
Incomplete outcome data (attrition bias)	Low	No missing data reported

Selective reporting (reporting bias)	Low	No analysis plan available but all stated outcomes were reported at all timepoints and analysis was appropriate.
Other bias	Unclear	The healthy control group used to create cut-off for the neglect assessments is significantly younger than the stroke group (median age 56, compared to 63.3), and may have performed better on the tasks due to this, potentially confounding results. The baseline session was also used as the sham session. It is possible that there was an improvement in performance due to sham and that the scores do not truly reflect baseline performance.
Carryover effects	Unclear	One day was left in between each stimulation session to control for this. However, research is yet to establish exactly how long the effects of GVS last, therefore we can't be sure if this period of time is truly long enough to rule out carryover effects.
Period effects	Low	Although spontaneous recovery does occur in neglect, and the majority of participants were in the subacute stage post-stroke, given that the study took place across a period of 5 days, it seems unlikely that this would have affected results.

Ruet et al. (2014) – study characteristics

Methods	**Design:** Repeated measures crossover (3 conditions)
Participants	**Description**: Four patients with unilateral spatial neglect **Inclusion criteria:** The main inclusion criteria were the occurrence of a first right ischemic or hemorrhagic stroke more than 3 months previously (to diminish the effects of spontaneous recovery), and a 20 cm line bisection test result suggestive of left USN (i.e. a rightwards deviation of more than 6.5 mm). **Exclusion criteria:** The exclusion criteria included the standard contra-indications to GVS (epilepsy, the presence of a pacemaker or intracranial ferromagnetic material, and skin damage over the mastoids), participation in another USN trial, corrected visual acuity that prevented close- up reading, vestibular damage and pre-existing neurological disease. **Method of neglect diagnosis:** Rightwards deviation greater than 6.5mm on a 20cm line bisection test. **Number randomised:** 4 **Mean age (SD):** 58.5 (14.06) **Sex (proportion male):** 1 **Type of stroke:** Not reported **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Median time since stroke:** 5.375 (4.42) **Presence of hemiparesis/plegia:** All patients displayed left proportional hemiplegia **Presence of comorbid visual field defects:** All patients displayed homonymous hemianopsia
Interventions	Right-cathodal GVS, left-cathodal GVS, sham GVS **Description:** Galvanic vestibular stimulation was applied with a regulated, direct-current device (Galvadyn, Electronic Conseil, Gallargues Le Montueux, France) with a maximum output current of 20 mA and a maximum output voltage of 30 V. The carbon electrodes (4 cmx6 cm) were covered with a saline- soaked sponge held in place over the mastoids with a strap. Each patient was exposed to three different stimulation conditions: cathode-left anode-right, cathode-right anode-left, and sham stimulation. The patients were not informed about the type of stimulation delivered at each session. During stimulation, the current intensity was increased manually by 0.1 mA per second until a value of 1.5 mA was reached. During increases and decreases in current intensity, GVS can induce a slight itching sensation. Hence, during sham stimulation, the current was increased in the same way and then turned off after a few seconds. Sham stimulations were performed with the cathode on the left mastoid and the anode on the right mastoid,

	making it impossible for the patient to distinguish between real and sham stimulations [32]. **Duration:** 20 mins **Timing:** The time interval between the stimulations was always greater than 48 h, so that the results were not perturbed by a post-effect of previous stimulation. **Co-interventions:** None reported
Outcomes	**Line bisection (batterie d'evaluation de la negligence (BEN)):** participants are asked to mark the midline of a 20cm line. Score is measured as deviation from midline (in mm; rightwards deviations = positive values, leftwards deviations = negative values). As all participants were suffering from left-sided neglect, a smaller value (closer to zero) = good. **Star cancellation task (BIT):** Participants are asked to cross out all the small stars on a page. Scores from this test range from 0 to 54, with a higher score indicating a greater number of cancelled stars and therefore better performance For each GVS condition, tests were performed before, during, immediately after and ten minutes after stimulation.

Ruet et al. (2014) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	**1.1 Was the allocation sequence random?** - stimulation order (unit of analysis in this case) was pseudorandomised - probably yes **1.3 Were there baseline imbalances that suggest a problem with the randomization process?** participants on study which means there must be an uneven number of participants allocated to each stimulation order. However, would be a very small difference so unlikely to be much of a problem - probably no **1.4 Is a roughly equal proportion of participants allocated to each of the two groups?** probably yes
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	High risk	**2.1.Were participants aware of their allocated intervention during each period of the trial?** - current turned on for a short period of time during sham to mimic any tingling or itchiness felt during true stimulation. However, for this to be an effective sham condition, true stimulation should be delivered at a subsensory threshold. Whilst the study claims that 1.5mA should be subsensory to all participants, another study in the the review (Oppenländer, 2013) determines this threshold

		individually and finds a range between 0.4-2mA, suggesting that some participants are likely to have been able to feel the stimulation in this study - probably yes. **2.2. Were carers and trial personnel aware of participants' allocated intervention during each period of the trial?** single blind design (participants only) - yes
Blinding of outcome assessment (detection bias)	Low risk	**4.1 Were outcome assessors aware of the intervention received by study participants?** single blind design (participants only) - yes **4.2 Was the assessment of the outcome likely to be influenced by knowledge of intervention received? -** Measurement of deviation from midline hard to interpret subjectively - probably no
Incomplete outcome data (attrition bias)	Low risk	Only 2 data points missing for whole study
Selective reporting (reporting bias)	Low risk	No analysis plan available. However, the stated outcomes are reported at all timepoints and the analysis used is appropriate.
Other bias	Low risk	
Carryover effects	Unclear risk	48 hours left between each stimulation session to control for any carryover effects. However, research is yet to establish exactly how long the effects of GVS last, therefore we can't be sure if this period of time is truly long enough to rule out carryover effects.
Period effects	Low risk	All participants had suffered their stroke at least 3 months prior to the study. This, coupled with the fact that the study was completed over a matter of days, not weeks or months, makes any period effects unlikely.

Sturt & Punt (2013) – study characteristics

Methods	**Design** **Experiment 1:** non-randomised, parallel (3 groups: left brain damage without neglect [LBD]; right brain damage without neglect [RBD-]; right brain damage with neglect [RBD+]). **Experiment 2:** non-randomised (one group, RBD+)
Participants	**Experiment 1** **Description**: 18 participants with first-ever stroke **Inclusion criteria:** All patients had a diagnosis of stroke confirmed by computed tomography (CT) scan. RBD patients were assigned to the neglect group (RBD+) if they scored 51 or less on the Star Cancellation Test (SCT; Wilson, Cockburn, & Halligan, 1987). To enter the study, patients must have been confirmed as being medically stable by the medical team. In addition, participants had their ear canals examined to ensure CVS was safe. **Exclusion criteria:** Patients were excluded from the study if they: (1) had a past medical history of inner ear problems, dizziness and nausea, (2) had excessive wax or a hole in their ear drum, (3) were unable to give informed consent, (4) were previously immobile and/or bed bound, (5) had an acute fracture, (6) were left handed and (7) had an initial Postural Assessment Scale for Stroke (PASS) score of above 33 or below 5. **Method of neglect assessment:** Participants were classed as having neglect if they had a score of 51 or less on the star cancellation test. **Number included:** 18 (6 LBD, 6 RBD-, 6 RBD+) **Mean age (SD):** LBD: 73.0 (15.9), RBD-: 67.8 (6.1), RBD+: 75.0 (13.3) **Sex (proportion male):** 3 of 6 in all 3 groups **Type of stroke:** Not reported **Lesion location:** 6 left hemisphere, 12 right **First ever stroke?:** Yes **Mean time since stroke (SD):** LBD: 47.2 (60.7) days, RBD-: 52.7 (48.2) days, RBD+: 19.2 (12.1) days **Presence of hemiparesis/plegia:** Not reported **Presence of comorbid visual field defects:** Not reported **Experiment 2** **Description:** Neglect as a result of right-sided stroke

	Inclusion criteria: See Experiment 1 **Exclusion criteria:** See Experiment 1 **Number included:** 6 **Mean age (SD):** 74.7 (3.4) **Sex (proportion male):** 3 of 6 **Type of stroke:** Not reported **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Mean time since stroke (SD):** 57.5 (92.6) days **Presence of hemiparesis/plegia:** Not reported **Presence of comorbid visual field defects:** Not reported
Interventions	**Experiment 1** **Description:** Caloric vestibular stimulation. "Participants were then positioned supine, lying with their head flexed 30 degrees forward, and made comfortable. The therapist (RS) then dribbled 60 ml of cold water (20˚C), using a syringe into the ear canal contralateral to their lesion side (i.e., right ear for LBD, left ear for RBD– and RBD+), over a period of 60 seconds." **Duration:** 60 seconds **Timing:** Administered once **Co-interventions:** None reported **Experiment 2** "The procedure was identical to Experiment One, except that CVS was administered to the ipsilesional (right) ear."
Outcomes	**Description:** Star cancellation test **Unit of measurement:** Number of stars cancelled. **Upper/lower limits:** Upper limit = 54, Lower limit = 0 High score is good.

Sturt & Punt (2013) - risk of bias

Bias	**Judgement**	**Support for judgment**
Random sequence generation (selection bias)	High risk	Non-randomised study. Bias due to confounding = moderate risk.
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding of participants and personnel (performance bias)	High risk	No mention of participants or personnel being blinded.
Blinding of outcome assessment (detection bias)	Low risk	Data assessed by a blinded researcher
Incomplete outcome data (attrition bias)	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	
Other bias	Low risk	No analysis plan available but all stated outcomes were reported at all timepoints and analysis was appropriate (however, not comparable to an RCT).
Carryover effects	Low risk	n/a to study design
Period effects	Unclear risk	Study carried out over a single day.

Utz et al. (2011) – study characteristics

Methods	**Design:** Repeated measures crossover (3 conditions)
Participants	**Description**: Six patients with right-hemispheric, vascular brain lesions and severe leftsided, visual neglect according to the results of six conventional neglect screening tests were included. Furthermore, another group of eleven patients with vascular, right-hemispheric brain lesions without visual neglect in the same screening tests was investigated. All Ps had visual acuity of at least 20/30 at a viewing distance of 0.4m and had received at least 8 years of education **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported **Method of neglect diagnosis:** Cutoff scores were calculated using data from a matched healthy control group. **Number included:** 17 (6 RBD+, 11 RBD-) **Mean age (SD):** RBD+: 70.8 (4.6), RBD-: 70.3 (12) **Sex (proportion male):** RBD+: 4 of 6, RBD-: 8 of 11 **Type of stroke:** RBD+: 2 haemorrhagic, 4 ischaemic, RBD-: 1 haemorrhagic, 10 ischaemic **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Time since stroke, mean (SD):** RBD+: 2.6 (1.6) months, RBD-: 1.9 (2.9) months **Presence of hemiparesis/plegia:** RBD+: 2 hemiplegia, 4 hemiparesis, RBD-: 3 = no, 1 hemiplegia, 7 hemiparesis **Presence of comorbid visual field defects:** RBD+: 2 = no, 4 = left homonymous hemianopia, RBD-: 10 = no, 1 = left homonymous hemianopia
Interventions	Left-cathodal GVS, right-cathodal GVS, sham GVS **Description:** Bilateral bipolar GVS was delivered by a (9-voltage) battery-driven constant direct current stimulator. Electrodes were covered with saline-soaked sponges with a size of 24cm2 and were put on the skin over each mastoid. Each patient underwent three different stimulation conditions. In one condition, the cathode was placed over the left mastoid and the anode over the right mastoid (left-cathodal GVS). In a second condition this electrode allocation was reversed (right-cathodal GVS) and the third condition consisted of sham (placebo) stimulation using the same electrode configuration as during left-cathodal GVS. Patients were blind regarding the type of stimulation they received. During the stimulation conditions current intensity was ramped up in steps of 0.1 mA/s until 1.5mA was reached and ramped down respectively at the end of stimulation. As the turning on of the current may be accompanied by slight itching and tingling sensations of the skin underneath the electrodes, current was

	increased in the same way during sham stimulation. However, after 10 s of GVS at 1.5 mA, current was ramped down again. **Duration:** 20 minutes **Timing:** The different stimulation sessions were separated by at least one day without GVS to prevent potential carry-over effects of prior stimulation on subsequent measurements. **Co-interventions:** none reported
Outcomes	An adapted Schenkenberg line bisection test was used to assess neglect at baseline and then during each of the three stimulation conditions. Participants were presented with 17 lines of different lengths, with five to the left of the page, five in the middle, and five on the right (and two used as an example). Participants had to mark the middle of the line and deviation from the midline was measured in mm (rightwards deviation = positive values, leftwards deviations = negative values). As all participants were suffering from left-sided neglect, a smaller score (closer to zero) indicates improvement. The authors also assessed the effects of GVS on deviation from midline in each section (left, right and middle) separately.

Utz et al. (2011) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Unclear risk	**1.1 Was the allocation sequence random?** Order of stimulation (unit of analysis in this case) was pseudorandomised - probably yes. **1.3 Were there baseline imbalances that suggest a problem with the randomization process?** Unit of analysis = intervention allocation sequence, not participants. If a Latin square was used to randomize, an imbalance is unlikely given that there are 6 participants and therefore should be an equal number allocated to each intervention sequence - probably not. **1.4 Is a roughly equal proportion of participants allocated to each of the two groups?** - probably yes.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias)	High risk	**2.1. Were participants aware of their allocated intervention during each period of the trial?** - However, for this to be an effective sham condition, true stimulation should be delivered at a subsensory threshold. Whilst the study claims that 1.5mA should be subsensory to all participants, another study in the the review (Oppenländer, 2013) determines this threshold individually and finds a range between 0.4-2mA, suggesting that some participants are likely to have been able to feel the stimulation in this study - probably yes.

		2.2. Were carers and trial personnel aware of participants' allocated intervention during each period of the trial? - only participant blinding mentioned - probably yes.
Blinding of outcome assessment (detection bias)	Low risk	**4.1 Were outcome assessors aware of the intervention received by study participants?** - no mention of outcome assessors being blinded - probably yes. **4.2 Was the assessment of the outcome likely to be influenced by knowledge of intervention received?** - line bisection results unlikely to be interpreted subjectively.
Incomplete outcome data (attrition bias)	Low risk	Outcome data available for all participants at all timepoints.
Selective reporting (reporting bias)	Low risk	No analysis plan available. However, the stated outcome (line bisection) is reported at all timepoints and the analysis used is appropriate.
Other bias	Unclear risk	Sham stimulation does not seem to be truly inert as it had an effect on results - "There was however no significant difference between left-cathodal and sham GVS regarding all bisected lines and furthermore an effect of sham stimulation occurred when right located lines were considered separately"
Carryover effects	Unclear risk	Stimulation sessions were separated by at least a day to minimise any potential effects of carryover. However, research is yet to establish exactly how long the effects of GVS last, therefore we can't be sure if this period of time is truly long enough to rule out carryover effects.
Period effects	Low risk	Although spontaneous recovery does occur in neglect, and some participants were in the subacute stage post-stroke, given that the study took place across a period of days rather than weeks or months, it seems unlikely that period effects would be an issue.

Volkening et al. (2018) – study characteristics

Methods	**Design:** parallel-arm RCT with minimisation (3 arms: cathode-left GVS [CL-GVS]; sham GVS; cathode-right GVS [CR-GVS])
Participants	**Description**: Right-handed stroke patients **Inclusion criteria:** (a) first-ever right-hemispheric stroke; (b) signs of left-sided spatial neglect according to a cut-off score criterion of ≤ 135 for mild neglect or suspicion of neglect in the Neglect test (NET, adapted German version of the behavioural inattention test); (c) age >18 years; (d) right-handedness (assessed during participation interview). **Exclusion criteria:** (a) any metal implants; (b) brain tumour; (c) previous epileptic seizure; (d) craniotomy; (e) degenerative or psychiatric disorder; (f) unable to perform the NET. **Method of neglect diagnosis:** A score of 135 or less on the NET **Number randomised:** 29 **Mean age (range):** CL-GVS: 70.6 (55-80), Sham: 70.4 (45-82), CR-GVS: 73 (61-83) **Sex (proportion male):** CL-GVS: 2 of 8, Sham: 4 of 8, CR-GVS: 4 of 8 **Type of stroke:** Not reported **Lesion location:** Right hemisphere **First ever stroke?:** Yes **Mean time since stroke (range):** CL-GVS: 1.9 (1.1-3.9) months, Sham: 1.0 (0.7-1.5) months, CR-GVS: 1.3 (0.4-2.2) months **Presence of hemiparesis/plegia:** Not reported **Presence of comorbid visual field defects (proportion with):** CL-GVS: 5 of 8, Sham: 5 of 8, CR-GVS: 6 of 8
Interventions	**Description:** Simultaneously, patients received GVS or sham stimulation. Bilateral bipolar GVS was delivered by a battery-driven, direct current stimulator (neuroConn Ilmenau, Germany). Two electrodes (anode and cathode) were inserted in natrium-chloride-soaked sponges (30 cm^2 each) and placed over both mastoids. Polarity placements were changed for each of the three stimulation conditions: For CL-GVS, the cathode was placed on the left and the anode on the right mastoid. This electrode setup was reversed for CRGVS. In the Sham-GVS condition, the electrodes were positioned as in the CL-GVS condition but the current was only ramped up and down for 30 s. The electrodes remained, however, attached to the head for the same duration as the verum stimulation sessions. For CL- and CR-GVS, the current was ramped up (in steps of 0.1mA/s) to 1.5 mA, kept there for 20 minutes, and ramped down again (in steps of 0.1 mA/s). Conforming to established safety limits, subjects were only stimulated for 20 minutes with a current intensity of 1.5 mA (Utz, Korluss, Schmidt, et al., 2011). Apart from the intervention,

	patients received occupational therapy and physiotherapy, but no other specific neglect training. **Duration:** 20 minutes **Timing:** The treatment started on the same day or the day after baseline assessments and consisted of daily training sessions (20 minutes), five days a week for a total of 10 to 12 sessions. **Co-interventions:** As standardised therapy, all patients received smooth pursuit eye movement training (SPT) and visual scanning training (VST). Both training programmes were presented on a 14.1-inch laptop monitor (60 Hz refresh rate). For SPT, computer-generated random displays of 350 dots (blue on a white background) moving coherently towards the left hemispace (speed: 6.9°/s), were presented (similar to Kerkhoff et al., 2013, 2014). Patients were instructed to look at the displays and make smooth pursuit eye movements towards the direction of motion and return to the rightward side of the screen whenever they had reached the leftward border of the screen. For VST, different training exercises from the therapy-program Cogpack® were used to facilitate exploration of the left hemispace. VST programmes and their difficulty levels were adjusted individually depending on each patient's capabilities. In each session, patients first received two–four runs of SPT, followed by VST.
Outcomes	**Description:** "Neglect test" battery (NET), a German adaptation of the Behavioural Inattention Test, which consists of 17 subtests (e.g. cancellation, reading, copying and picture scanning tasks). **Unit of measurement:** n/a **Upper/lower limits:** Lower limit = 0, Upper limit = 170 High score = good Used to classify neglect severity into three categories: 0–72 = very severe spatial neglect, 73–135 = severe neglect, 136–166 = mild neglect/ suspected neglect.

Volkening et al. (2018) - risk of bias

Bias	**Judgement**	**Support for judgment**
Random sequence generation (selection bias)	Low	For 17 participants, cards were drawn from sealed envelopes to ensure random allocation. The remaining 7 participants were allocated using minimisation according to score on the NET by a researcher not otherwise involved in the study.
Allocation concealment (selection bias)	Low	See above
Blinding of participants and personnel (performance bias)	Unclear	All participants stimulated at 1.5mA, individual sensory thresholds not determined. No mention of person delivering intervention being blinded.
Blinding of outcome assessment (detection bias)	Low	"Outcome measures were assessed by trained neuropsychologists, masked to treatment allocation and not otherwise involved in patients' treatment."
Incomplete outcome data (attrition bias)	High	Data only available for 83% of participants. **Analysis used**
Selective reporting (reporting bias)	Unclear	No analysis plan available, however, outcome was reported at all timepoints and an appropriate analysis was used.
Other bias	Unclear	All participants received optokinetic stimulation and visual scanning training alongside GVS, which the authors state may have led to an underestimation of the effect of the intervention.
Carryover effects	Low	Parallel design
Period effects	Unclear	Mean time since stroke is less than 2 months for all 3 groups. Given that the study takes place over 6 weeks+, there is the possibility that spontaneous recovery may have occurred.

Wilkinson et al. (2014) – study characteristics

Methods	**Design:** RCT with 3 parallel arms: participants assigned to either 1 active, 9 sham GVS sessions, 5 active, 5 sham GVS sessions, or 10 active, 0 sham GVS sessions.
Participants	**Description**: Individuals with neglect. A power analysis was used to calculate the number of participants needed in each arm to detect an effect size of 0.8 at 80% power with an alpha of 0.05. **Inclusion criteria:** Individuals were eligible if they scored ≤129 on the conventional tests of the Behavioral Inattention Test (BIT; Halligan et al., 1987); suffered a right unilateral stroke (confirmed by CT or MRI scan); ≥6 weeks post-stroke; ≥18 years; scored ≤2 on the 6-item screener for dementia (Callahan et al., 2002), and scored ≤29 on the Beck Depression Inventory (Beck et al., 1996). **Exclusion criteria:** Individuals were excluded if they showed evidence of moderate to severe aphasia on clinical examination and/or prior significant neurological or vestibular illness. Patients with electronic implants, such as cardiac pacemakers, were also excluded given the potential for electrical interference from the vestibular stimulator. **Method of neglect assessment:** Score of 129 or less on the conventional subtest of the BIT **Number randomised:** 55 **Mean age (SD):** 1 Active: 66.9 (10.6), 5 Active: 66.0 (9.37), 10 Active: 65.7 (8.72) **Sex (proportion male):** 1 Active: 12 of 15, 5 Active: 12 of 18, 10 Active: 13 of 16 **Type of stroke:** Not reported **Lesion location:** Not reported **First ever stroke?:** Not reported **Median time since stroke (interquartile range):** 1 Active: 68 (39-229) days, 5 Active: 75 (41-479) days, 10 Active: 94 (39-534) days **Presence of hemiparesis/plegia:** Not reported **Presence of comorbid visual field defects:** Individuals with suspected visual field loss were included but the presence of these defects were not recorded because formal field perimetry was not available for many participants
Interventions	**Description:** Bipolar, binaural current was delivered through a pair of 2x4 cm carbon-rubber, self-adhesive, disposable stimulating electrodes placed over participants' mastoid processes. To ensure complete electrical contact with the electrodes, surrounding skin was cleansed with an alcohol swab and conductive gel coated on the undersides of the electrodes. To induce leftward deviation in the lateral plane, the anode was placed over the left mastoid and the cathode over the right mastoid. The electrodes were connected to

	a Magstim Eldith Transcranial DC Stimulator Plus™ device that was pre-programmed to deliver either 0 or 1mA mean (0.5–1.5mA) noisy current. Participants were informed that although all participants would receive at least one session of active stimulation, the number of active sessions would vary from participant to participant. **Duration:** 25 minutes **Timing:** Stimulation was performed daily from Monday to Friday for two consecutive weeks. All sham sessions were administered first to ensure that, across participants, equal time had elapsed between the final session of active stimulation and the first follow- up assessment. In this condition, active stimulation was administered on the final (i.e. 10^{th}) stimulation day. **Co-interventions:** Participants' in-patient neglect treatment (typically visual scanning therapy but sometimes limited to the informal reminders given by occupational therapy staff to look left during functional activities) was suspended while they remained on-study.
Outcomes	The conventional subtest of the BIT (BITC) was used to assess neglect at baseline, on the final day of treatment, and 1, 2, and 4 weeks after this. **Upper/lower limits:** Lower limit = 0, upper limit = 146. High score is good. Cutoff of <129 indicates the presence of neglect Data regarding adverse events (including sickness, headache, tiredness, dizziness, pain behind ears or visual disturbance) and participant satisfaction was also recorded.

Wilkinson et al. (2014) - risk of bias

Bias	Judgement	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomisation was conducted at an independent facility.
Allocation concealment (selection bias)	Low risk	A stimulation protocol (active or sham) pre-determined by the randomization officer was naively administered by the experimenter by typing a 4 digit code (which changed every time) into the stimulation device.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind - GVS delivered at mean of 1mA for everyone (not individually determined). However, participants were asked about any sensations they felt during stimulation and the incidence of this was no higher in active than sham sessions. Experimenters were given a pre-determined code to administer sham or real stimulation.
Blinding of outcome assessment (detection bias)	Low risk	Study personnel administering GVS was blinded to condition - assume the same person also assessed outcome.
Incomplete outcome data (attrition bias)	Low risk	Outcome data available for nearly all participants.
Selective reporting (reporting bias)	Unclear risk	Reported analysis seems appropriate. However, no analysis plan is available to confirm what analysis was planned a priori.
Other bias	Unclear risk	There is no unconfounded control group for the study. Each arm received at least one session of active stimulation, therefore there is no 'pure' sham condition to compare active stimulation to. Although baseline measurements were taken, there were differences between the three arms in time since stroke and baseline BIT scores, which have been considered and controlled for using ANCOVA. However, this analysis method may not have fully controlled for these differences.
Carryover effects	Low risk	n/a to this study design
Period effects	Unclear risk	Some participants not yet in chronic phase of stroke so the potential for spontaneous improvement is there given that the study takes place over a matter of weeks.

Appendix C.

GRADE tables

In the main body of the review, differing stimulation conditions (e.g. CL-GVS and CR-GVS) were analysed separately, if possible. However, these data came from the same studies and subsequently share the majority of the characteristics evaluated here. Therefore, to save space and prevent the repetition of information, they been combined into single GRADE tables by outcome, with separate comments for each stimulation condition within the tables where necessary.

Effect of CL-GVS and CR-GVS vs. sham on line bisection (Oppenländer et al., 2015; Ruet et al., 2014; Utz et al., 2011).

Domain	Judgment	Support for judgement
Study design	Crossover trials	Pseudorandomised/counterbalanced
Overall risk of bias	Serious	Whilst many RoB domains were judged as low risk, several were judged as unclear risk, and blinding of participants and personnel was high risk.
Inconsistency	Very serious	**Clinical homogeneity:** all participants had neglect as a result of right hemisphere stroke. However, the samples differed in the prevalence of visual field defects (VFDs) and in length of time since stroke. **Methodological homogeneity:** there were differences in the way in which neglect was assessed across studies. The duration and intensity of stimulation differed across studies. The method for line bisection was not standardised across studies. **Statistical homogeneity:** **CL-GVS:** as revealed on the forest plot, the effect sizes from the three studies are inconsistent, with two favouring GVS, and one sham. **CR-GVS:** as revealed on the forest plot, the effect sizes from the three studies are inconsistent, with one study favouring GVS, one null, and one sham. **Both:** Although the I^2 statistic = 0%, and there is overlap between the 95% CIs, this information is not useful given how wide the CIs are, suggesting there is high uncertainty as to where the true effect may lie.
Indirectness	Not serious	These studies use populations, interventions, and outcomes which fit with our protocol. Although Utz and Oppenländer use participants with right-sided lesions but no neglect as a control group, we did not include these participants in the meta-analysis, rather using the neglect patients as their own control.
Imprecision	Very serious	The sample size for this outcome was very small (22 participants in total). In addition to this, the 95% CIs for the studies are imprecise, covering all three potential outcomes (favours GVS, sham, or null).
Publication bias	No	Although there were not enough studies included in this meta-analysis to formally test for publication bias, the fact that for CL-GVS, one study favoured sham, and for CR-GVS, one study favoured sham and one null, seems to imply that publication bias is not an issue for this comparison.
Dose response gradient	No	Oppenländer stimulated for the longest period (approximately one hour compared to the other studies' 20 minutes) and found the greatest intervention effect. However, the mean current intensity

		for the study was only 0.7mA, compared to 1.5mA used in the other studies, so they are not directly comparable. Therefore, it is difficult to come to a judgement about any potential dose response gradient.
Large effect	No	**CL-GVS:** dz = 0.33, **CR-GVS:** dz = 0.16
Plausible confounding	Yes	The results of Utz suggest that the sham condition in the study may have not been completely inert: there was no difference between sham and CL-GVS conditions when looking at overall performance, and an improvement during sham was seen when right lines only were considered. This may have reduced the estimate of effect size given that there would be a smaller difference between the experimental and sham conditions than if the sham was truly inert.
Overall certainty of findings	Low	

Effect of GVS vs. sham on cancellation score post-intervention (Nakamura et al., 2015; Oppenländer et al., 2015; Ruet et al., 2014)

Domain	**Judgement**	**Support for judgement**
Study design	Crossover trials	Pseudorandomised/counterbalanced
Overall risk of bias	Serious	Whilst many RoB domains were judged as low risk, several were judged as unclear risk, and blinding of participants and personnel was high risk for one.
Inconsistency	Very serious	**Clinical homogeneity:** all participants had neglect as a result of right hemisphere stroke. However, samples differed in the length of time since stroke. **Methodological homogeneity:** there were differences in the way in which neglect was assessed across studies. Whilst cancellation tasks were used for all, they were not identical. The duration and intensity of stimulation also differed across studies. **Statistical homogeneity:** **CL-GVS:** all studies found no significant difference between the intervention and control **CR-GVS:** two studies found no significant difference between intervention and control, whilst one found a positive effect of the intervention
Indirectness	Not serious	These studies use the population, intervention, and outcome which fit with our protocol. Although Oppenländer uses participants with right-sided lesions but no neglect as a control group, we did not include these participants in the meta-analysis, rather using the neglect patients as their own control.
Imprecision	Very serious	The sample size for this outcome was very small (23 participants in total). The standard deviations (in particular for Ruet), are large compared to the means.
Publication bias	No	There were not enough studies included in this comparison to formally test for publication bias. However, whilst two of the studies report a favourable effect of GVS using their own comparisons, one found no significant changes, possibly suggesting the absence of publication bias.
Dose response	Yes	Nakamura finds a significant positive correlation between total charge and cancellation score, suggesting that a dose response may be present.
Large effect	n/a	No statistical analysis performed therefore effect size was not calculated
Plausible confounding	No	
Overall certainty of findings	Low	

Effect of GVS on pre- and post-stimulation BIT/NET score (Volkening et al. 2018; Wilkinson et al., 2014)

Domain	**Judgement**	**Support for judgement**
Study design	Randomised trials	3 parallel arms
Overall RoB	Serious	Whilst many RoB domains were judged as low risk, several were judged as unclear risk, and incomplete outcome data was high risk for one.
Inconsistency	Very serious	**Clinical homogeneity:** all participants had neglect as a result of right hemisphere stroke. Some participants from both samples had hemianopia. The study samples differed in their length of time since stroke. **Methodological homogeneity:** both studies used clinical cut-offs on the BIT/NET to diagnose neglect. The duration and intensity of stimulation differed across studies. Volkening also uses concurrent optokinetic stimulation and visual scanning training. **Statistical homogeneity:** for CR-GVS, one study showed a positive effect of the intervention, and one showed no difference. n/a to CL-GVS as only one study investigated this intervention.
Indirectness	Not serious	These studies use populations, interventions, and outcomes which fit with what was outlined in the protocol.
Imprecision	Serious	The sample size for this outcome was small (8 for CL-GVS and 24 for CR-GVS).
Publication bias	No	There were not enough studies using this outcome to conduct a formal assessment of publication bias. However, the fact that one study found positive effects of GVS and one found no significant effects suggests a lack of publication bias.
Dose response	No	Wilkinson found that one session of active GVS resulted in the same level of improvement as 10 sessions.
Large effect	n/a	No statistical analysis performed therefore effect size was not calculated.
Plausible confounding	Yes	The use of concurrent optokinetic stimulation and visual scanning training in Volkening's study may have led to an underestimation of the effects of the intervention.
Overall certainty of findings	Low	

Effect of CVS on pre- and post-stimulation cancellation score (Cappa et al. 1987; Sturt &Punt, 2013)

Domain	**Judgement**	**Support for judgement**
Study design	Non-randomised	
Overall risk of bias	Very serious	The non-randomised nature of these studies meant that multiple RoB domains were classed as high risk
Inconsistency	Very serious	**Clinical homogeneity:** all participants had neglect as a result of right hemisphere stroke. However, the samples differed in their length of time since stroke. **Methodological homogeneity:** both studies utilised cancellation tasks to diagnose neglect in their respective samples, however, the tasks themselves were not identical. Cappa uses iced water to irrigate the ear canal, whilst Sturt uses water at 20 degrees. Cappa also uses iced water in the contralesional ear in three participants and warm water in the ipsilesional ear for one (in the same sample) yet makes no reference to the fact that this may have had differing effects. **Statistical homogeneity:** for contralesional stimulation, one study found no effect and one favoured CVS. n/a to ipsilesional stimulation as only one study investigated this.
Indirectness	Not serious	These studies use the population, intervention, and outcome which fit with our protocol. Although Sturt uses participants with right- and left-sided lesions but no neglect as control groups, we did not include these participants in our comparison, rather using the neglect patients as their own control so this does not affect directness.
Imprecision	Very serious	The sample size for this outcome was very small (10 participants for contralesional CVS and six for ipsilesional). The standard deviations (in particular for Cappa), are large compared to the means.
Publication bias	No	There were not enough studies included in this comparison to formally test for publication bias.
Dose response	No	As both studies administered the treatment only once, and for the same length of time (1 minute), it is not possible to ascertain whether there is any dose response.
Large effect	n/a	No statistical analysis performed therefore effect size was not calculated
Plausible confounding	No	n/a
Overall certainty of findings	Very low	

Effect of VR vs control on BIT score (Dai et al., 2013)

Domain	**Judgement**	**Support for judgement**
Study design	RCT	Cluster-randomised
Overall risk of bias	Serious	The study was judged to be at high risk of bias in the selective reporting domain.
Inconsistency	Serious	**Clinical homogeneity:** all participants enrolled in the study were suffering from neglect as a result of right hemisphere stroke. There were no significant differences in age, gender, number of days since stroke, or cognitive functioning at baseline. However, the presence of visual field defects was not reported.
Indirectness	Not serious	The study uses populations, interventions, and outcomes which fit with our protocol.
Imprecision	Very serious	The sample size for the study was only 48 and the standard deviations were large compared to the mean.
Publication bias	No	It was not possible to formally test for publication bias.
Dose response	Yes	A significant effect of time was found, with participants showing greater improvement with more VR, which suggests a dose response.
Large effect		No
Plausible confounding	Yes	The control group completed exercises which are likely to have activated the vestibular system in a similar way to VR, potentially reducing the difference between experimental groups.
Overall certainty of findings	Low	