The Modulation of Visual Spatial Memory by Galvanic Vestibular Stimulation

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Declaration

The research presented in this thesis was conducted at the School of Psychology, University of Kent, whilst the author was a full-time postgraduate student. The author received a University of Kent 50th Anniversary Graduate Teaching Assistantship Award to support this research. The theoretical and empirical work presented is original work completed by the author under the supervision of Professor David Wilkinson and the experiments were conducted with limited assistance from others. The author has not been awarded a degree by this, or any other University for the work included in this thesis.

Publications

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Abstract

It is now widely accepted that the vestibular system not only affects autonomic motor function but cognitive function too, most notably visuospatial learning and memory. While many studies have explored this association from a biological perspective, few have done so from a psychological one. The aim of this thesis was to identify a possible psychological mechanism by which the vestibular system specifically interacts with spatial memory processes. Artificially stimulating the vestibular system via trans-mastoidal galvanic current (aka GVS) provides a controlled means by which this vestibular-visual spatial interaction can be explored. In a previous study, we showed that search for a location of a 2-D static visual target was facilitated when that target location was initially encoded with in the presence of a brief, subsensory galvanic signal (L. Smith, Gkioka & Wilkinson, 2020). In Chapter 2, I replicated this GVS advantage in new 2-D visual arrays, showing that temporally co-incident vestibular activation can facilitate visual search and spatial memory in subsequent encounters of that same 2-D spatial representation presented during encoding. Chapter 3 explored whether this cross-modal priming would hold in a dynamic 3-D virtual environment, in which external landmarks were manipulated (present/absent) to test whether the GVS priming is dependent on the location of the target relative to other visual stimuli. The GVS prime was more effective in the presence of visual landmarks, whereby participants chose direct routes more frequently and navigated to the target location with higher accuracy. Finally in Chapter 4, I demonstrated that these beneficial priming effects were also evident in people with dementia who showed visuo-spatial short-term memory impairment. Together these studies suggest that the human brain can make use of momentary vestibular signals to help individuate the encoding of visuospatial memories. The results also provide justification for trialling the therapeutic effects of GVS in amnestic populations.

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First and foremost, I would like to express my sincere gratitude to Professor David Wilkinson for his supervision on the project. I have been more than fortunate to be included in his team and receive his supportive and insightful guidance. I would also like to extend a huge thank you to Laura Smith, Ph.D. for her helpful advice and input, as well as Dr Mo Sakel for all his crucial input in the patient study. A special thank you also goes to John Allen and the rest of the technical team; without their expertise I would never have been able to develop the paradigms used in this thesis.

Due to the COVID-19 pandemic, the study described in Chapter 4 was interrupted and the people with Alzheimer's disease who were due to take part in the study no longer could. These people could also not participate in a VR study using the paradigm described in Chapter 4.

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Chapter 1
General Introduction

The vestibular system

Although not first in mind when thinking about traditional sensory systems, the vestibular system comprises our sixth sense. The vestibular organs, also known as the balance organs, are elegant sensory receptors housed inside the inner ear within the space equivalent to that of an aspirin tablet and are enclosed within the petrous part of the temporal bone, which also contains a part of the hearing apparatus, the cochlea (Sohmer & Freeman, 2000). Evolved around 500 million years ago, they constitute one of the most complex anatomical structures in vertebrates; first to develop during embryogenesis and almost fully functional at the time of birth (Zabolotnyi & Mishchanchuk, 2020), they have evolved to detect head movement relative to the world around us to provide information about the position of the head and body in space at all times and to keep them balanced and oriented towards objects of interest (Angelaki & Cullen, 2008). In addition, as is the case with all terrestrial and aquatic animals that need to know which way is up and which way gravity acts, the vestibular organs provide our brains with a deep understanding of how the force of gravity affects our bodies, therefore contributing to an internal representation of gravity at any time, as well as with a sense of how gravity affects moving objects around us, hence helping predict their trajectory around our bodies with startling accuracy (Day & Fitzpatrick, 2005; Khan & Chang, 2013)

Until recently these small structures in the inner ear were considered just a mechanical system that senses rotational movements and linear accelerations of the head in three dimensions to generate spinal and occular reflexes that control postural balance and ocular fixation during head and body movement (Bronstein, Patel & Arshad, 2015; Hitier, Besnard & Smith, 2014). Although the vestibular apparatus is considered to be the sixth sense, it differs from the traditional sensory systems (visual, haptic, auditory, olfactory and gustatory) in that vestibular

signals in the central nervous system do not, unless damaged, produce a readily recognisable, conscious sensation; instead they become immediately multimodal as visual, proprioceptive and motor inputs are continuously integrated in the vestibular pathways to co-ordinate bodily movements, posture and gaze control (Angelaki & Cullen, 2008). Even if there is no over sensation from these organs, the vestibular apparatus continuously bombards the brain with messages; when the head is not accelerating or rotating in space for example and there is complete lack of motion, the vestibular system is still firing, signalling the relentless pull of gravity (Fitzpatrick & Day, 2004).

This silent sense, although highly complex and different to other senses, has remained an underappreciated sensory organization until recently (Leong et al., 2019). It has been only these last two decades that a substantial body of evidence has emerged suggesting that the contribution of this sensory system goes beyond the low-level reflex control of gaze orientation and postural control (Ferrè & Haggard, 2020) and has now a crucial role in cognition (Hitier et al., 2014). Indeed, it has now been established that vestibular cognition involves communication between the peripheral vestibular apparatus, the ocular system, postural muscles and several brain areas (the brainstem, cerebellum and the cortex, Dobbels et al., 2020; Grabherr et al., 2015; Khan & Chang, 2013) as it will be explained later in this chapter. Vestibular contributions to motor, cognitive, affective and perceptual functions are increasingly being reported that go beyond autonomic control and allow the body not only to maintain balance and process correctly visual images during motion (Fitzpatrick & Day, 2004; Khan & Chang, 2013) but also play an important role in spatial perception and memory (Hitier et al., 2014; P. F. Smith & Zheng, 2013).

Because of the multimodal integration explained above, the unique contribution of the vestibular system goes undetected under normal life conditions and its existence is only recognizable under pathological conditions such as when damage to the vestibular system occurs; then symptoms such as vertigo (a sensation of spinning and loss of balance), seasickness or dizziness present themselves. Indeed, when one experiences vestibular-induced vertigo, one

can really appreciate its role in spatial perception and cognition which appear to change dramatically when the environment starts spinning and spatial perception seems distorted (Hitier et al., 2014). Indeed, the cognitive effects of vestibular loss are believed to be mainly due to the critical contribution that the vestibular apparatus makes to brain areas involved in spatial perception and memory (P. F. Smith & Zheng, 2013). Within the scientific community, this emerging notion of vestibular cognition has attracted curiosity and intrigue although the mechanisms behind this interaction remain largely unknown (P. F. Smith & Zheng, 2013).

Overview

This thesis aims to build on the current understanding of how the vestibular system affects cognition, particularly visuospatial memory. As it will be mentioned in more detail in the next section, the vestibular system has had a long association with spatial memory in the neurobiological literature (P. F. Smith, Geddes, Baek, Darlington & Zheng, 2010) however in psychological terms this has not been well investigated. In this thesis, three empirical chapters will explore how visuospatial memory is affected by artificially stimulating the vestibular system in normative and clinical populations. In short, the findings unveil significant improvements in spatial memory tasks in both normative and clinical populations when vestibular signals can be used to individuate one visuospatial memory from another. These data help clarify our understanding of how the vestibular system interacts with other perceptual systems and may also be of neuro-rehabilitative relevance too.

This chapter will begin by highlighting the anatomical structures of the vestibular system followed by a review of what is already known about how vestibular and visuo-spatial processes interact. Finally, the chapter will summarize the specific aims of the thesis and briefly introduce the experiments conducted in order to investigate these aims.

Anatomy

The vestibular system consists of peripheral and central components. The peripheral components are situated in the inner ear labyrinth of the pyramid of the petrous portion of the temporal bone, in close proximity to the cochlea, and consist of a body labyrinth and a membranous labyrinth (Khan & Chang, 2013; Zabolotnyi & Mishchanchuk, 2020). The bony labyrinth consists of the cochlea, an oval cavity called the vestibule and the semi-circular canals (see Figure 1.1). The structures of the bony labyrinth are filled with a fluid that is continuous with and similar in composition to cerebral spinal fluid, known as perilymph (Khan & Chang, 2013). The membranous labyrinth houses the sensory epithelium and structures of the vestibular apparatus and is suspended in the perilymph within the bony labyrinth. Endolymph flows throughout the structures of the membranous labyrinth and is similar in composition with intracellular fluid (Khan & Chang, 2013). The central components on the other hand are composed of the conductive part and vestibular centres in the brain stem, cerebellum and cortex (Khan & Chang, 2013; Zabolotnyi & Mishchanchuk, 2020).

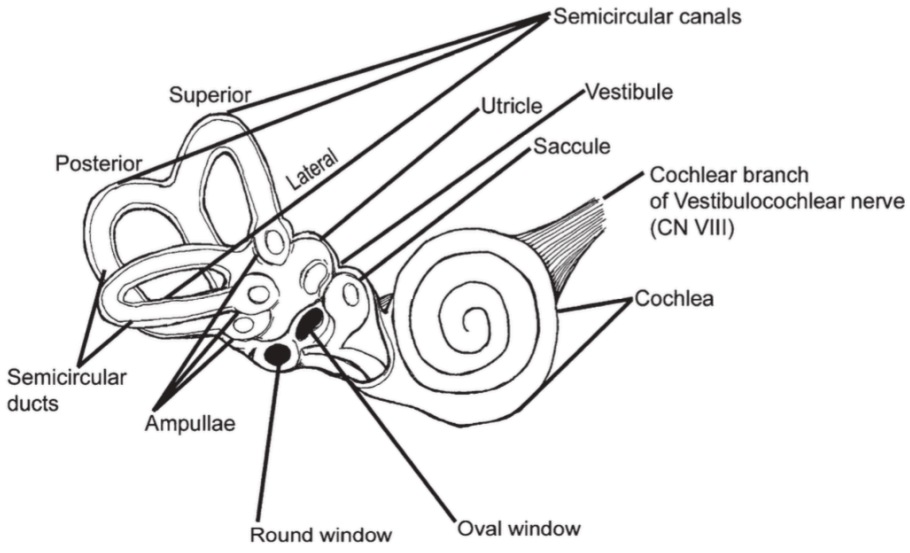

Figure 1.1. Schematic representation of the structures consisting the peripheral vestibular organs. Retrieved from Khan and Chang (2013).

The peripheral vestibular apparatus is composed of five distinct sensory end-organs: two

otolith organs (the utricle, which is orientated horizontally, and the saccule oriented vertically), and three semi-circular ducts (lateral, superior and posterior, see Figure 1.1). The two otolith organs are located in the vestibule whereas the semi-circular ducts are enclosed within the bony semi-circular canals (see Figure 1.1). These organs help perceive the variety of physical head motions we experience while we move in space and are critical for the body to maintain equilibrium within the environment (Khan & Chang, 2013). The semi-circular canals are involved in detecting head rotations whereas the otolith organs detect linear acceleration and head orientation with respect to gravity (Angelaki & Cullen, 2008).

Similar to hearing processes, signals from the above sensory receptors are transduced into behaviourally relevant receptor potentials by the use of rod-shaped sensory mechanoreceptors called hair cells embedded in a membrane of neuroepithelium, as well as the use of fluid movements (Khan & Chang, 2013; Highstein, Fay & Popper, 2020). Hair cells are located in both structures of the vestibular apparatus (otolith organs and semi-circular ducts) and the semicircular canals (Highstein et al., 2020). They are comprised of 70-100 stereocilia and a single large kinocilium immersed in a gelatinous mass (the cupula, see Figure 1.2) which contains calcium carbonate crystals known as otoliths that help provide weight to the cupula (Khan & Chang, 2013). When the head is rotated, movement of the endolymph fluid distorts the shape of the cupula which in turn bends the stereocilia and increases/decreases the firing rate (vestibular afferents continuously fire even when the body and head are at rest and motionless, Angelaki & Cullen, 2008) depending on the direction of movement (see Figure 1.2 A). In a similar fashion, when the head undergoes a gravitational acceleration (either vertical or horizontal, see Figure 1.2 B), the gelatinous mass moves and bends the hair cells within the ultricle and saccule which transform mechanical displacement into electric energy (Kingma & van de Berg, 2016) and in turn transmits information to primary processing centers in the brain stem and the cerebellum via the vestibular nerves to help perceive head motion or tilt (Khan & Chang, 2013).

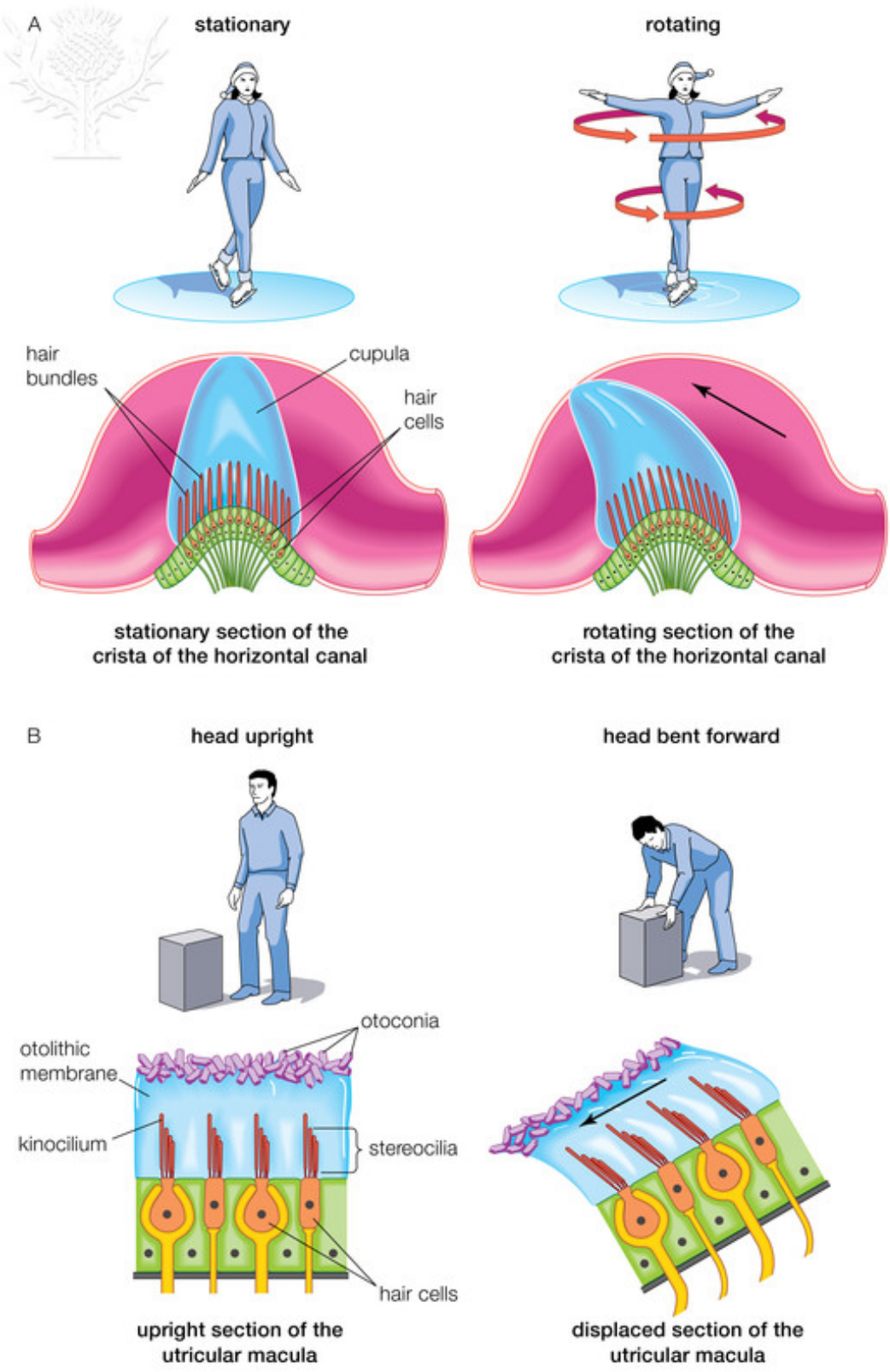

Figure 1.2. Schematic representation of the vestibular hair cells under stationary/rotating (A) and head upright/bent forward (B) conditions. (Downloaded from https://content.byui.edu/file/a236934c-3c60-4fe9-90aa-d343b3e3a640/1/module12/readings/sense_balance_equilibrium.html).

Information from the semicircular canals and the otolith organs is complementary in helping estimate the relative position of the body within space (Highstein et al., 2020) and is in turn used in conjunction with information from postural muscles, the ocular system and cortical areas (the brainstem, cerebellum and cortex) to coordinate vital primary reflexes, such as the vestibulo-ocular-reflex - VOR - and the vestibulospinal reflex which help with correct processing of visual representations during movement and proper orientation of the eyes and body in response to head motion (Khan & Chang, 2013; Tascioglu, 2005). This information also contributes towards maintaining balance, spatial orientation and similar physical motions experienced in day-to-day life (Angelaki & Cullen, 2008), as well as more complex cognitive functions, which are explained in detail in the next section.

Vestibular – cortical interactions

As mentioned briefly in the previous section, vestibular information becomes immediately multisensory and multimodal at the central level (Angelaki & Cullen, 2008), with visual/vestibular and proprioceptive/ vestibular interactions taking place throughout the central vestibular pathways. Signals from postural muscles, skin and joints are used in conjunction with information from the ocular system and cortical areas (the brainstem, cerebellum and cortex) to coordinate a wide range of brain functions, ranging from the most automatic reflexes (the VOR and the vestibulospinal reflexes) that maintain balance and motor control (Angelaki & Cullen, 2008; Khan & Chang, 2013; Tascioglu, 2005), to the highest levels of bodily self-consciousness (Blanke, Ortigue, Landis & Seeck, 2002) and self-motion perception (Angelaki & Cullen, 2008).

The vestibular system's contribution to this range of reflexive and higher-level operations is partly evidenced by its widespread connectivity. These small structures in the inner ear differ from other primary sensory processing systems in that the latter systems are organized in a topographic and orderly manner, whereby projections from peripheral sensory organs extend through modality-specific, primary thalamic nuclei to their respective primary cortical maps (Leong et al., 2019). The vestibular signals on the other hand converge with other sensory

modalities throughout the central nervous system. Indeed, an increasing amount of cortical and subcortical areas activated by the vestibular system (also known as vestibular cortical projection areas) have been revealed over the last years from both neuroanatomical and functional studies (Hitier et al., 2014) as well as studies that selectively and artificially stimulate the vestibular system (Gurvich, Maller, Lithgow, Haghgooie & Kulkarni, 2013; Lopez & Blanke, 2011). It is now widely known that a continuous flow of central vestibular processing is distributed across multiple brain regions, such as the temporo-parieto-insular and retro-insular cortices; the parietal, cingulate and frontal cortices as well as several subcortical areas such as the thalamus, basal ganglia and cerebellum (Highstein et al., 2020; Hitier et al., 2014). This multisensory convergence of vestibular signals with somatosensory and visual inputs has been shown to occur across multiple vestibular relays located, inter alia, in the vestibular brainstem nuclei, central thalamic nuclei, basal ganglia and cerebral cortex (especially insula, parietal operculum and temporo-parietal junction; Hitier et al., 2014; Lopez, 2013; Lopez et al., 2012; Lopez & Blanke, 2011; Mazzola et al., 2014; Zu Eulenburg et al., 2012).

Given the physical constraints that limit subjects inside the scanner (i.e., inability to perform balance- and motion-based tasks), one could argue that the cortical areas so far identified by means of fMRI and PET under-estimate the full pattern of cortical connections. To help overcome this, a recent animal study used optogenetic stimulation, a technique that modulates the activity of excitatory neurons in the ipsilateral medial vestibular nucleus using light (instead of stimulating the vestibular nerve or labyrinth) and uncovered extensive fMRI activations bilaterally at the level of thalamus and sensorimotor cortex (Leong et al., 2019). Most importantly and of most relevance to this thesis, this study showed that the spatial extent of vestibular projections (dentate gyrus, entorhinal cortex and subiculum) is wider than previously shown by previous neuroimaging studies that have artificially stimulated the vestibular system (see Bense, Stephan, Yousry, Brandt & Dieterich, 2001; Dieterich & Brandt, 2008; Kirsch et al., 2016). There projections were shown to spread across cortical and sub-cortical areas specifically

involved in spatial navigation and spatial memory and especially engaging thalamic nuclei and hippocampal formation regions (Leong et al., 2019).

The complexity and limitations of applying the invasive technique by Leong et al., (2019) in humans leaves still many unanswered questions about whether vestibular signals follow these wider cortical distributions in human cortices. The manner in which this input influences cognitive processes also remains still unclear (Hanes & McCollum, 2006; Lajoie, Marigold, Valdes & Menon, 2021; Leong et al., 2019). However, as it will be explained in detail in the next section, these data combined with other studies (such as neuroimaging /lesion/ neurochemical studies) in humans and animals have provided strong evidence that the vestibular system plays an especially crucial role in various cognitive functions linked to spatial cognition.

Vestibular cortices and spatial cognition. Several studies that have selectively stimulated the vestibular system have enriched the neuroanatomical understanding of the involvement of vestibular signals in spatial cognition by highlighting vestibular cortical projections areas influenced by vestibular input (Hitier et al., 2014; Hüfner et al., 2007; Lajoie et al., 2021; Leong et al., 2019). Five different central vestibular processing pathways (see Figure 1.4) have been hypothesised to convey vestibular information to the hippocampus during spatial processing: (1) the vestibulo-thalamo-cortical pathway, which is hypothesised to transmit spatial inputs about one's surroundings through the thalamus via the parietal cortex and the ento- or perirhinal cortices to the hippocampus where it provides information about spatial representations and self-object motion inputs; (2) the head direction system passing through the dorsal tegmental nucleus and anterodorsal thalamic nucleus to the entorhinal cortex and hippocampus, proposed to convey inputs about head direction; (3) the pathway passing through the nucleus reticularis pontis oralis, the supramammillary nucleus and the medial septum to the hippocampus, suggested to provide information about hippocampal theta rhythm and memory processing, learning and self-motion; (4) the pathway via the cerebellum and the ventral lateral nucleus of the thalamus, which transmits information for spatial learning, and (5) a putative

pathway passing through the basal ganglia (Hitier et al., 2014).

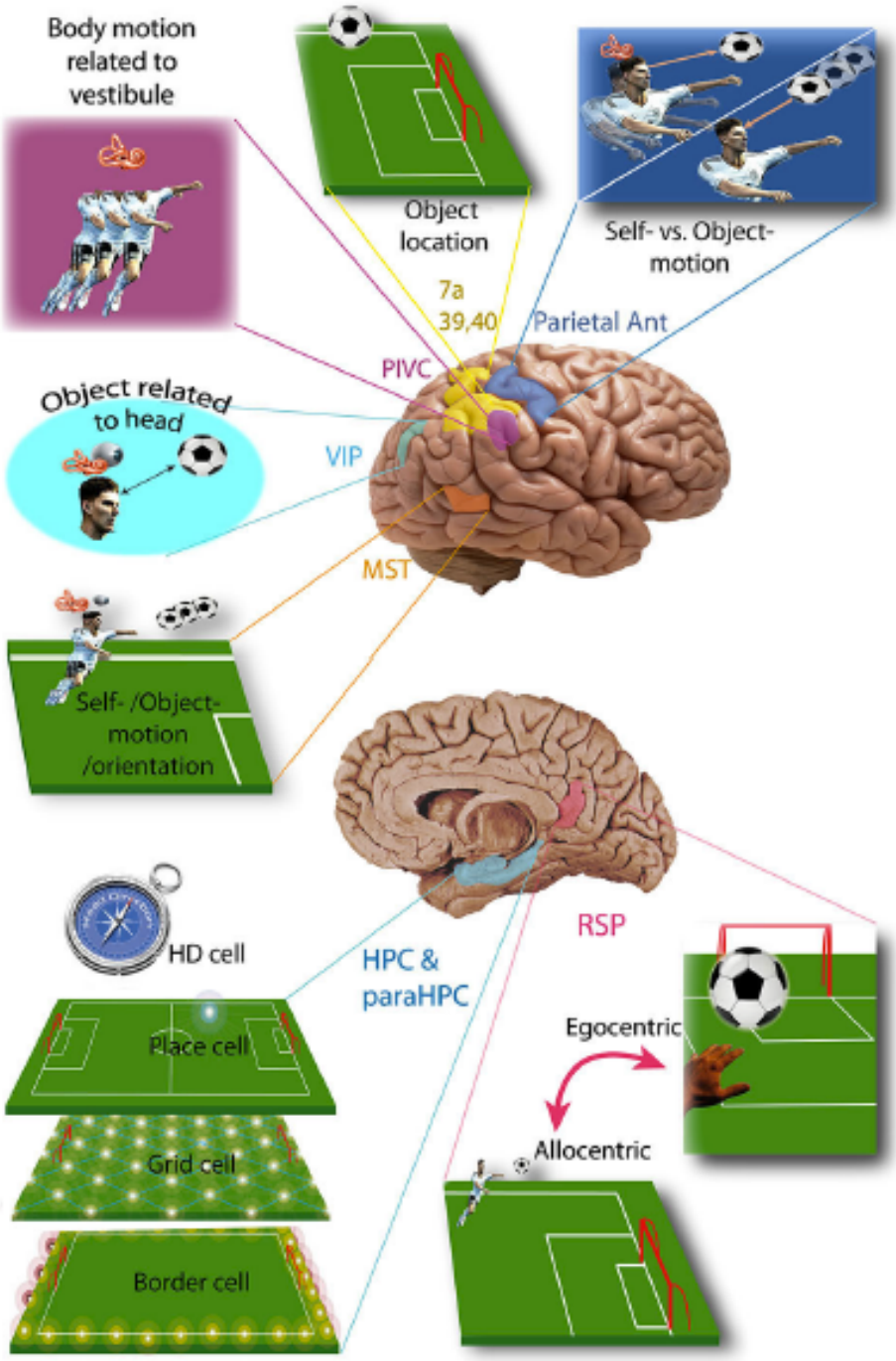

Figure 1.3. Vestibular and spatial cognition link. See text for more information. Illustration taken from Hitier et al., (2014).

Although the above studies contribute towards our understanding of the anatomical network that serves vestibular cognition, it is worth noting that the high level of multi-sensory convergence and pathway overlap muddle the picture (Hitier et al., 2014). Major questions still remain unanswered and require further investigating (Hitier et al., 2014).

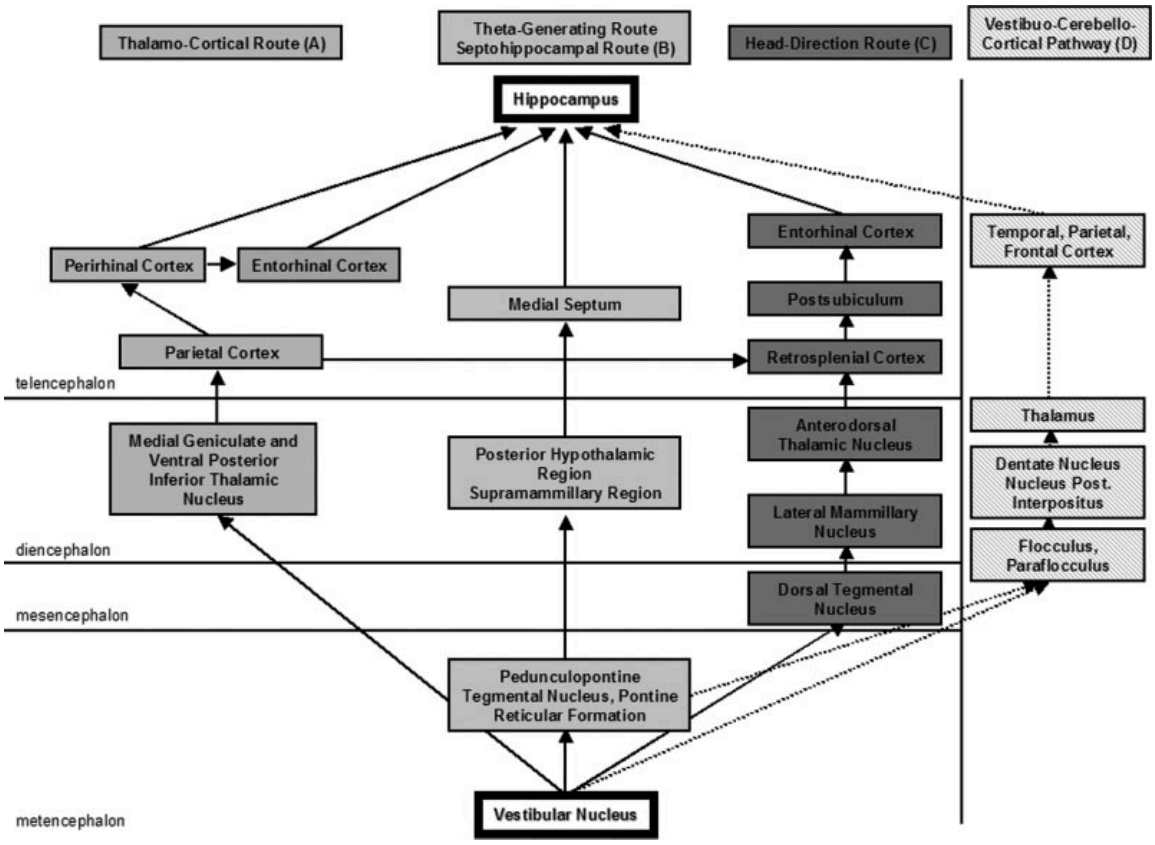

Figure 1.4. Hypothetical pathways used by vestibular inputs to reach the hippocampus formation and therefore putative ways that the vestibular system could be contributing to spatial memory and navigation. Data for pathways are derived mostly from animal studies. See text for a firth pathway. Illustration taken from Hüfner et al., (2007).

The next paragraphs will summarise an emerging body of animal, normative and clinical studies that selectively stimulate the vestibular system and investigate further the relationship between the vestibular system and spatial memory. To summarise the points expanded upon in the next section, all the following studies are in line with the neuroanatomical studies described above and help construct a strong connection between vestibular input and spatial memory, however, the psychological mechanisms that underlie such interactions still remain unclear.

Vestibular input and spatial memory. It is now well-known that spatial navigation requires the creation of an "inner cognitive map", a continuous representation of an animal's movements within a three-dimensional (3-D) environment whose coordinates are provided by idiothetic cues from peripheral vestibular and proprioceptive inputs, alongside visual (and

auditory/olfactory) cues that are used by the animal to remember their way through a familiar environment (Brandt, Glasauer & Zwergal, 2017; Dobbels et al., 2020; P. F. Smith et al., 2010). During locomotion, these cues are essential to continuously update this map which is believed to be partly computed in the hippocampus and the parahippocampal area (entorhinal, perirhinal and postrhinal cortices, Brown & Taube, 2007). Its construction is based on several cooperative cell types: place cells, border cells, grid cells, angular head velocity cells and head direction cells, which are all prominent in these brain areas (Brandt et al., 2017; Dobbels et al., 2020; Hitier et al., 2014). Place cells are believed to be the cellular substrate for integration of this spatial representation and their activity is highly correlated with the location of the subject in a particular place in the environment (Hitier et al., 2014; O'Keefe, 1976). Contrary to place cells, grid cells fire in multiple specific locations forming a grid like pattern and provide a 2-dimensional metric of space (Hafting, Fyhn, Molden, Moser & Moser 2005). Border cells are highly activated at the boundaries of an environment whereas the head direction cells discharge when the head is tuned to a particular direction (Hitier et al., 2014).

The construction of inner cognitive maps of the environment (Gavrilov, Wiener & Berthoz, 1995; Moser, Kropff & Moser, 2008; Wiener, Kurshunov, Garcia & Berthoz, 1995) and the retrieval of navigational paths is of vital importance in spatial memory (Pfeiffer & Foster, 2013). Interestingly, by contributing to spatial memory and navigation, these cells provide information to temporal representations of the past – current path data is accumulated and stored - and the future – stored data is retrieved for path planning during navigation of the same paths - respectively (Leutgeb, Leutgeb, Moser & Moser, 2005; Pfeiffer & Foster, 2013).

Early electrophysiological studies in rodents have shown that vestibular stimulation modulates the activity of head direction cells and place cells in the thalamus and hippocampus (E. E. Smith & Jonides, 1997; Stackman, Clark & Taube, 2002; Yoder & Taube, 2009). In fact, vestibular inputs appear to be crucial for normal place cell activity as vestibular abnormalities result in the disruption of location-specific hippocampal cell firing (Russell, Horii, Smith,

Darlington & Bilkey, 2003; Stackman et al., 2002), further strengthening the direct link between vestibular inputs and brain structures associated with spatial memory function on a cellular level.

Animal behavioural studies have also established that spatial memory and navigation are strongly linked to normal vestibular function (Brandt et al., 2017; P. F. Smith, Geddes, et al., 2010; P. F. Smith & Zheng, 2013). A substantial animal literature has shown that rodents with vestibular lesions exhibit spatial learning deficits when tested in spatial working memory specific tasks such as the Radial Arm Maze Task (P. F. Smith et al., 2010; P. F. Smith & Zheng, 2013). This task traditionally uses an eight radial arm maze in which subjects show their spatial memory skills by avoiding re-entry to identical arms and relying on memory for spatial location based on extramaze landmarks in the testing environment (Russell et al., 2003). Rodents with bilateral vestibular damage made more errors during place learning in these tests (Russell et al., 2003). Similar results have been found by Wallace, Hines, Pellis and Whishaw (2002) from foraging tasks on rodents with bilateral vestibular loss, with the degree of spatial impairment correlated with the severity of vestibular reflex deficits. These studies show that non-visual, idiothetic cues such as vestibular (and proprioceptive information) are needed for animals to remember their way through a familiar environment and that vestibular information contributes to place learning (Wallace et al., 2002; Zheng, Darlington & Smith, 2006) Given the vital role of the hippocampus on spatial memory, it is believed that vestibular information is transmitted in the hippocampus where it is integrated with other sensory information that is relevant to the creation of representations of space (P. F. Smith et al., 2010).

To summarize, the above animal studies emphasize the fundamental role of the integration of the vestibular cues in the creation of cognitive maps. Their creation and maintenance heavily depend on the aforementioned cells in the hippocampus and entorhinal cortex receiving polysynaptic inputs from the vestibular brainstem nuclei. While this anatomical link points towards a direct relation between the vestibular system and spatial memory processes and navigation, the importance of vestibular inputs in spatial memory in humans, as opposed to

animals, has however only recently attracted research (Brandt et al., 2017; P. F. Smith et al., 2010). I review this research below.

Some of the most compelling insights in humans have been drawn from clinical studies. Although written as a report on general memory deficits rather than spatial memory deficit, Grimm, Hemenway, Lebray and Black (1989) provided the first clinical evidence that, in addition to vestibular symptoms, patients with a perilymph fistula syndrome (a rupture in the labyrinth) self-report short-term memory loss. The authors tested 102 patients and more that 80% reported general memory deficits in objective tasks such as auditory recall and paired associate learning, despite normal levels of intellectual function (as tested using IQ, visual reproduction and digit span tests (Grimm et al., 1989; P. F. Smith et al., 2010).

Another example of spatial memory impairment associated with vestibular loss comes from Schautzer, Hamilton, Kalla, Strupp and Brandt (2003) who demonstrated that damage to one or both vestibular labyrinths in humans compromises the ability to recall spatial locations and navigate to recently learnt landmarks. The authors used a virtual variant of the MWM task, an adaptation of the spatial learning task mentioned above that is used extensively in rodents. In the virtual version however, vestibular (and proprioceptive) signals usually present in the real-life environments are lacking and any impairment resulting from vestibular loss in patients was not detrimental to the task, as normal vestibular signals are not required for accurate performance in the virtual task (Schautzer et al., 2003). The authors demonstrated that, compared to 10 healthy participants who navigated easily to the hidden target platform, the 12 patients with chronic bilateral vestibular loss (defined as impairment or loss of function of either the labyrinths or the eighth nerves, Baloh, Jackobson & Honrubia, 1989) showed larger heading error, took longer to arrive at the target platform and spent significantly less time around the target area. Given that it was shown that patients were impaired relative to controls in the hippocampal-dependent spatial learning, whereas all participants had a similar performance in cued navigation to a visible platform that marked the location (which has been shown to occur independently of

hippocampal circuitry in rats), the authors concluded that the deficits revealed were not due to visual, somatosensory or motor skills but instead were vestibular input in origin (Schautzer et al., 2003). Based on animal studies that have shown spatial learning deficits following vestibular loss and that stimulation of the vestibular system has been shown to modulate "head direction cells" of the thalamic nuclei and "place cells" in the hippocampus, the authors hypothesized that lack of vestibular input could modulate how the hippocampal formation processes spatial information (Schautzer et al., 2003). The authors were the first to demonstrate the importance of the vestibular system in navigation and spatial memory specifically in humans. The same results were reproduced shortly after by Brandt et al., (2005), who showed that patients with chronic bilateral vestibular loss manifested significant spatial memory and navigation deficits when tested in a similar virtual MWM paradigm, whereas general memory (as measured by standardized tests that measure general memory, visual/verbal memory and delayed recall) deficits remained intact. In addition, patients exhibited 17% less hippocampal volume than age- and sex-matched controls. Given that the posterior hippocampus is considered to play a significant role in encoding and retrieving spatial memory information, the selective atrophy observed was considered a direct or indirect result of the vestibular loss incurred (Brandt et al., 2005, 2017; Brandt & Dieterich, 2016).

Interestingly, Hüfner et al., (2007) showed that place learning and spatial navigation deficits found in patients with vestibular loss were limited to these patients with right unilateral vestibulopathy, whereas outcome measures in those with left unilateral vestibulopathy did not differ from healthy controls. These results are in line with neuroimaging and clinical studies that have shown that the right hippocampus is primarily involved in human spatial navigation (de Toledo-Morrell et al., 2000; Maguire, Frackowiak & Frith, 1997). A more recent study by Kremmyda et al., (2016) investigated navigational ability and hippocampal atrophy on the same clinical population but in patients who did not have complete loss of vestibular function; on the contrary they had asymmetrical residual vestibular function. Patients exhibited impairment in

direct and indirect navigation and spatial learning in the Morris Water Maze task, however the spatial impairment was more subtle than the one observed on the Brandt et al., (2005) study, possibly due to the patients' residual vestibular input (Dobbels et al., 2020; Kremmyda et al., 2016). A significant decrease in the grey matter mid-hippocampal and posterior parahippocampal volume compared to age matched controls was also observed, suggesting that even partial bilateral vestibular loss leads to both anatomical and functional changes in the hippocampal formation (Kremmyda et al., 2016). As with previous studies, patients did not differ from controls in terms of general memory or whole brain grey matter volume. Spatial anxiety (as measured by the Spatial Anxiety Scale, which is an objective measure of the difficulties patients face when navigating in real life, e.g. driving or finding their way around, Lawton, 1994) was higher in patients compared to the control group, firstly, confirming previously reported spatial deficits as a result of vestibular loss and secondly, suggesting that partial vestibular function is not sufficient for normal hippocampal function (Brandt et al., 2017; Kremmyda et al., 2016).

Instead of a virtual environment, Guidetti, Monzani, Trebbi and Rovatti (2008) tested spatial navigation using a physical paradigm in which participants were asked to visually memorize three different routes marked on a carpet and then repeat these routes from memory with their eyes open or closed. Patients with unilateral labyrinthine disorders performed slower than age-matched controls on this navigation task with their eyes closed (thus relying on vestibular cues when visual cues are absent), confirming previous reports that short-term visuospatial memory is impaired following peripheral vestibular damage and that peripheral vestibular information may contribute to cortical and hippocampal processes required for map navigation (Guidetti et al., 2008). Further in support of these results, patients' performance on a Corsi block-tapping test (sensitive to visuospatial short-term working memory which involves mimicking the researcher as they tap an increasingly difficult sequence of up to nine identical spatially separated blocks (Brunetti, Gatto & Delogu, 2014) was also poorer than the controls (Guidetti et al., 2008). In a similar ecologically valid spatial memory study, patients with

bilateral vestibulopathy were tested in a real navigation task in a hospital, with derived data confirming the findings of studies in virtual environments; patients demonstrated deficits in their way-finding strategies, relying mainly on visual cues for orientation according to landmarks, instead of finding new shortcuts as their age-matched controls. The conclusion that the spatial memory deficits observed were due to the creation of faulty cognitive maps was associated with a decreased activation of the posterior hippocampus, possibly because of visual substitution of the missing vestibular signals (see Brandt et al., 2017).

One should note that although the paradigms used in these last two reports are more ecologically valid, the confounding effect of the vestibular impairment on motor responses in these physical navigation tasks was not taken into consideration, which could have contributed to the results of reduced memory function and lead to patients exhibit impairment in path navigation (see Abekawa, Ferre, Gallanger, Gomi & Haggard, 2018; P. F. Smith et al., 2010) Nevertheless, these results are consistent with other studies that have involved patients with various vestibular syndromes, each with different duration of the vestibular loss and left and/or right hemisphere impairment (see Bigelow & Agrawal, 2015; Lajoie et al., 2021; P. F. Smith & Zheng, 2013; Zheng et al., 2009 for detailed reviews). These studies have not only have highlighted the importance of vestibular signals in spatial short-term memory but also have demonstrated that spatial navigation depends on preserved vestibular function (Bigelow & Agrawal, 2015; Brandt et al., 2005), with the severity of spatial impairment increasing as a function of vestibular loss (Dobbels et al., 2020).

Despite this coherent body of evidence, some of the above findings have been recently challenged by studies that have implicated hearing loss as a potential contributor to general cognitive dysfunction, suggesting that the above conclusions of cognitive impairment attributed to vestibular dysfunction may be due to hearing loss instead (Dobbels et al., 2020; L. Smith et al., 2020). Hearing loss as a confounding effect is not surprising as the peripheral auditory structures are partly housed together with the vestibular organs in the inner ear (see previous

section) and auditory input is also transmitted to areas such as the hippocampus (Hitier et al., 2014; L. Smith et al., 2020). Indeed, in a recent study, Dobbels et al., (2020) found that patients with partial or complete bilateral vestibulopathy (BVP) performed worse than healthy controls in a virtual MWM task, however, after correcting for hearing (dys)function, this difference did not reach statistical significance as other similar studies described above have shown. Interestingly, they found a statistically significant link between hearing loss and spatial ability; the worse the hearing, the longer patients took to navigate to the hidden platform in the virtual environment and the less time they spent in the correct quadrant where the platform was situated. Based on these results, the authors suggested that hearing loss may play a crucial role in the spatial deficits previously reported (Dobbels et al., 2020). However, as the authors state themselves, patients were not adequately counterbalanced/matched to controls, with the majority of hearing loss patients allocated in the BVP group, some of whom presented with only partial vestibular loss. This limitation allowed for the putative outcome of spatial impairment being potentially more significant when patients suffer from complete loss of vestibular function, therefore being consistent with the studies described above (Dobbels et al., 2020; P. F. Smith, 2022). Moreover, due to the study protocol including healthy controls without severe hearing loss, the authors failed to investigate whether vestibular loss had an additional effect on the spatial deficits observed (Dobbels et al., 2020). Further to the shortcomings declared above, patients in this study differed from previously mentioned studies in the recency of the condition, which further complicates comparisons. For example, in Dobbels et al., (2020), the time period that patients had suffered from BVL varied between 6 months or more, whereas in the Brandt et al., (2005) study between 5 and 10 years. Based on animal studies that have been shown that spatial memory impairment declines over time in BVL conditions, it could be interpreted that the lack of significant results on spatial memory deficits could be due to the recency of the vestibular loss (P. F. Smith, 2022).

Given that the two systems interact physiologically and clinically, dissecting the individual contributions of auditory and vestibular function to cognitive performance may be impossible in real clinical settings (P.F. Smith, 2022). However, a recent review of epidemiological and experimental studies highlighted that 43% of the studies conducted in the role of the vestibular system in cognitive impairment and spatial memory specifically, have actually controlled for hearing loss (see review by P.F. Smith, 2022) and still reported cognitive dysfunction associated with vestibular impairment. In line with previous publications, the most common cognitive deficit reported in the reviewed studies was spatial memory with most studies controlling for hearing loss reporting spatial memory impairment (P.F. Smith, 2022 apart from the Dobbels et al., 2020). These conclusions further support the notion that vestibular loss is strongly associated with cognitive dysfunction, especially spatial memory and that hearing loss is not the main factor contributing to spatial memory impairment (P.F. Smith, 2022). This is particularly evident when one takes into account the plethora of animal and biological studies that show that the vestibular system transmits specific information about self-motion to cortical structures and the hippocampal formation (P.F. Smith, 2022).

To summarize, the above clinical reports provide evidence that intact vestibular inputs are important for normal spatial memory not only in animals but also in humans (Brandt et al., 2017). Although chronic unilateral (as opposed to bilateral) vestibular loss does not always result in significant spatial memory deficits in all studies, a decrease in hippocampal volume is still often seen which again highlights the primacy of vestibular input (Brandt et al., 2017; Kremmyda et al., 2016).

Taken together, the above neuroanatomical, clinical, biological and functional neuroimaging studies provide evidence that there is a clear and strong link between cortical and hippocampal areas implicated in spatial memory processes and vestibular input, both on a behavioral (spatial memory deficits) as well as on a clinical (hippocampal atrophy) and cellular level. As described below, these results are further supported and extended by studies in healthy

individuals that have artificially stimulated the vestibular system by means of thermal or galvanic current.

Artificial vestibular stimulation and spatial memory

Investigations into the cellular and neuroanatomical bases of sensory contributions to complex behaviors such as spatial memory are by far easier in animals than in humans, where extracting the vestibular contribution is much more complex due to multisensory integration (Angelaki, Klier & Snyder, 2009; Day & Fitzpatrick, 2005). Indeed, a major obstacle to such a task is that vestibular inputs are so widely distributed across the cortex and converge with other sensory inputs and motor signals, that any forced activation will feed off multiple sensory channels, making it incredibly difficult to capture the vestibular system's unique response (Angelaki & Cullen, 2008; Fitzpatrick & Day, 2004; Hitier et al., 2014). In order to bypass the process of mechanical activation of the vestibular organs and in an attempt to directly stimulate the vestibular nerves, scientists have applied small thermal or electrical currents to the vestibular organs instead (Fitzpatrick & Day, 2004; Lajoie et al., 2021). Studies of this nature are based on the notion that since certain cognitive processes are impaired when normal vestibular function is interrupted by injury or disease, modulating the vestibular input by external currents may likewise affect cognitive function, potentially in a beneficial way if carefully calibrated (Zheng et al., 2009).

Thermal (or caloric) vestibular stimulation is achieved with the use of water or air irrigators that warm or cool the external auditory canal (Black et al., 2016). Both warming and cooling temperature changes introduced to the external ear canal lead to density changes in the endolymphatic fluid of the semi-circular canals and create convection currents that in turn change the firing rates of the vestibular afferents (Black et al., 2016; Wilkinson, 2021). Historically, its use has been reliant on in-clinic administration and side effects such as nausea and vertigo have been commonly reported shortly after application (Black et al., 2016; Wilkinson, 2021). The administration of electric currents to the vestibular periphery on the other

hand is known as galvanic vestibular stimulation (GVS) and involves the application of low amplitude, transcutaneous galvanic currents through electrodes placed on the mastoid processes, the bony structures located behind the ears (J. Kim & Curthoys, 2004; Lajoie et al., 2021; Wilkinson, 2021). Several electrode configurations are available, however the most commonly used is a bilateral bipolar configuration in which the anode and cathode are placed on opposite mastoids (Wilkinson, 2021). This bilateral bipolar configuration infers a perceived head rotation towards the cathode side and leads to compensatory postural movements and oculomotor responses towards the opposite anodal side to counteract the perceived sway (Lajoie et al., 2021; Wilkinson, 2021). GVS is believed to work thought modulating the spontaneous firing of vestibular afferents, including those related to the otoliths and semicircular canals (Kim & Curthoys, 2004; Lajoie et al., 2021; P. F. Smith, et al., 2010) in a manner which either increases or decreases the afferents' firing frequency (cathodal or anodal stimulation respectively, (Goldberg, Smith & Fernández, 1984; Kim & Curthoys, 2004; Lajoie et al., 2021; P. F. Smith et al., 2010). What is more, neurophysiological studies of single neuron recordings from the vestibular nerve have shown that GVS directly stimulates the Scarpa's ganglion neurons of guinea pigs and squirrel monkeys, showing that GVS directly affects the discharge of neurons in the vestibular nerve (Goldberg et al., 1984; Kim & Curthoys, 2004; P. F. Smith et al., 2010).

A surge in animal and human studies that have investigated the effects of artificial vestibular stimulation on spatial perception and memory has been reported in the last two decades. Animal studies have shown that repeated exposure to five 30-minute GVS sessions improves spatial memory performance in MWM tasks in rats and induces hippocampal morphological changes as indicated by hippocampal-specific neuronal activity markers (Ghahraman et al., 2016). Recall from previous sections that vestibular cortical projection areas involve brain regions responsible for spatial memory and construction of cognitive map (Hitier et al., 2014; Lopez, Blanke & Mast, 2012; Suzuki et al., 2001; Vitte et al., 1996) such as the hippocampus, which receives indirect, afferent projections from the vestibular brainstem nuclei.

The authors suggested that repeated exposure to GVS may have resulted in frequent activation of the vestibular afferents of rats possibly by activating the hippocampal regions connected to them, which in turn improved spatial memory (Ghahraman et al., 2016). In humans, functional imaging has revealed that GVS (as well as caloric vestibular stimulation) leads to activation or inactivation of hippocampal and parahippocampal areas (Bottini et al., 1994; Dieterich et al., 2003; Suzuki et al., 2001; Vitte et al., 1996) where similar cells to place cells identified in rodents have been found (Ekstrom et al., 2003). GVS has also been used to improve spatial performance in patients with various neurological disorders, including figure copying deficits (Wilkinson, Zubko, DeGutis, Milberg & Potter, 2010) and visuo-spatial neglect in stroke patients (Rorsman, Magnusson & Johansson, 1999).

Promising results have also been reported in neuro-typical participants. Bächtold et al. (2001) were first to show that the locations of objects were recalled significantly faster than the control group after participants memorized object-location associations while being stimulated with unilateral (cold water) left ear CVS (whereas right ear stimulation improved verbal memory for visually presented words). The authors concluded that caloric vestibular stimulation had improved visual memory by facilitating cerebral blood flow to the contralateral brain structures required for these specific (spatial and verbal) cognitive processes associated with them (Bächtold et al., 2001). Ghaheri, Ghahraman, Jarollahi and Jalaie (2014) performed the Corsi block-tapping test on 60 (18 - 30-year-old) women before and after administering sub-sensory GVS. As mentioned above, this test is sensitive to visuospatial short-term working memory and involves remembering and replicating an increasingly difficult sequence that is tapped in a number of blocks (Brunetti et al., 2014). The authors found that participants who received sub-sensory GVS showed a significant improvement in re-test visuo-spatial measures (block span, learning score as well as total scores) compared to those who received sham stimulation (Ghaheri et al., 2014). A more direct example of spatial memory improvement during GVS comes from Hilliard et al., (2019), who examined the effects of sub-sensory GVS on a virtual

visuospatial navigation task. Prolonged waveforms of GVS or sham stimulation were applied while participants were instructed to navigate to a memorized position of an object in the virtual environment. During a transfer phase, the authors either enlarged the boundary of the virtual environment (which is believed to be sensitive to hippocampal associated spatial learning) or changed the location of the object within the environment (which is sensitive to striatal associated spatial learning), to assess whether GVS would alter hippocampal- or striatal-associated spatial information respectively. When participants were instructed to navigate to the memorized object location, results indicated that GVS improved spatial learning performance overall, with stronger effects in the enlarged boundary condition, suggesting that GVS enhances tasks that recruit hippocampal activity and influences visuospatial representations stored in the hippocampus (Hilliard et al., 2019).

Although the above studies have enriched our understanding of direct effects of enhanced vestibular activation on spatial memory, several ambiguities still remain. For example, prolonged waveforms of GVS employed in the above studies simulate the equivalent of the head continually rotating along the same head movement vector and are far from resembling real-life conditions (Angelaki & Cullen, 2008; L. Smith et al., 2020). In addition, because GVS is applied continuously, it remains unclear which aspect of the spatial learning process was influenced by the prolonged vestibular input (i.e., encoding, retention or retrieval). Indeed, similar studies often employ experimental paradigms that probe cross-modal interactions in which multiple visual stimuli are presented during stimulation (Bächtold et al., 2001), instead of carefully orchestrating a systematic vestibular-visual pairing (L. Smith et al., 2020). Most importantly, a psychological account of why or how vestibular signals are incorporated within spatial memory representations still remains unclear (Hanes & McCollum, 2006). The results obtained from Bächtold et al. (2001) for example prevail towards a theory of generic upregulation by suggesting that the vestibular effects on spatial memory were dependent on the side of the stimulation (therefore hemispheric in nature and a result of activation of particular brain structures, described in detail

in Chapter 2). However, since these studies were not designed to dissociate generic arousal from an alternative account which entails visuospatial processes making use of the vestibular sensory information in a more specific and direct account (Bottini & Gandola, 2015), this question still remains unanswered. Given that many visual events are brief and often accompanied by a unique vestibular signal with the position of the body and head often different that the last (L. Smith et al., 2020), momentary changes in vestibular signalling that accompany head/body movement in space could have a potential role to play in individuating one sensory experience from another (L. Smith et al., 2020). An alternative therefore mechanism of interaction to the prevailing theory above could be that cross-modal integration of visual and vestibular inputs may be incorporated into visuospatial representation (Laurienti, Kraft, Maldjian, Burdette & Wallace, 2004) and subsequently may enrich visual memory representations.

Indeed, only one study so far was designed to address the above ambiguities and provide a mechanistic account of how visuospatial memory processes make use of vestibular inputs by implementing a unique cross-modal (vestibular-visual) interaction approach (L. Smith et al., 2020). The authors used a visual search paradigm in which participants were first encoded with objects at random locations on a computerized grid. Unknown to participants, the appearance of a pre-determined object was paired with a brief, sub-sensory GVS signal, whereas control objects were presented to them in the absence of GVS. Participants' memory was subsequently tested when they were instructed to find the target-object in an array of stimuli. The authors reported that searches were faster when targets were presented in that grid location where the GVS-paired visual stimulus had appeared during the encoding phase. These results indicated that when subjects return to a familiar scene, visual judgments are facilitated for those targets that appear at the location previously associated with the vestibular input (L. Smith et al., 2020).

These data provided preliminary evidence that task-irrelevant but temporally coincident vestibular signals facilitated subsequent search by possibly enriching the concurrent encoding of the visual stimulus which in turn was stored in memory more effectively and was later retrieved

quicker during recall (L. Smith et al., 2020). These momentary changes in vestibular input could be a potential mechanism by which visual memory processes make use of vestibular signals to individuating one visual memory from another. Additional studies that explore these effects on similar paradigms are needed to replicate and confirm the above results but also further characterize the effect and establish its longevity. Continued research is therefore needed to build upon the theoretical underpinnings of how vestibular inputs interact with visuospatial processes to i) enrich the mechanistic account of vestibular-visuospatial memory interactions; ii) better understand how vestibular enhancement benefits visuospatial memory processes and in turn iii) improve clinical practices aiming at using vestibular enhancement as a putative therapeutic method to improve spatial memory deficits.

Chapter Summary

The preceding discussion presented clinical and behavioural evidence that vestibular modulation is not only restricted to these low-level processes of autonomic control but also affects higher-level functions concerned with cognition (P. F. Smith et al., 2010). A substantial animal literature provides strong evidence that vestibular signals project to cortical areas highly involved in spatial memory formation (Hitier et al., 2014; Lopez et al., 2012; P. F. Smith, 2022; Suzuki et al., 2001; Vitte et al., 1996). Complementary clinical evidence highlights that an intact vestibular function is vital for spatial orientation in humans (Brandt et al., 2017) and it is highly evident that, when the vestibular input is disturbed, spatial memory deficits and hippocampal atrophy are observed (P. F. Smith, 2022). Furthermore, selectively activating the vestibular system with galvanic currents can improve performance in spatial learning tasks.

Although the above studies tell us that vestibular information is important for spatial memory, they tell us relatively little about how – in psychological terms – the information is used. The above accounts speak to a generic mechanism that upregulates activity in key parts of the brain but I propose that this under-specifies the degree to which the vestibular input is utilised. In particular, I suggest that the near continual changes in vestibular input that

accompany moment to moment changes in head movement can be used to help individuate one visual event from another.

Current research questions

As intimated, to date, there is no psychological model that explains, in cognitive terms, how vestibular signals can be used to help index visual memory processes. To this end, my thesis uses GVS to test whether brief vestibular perturbations can improve spatial memory performance.

Chapter 2 presents a series of 2-dimensional (2-D) experiments that explore whether visual recall is enhanced if at the time of encoding, the visual event is accompanied by a salient vestibular stimulus. By administering a co-incident sub-threshold vestibular signal simultaneously with a target-object shown on a pre-determined location on a computer screen during encoding, it was tested whether GVS facilitates subsequent visual search for this object by comparing it to objects that were encoded in the absence of vestibular stimulation. The last experiment in the chapter focuses specifically on spatial memory function and tests whether it could be modulated with co-incident increased vestibular input.

Given that Chapter 2 identified beneficial effects but also some methodological limitations that could potentially be bypassed by using a virtual environment. Chapter 3 used a 3-dimensional (3-D) version of a spatial memory task to further our understanding of how vestibular signals are integrated with visuospatial memories and to explore how the vestibular signals enhance mental representations of space in settings that resemble more closely real-life environments.

Chapter 4 explored whether the observed favourable effect would hold in individuals with Alzheimer's disease (AD), a clinical population that presents with spatial memory impairment as one of the earliest symptoms (Previc, 2013). A group of individuals with recorded spatial memory deficits performed a short neuro-assessment battery and then conducted the 2-D spatial memory task from Chapter 2. Since previous research has suggested that vestibular loss

contributes to the development of AD, the data obtained in the current study could be useful in developing approaches to prevent or slow the progress of the disease. Shedding light onto how the vestibular signals enhance mental representations of space could in turn inform strategies of manipulating mental maps of space in patients with spatial memory deficits and data derived from this thesis could help to further characterize and better utilize these strategies.

To summarize, this thesis presents research in normative and clinical populations that investigates whether spatial memory processes are affected by co-incident vestibular inputs as generated by GVS.

Chapter 2

Introduction

Chapter 1 reviewed a number of studies evidencing a strong link between vestibular and cognitive processes, notably visuospatial memory, which has been shown to be affected by vestibular input. Despite the aforementioned clinical, biological and anatomical evidence for this association, there is currently no established psychological model that explains, in cognitive terms, how visual memory processes exploit vestibular sensory information. The key aim of this chapter is to provide a possible account of this interaction by examining how vestibular inputs are integrated in visual processes.

This introduction will first discuss possible psychological mechanisms behind vestibular and visual interactions. Next, it will recap studies that have investigated these interactions and outline the questions that this chapter is aiming to address. Finally, the experimental paradigm implemented in the first study will be introduced and the hypotheses presented.

Potential psychological mechanisms

As noted in the General Introduction section, vestibular inputs have long been implicated in spatial learning and memory, however the underpinning cognitive processes still remain unknown. There are at least two potential psychological mechanisms by which the vestibular-visual interaction could occur; vestibular inputs could interact with memory processes via a generalized cognitive enhancement and/or by providing specific and direct content which is integrated into the visual memory representation. These two mechanisms are discussed in length in the following paragraphs.

The first mechanism would entail vestibular stimulation exerting a generic arousing effect on cognition by up-regulating cognitive functions non-selectively and by inducing a general cognitive enhancement that potentially increases attentional focus via a widespread boost in metabolic activity (Wilkinson, Nicholls, Pattenden, Kilduff & Milberg, 2008; Wilkinson et al., 2014). Indeed, both imaging (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Lopez et al.,

2012) and EEG studies (Kim et al., 2013; Lee et al., 2014) have shown that artificially stimulating the vestibular nerves induces non-specific arousal by broad-scale activation of cortical and sub-cortical regions and widespread increases in spectral power respectively. These regions include the retroinsular cortex, cingulate cortex, insula, Sylvian fissure and temporal-parietal cortex, as well as the reticular activating system, which is the brain's core arousal system (Bense et al., 2001; Wilkinson, Ferguson & Worley, 2012). The reticular activating system projects to many cortical regions (Purpura & Schiff, 1997) coordinating the activity of attentional and perceptual systems (Schiff & Pulver, 1999; Wilkinson et al., 2012), which would suggest that vestibular activation most likely facilitates memory through broad-scale cortical modulation (Wilkinson et al., 2012) instead of benefiting a single cognitive process such as spatial ability. Indeed, artificial vestibular stimulation via CVS in single case studies of two TBI patients in a low awareness state has been shown to elicit general behavioral improvements (Vanzan, Wilkinson, Ferguson, Pullicino & Sakel,, 2017). This could be further supported from the fact that vestibular afferents are constantly firing even at rest (Angelaki & Cullen, 2008) as otolith organs are continuously active sensing the pull of gravity even when one remains motionless (Angelaki & Cullen, 2008; Day & Fitzpatrick, 2005). In fact, combined activation of semicircular and otolith canals is necessary to sense linear accelerations and rotational movements (Angelaki & Cullen, 2008), and the nervous system may need these signals to calibrate a constant representation of space (Fitzpatrick & Day, 2004). In turn, constant inhibitory or activating information from the vestibular system (Bense et al., 2001) may be used in conjunction with visual and proprioceptive signals leading to the processing of sensorimotor control and reflexes, as well as the highest levels of consciousness and spatial perception, as a result of a multimodal integration from various sensory signals (Angelaki & Cullen, 2008). This would mean that decreased vestibular sensory input due to vestibular dysfunction could be purely deriving from low awareness and failure to comprehend the full range of physical motions of the head and body that the vestibular system helps coordinate when moving in space

(Angelaki & Cullen, 2008) and is not specific to one cognitive function in particular, in this case, spatial ability.

Apart from animal studies that suggest a strong link between spatial memory and vestibular input (P. F. Smith et al., 2010), reports investigating vestibular interactions with spatial memory in clinical populations affected by vestibular dysfunction dispute the above hypothesis. Indeed, populations with bilateral vestibular dysfunction have been found to present with impairments mainly in spatial memory, whereas general memory have been shown to remain intact with participants showing superior memory performance on standardized tests (Brandt et al., 2005; Kremmyda et al., 2016; Schautzer et al., 2003, although emotional deficits such as depression and anxiety have been reported, see (P. F. Smith & Darlington, 2013). The same is observed in clinical populations such as individuals with Alzheimer's, whereby spatial memory deficits are strongly linked to vestibular loss but not associated with verbal memory or language skills for example (Bigelow & Agrawal, 2015; Previc, 2013; Semenov, Bigelow, Xue, Lac & Agrawal, 2016). These reports dispute, fully or partially, the aforementioned hypothesis of generalized cognitive and attentional arousal and suggest that reduced vestibular input as a result of vestibular dysfunction or loss is relatively limited to spatial ability (Agrawal et al., 2020; P. F. Smith et al., 2010). These studies provide sufficient evidence that hint towards an alternative hypothesis; that is cognitive processes making use of the vestibular sensory information in a more specific and direct manner (Bottini & Gandola, 2015) with visual memory processes being particularly receptive to the vestibular sensory input (P. F. Smith et al., 2010).

One potential explanation for the fact that vestibular sensory input is necessary for spatial memory is that vestibular signals deriving from the otoliths and semicircular canals provide important information in reference to which way is up, which way the body is moving and other relevant information about spatial perception (Fitzpatrick & Day, 2004). Indeed, self-motion and positional information contained within vestibular signals is likely to be particularly relevant to spatial aspects of visual memory processes as vestibular inputs help update spatial

representations, regardless of whether it is 2- or 3-dimensional environments and stationary or mobile subjects (Brandt & Dieterich, 2016). As noted above, the fact that the vestibular afferents are continuously active may contribute to the production of a constant representation of space with vestibular signals providing updated self-motion information about the constant changes in body and head position that subsequently help the brain adjust the ever-changing posture and gaze as the body moves in space relatively to other objects in the environment (Angelaki & Cullen, 2008; Dilda, MacDougall, Curthoys & Moore, 2012; Fitzpatrick & Day, 2004; P. F. Smith et al., 2010). However, many visual events are brief and often accompanied by a unique vestibular signal as at any moment in space that the body and head move in space, their position is often different that the last (L. Smith et al., 2020). These subtle variations in vestibular input induced by these momentary, unique changes in head movement could potentially be used via visual processes to enrich or individuate stimulus encoding (L. Smith et al., 2020). The cross-modal integration of visual and vestibular inputs may be incorporated into the unimodal visual representation of space (Laurienti et al., 2004) and subsequently may enrich that visual memory event thus strengthening memory encoding. This enhancement is commonly observed among other sensory modalities in the cross-modal literature in which visual recall for a visual event is facilitated if at the time of encoding, the visual event is accompanied by a unique, temporally coincident stimulus from another sensory domain, for example a tactile or auditory stimulus (Driver & Spence, 2000; Lacey, Lin & Sathian, 2011; Lehmann & Murray, 2005). For example, Lehmann and Murray (2005) showed that the encoding of a uni-sensory visual memory resulted in improved memory performance when presented as auditory-visual pairs during encoding, compared to stimuli encoded in a visual-only context (the same results were found for tactile-visual pairs, see Lehmann & Murray 2005). Visual memory processes could be using the coincident information derived from the vestibular system in a similar manner to enrich visual memories or individuate one visual memory from another (L. Smith et al., 2020). This hypothesis would imply that vestibular inputs may assist spatial memory by contributing distinct

and specific spatial information that is exploited by visual memory processes. By casting light into these visual-vestibular interactions, a theoretical mechanism of how vestibular inputs are integrated into representations of space could be defined.

L. Smith et al., (2020) attempted to provide such a mechanistic account by investigating whether cross-modal facilitation could be shown for the recollection of individual vestibular-visual paired stimuli. The approach the authors used was based on the enhancement of uni-sensory visual stimuli via simultaneous encoding of a stimulus from another sensory domain, as described above, but also on studies that have shown a priming advantage based on a contextual cuing effect (Chun & Jiang, 1998; L. Smith et al., 2020). This priming effect is achieved be embedding targets within configurations of irrelevant, background stimuli, the features of which have been shown to influence later visual search by deploying visual attention sensitive to the broader configuration of the visual scene in which stimuli were encoded (Chun & Jiang, 1998; Á. Kristjánsson & Campana, 2010; L. Smith et al., 2020). Interestingly, even task-irrelevant cross-modal associations are beneficial to visuo-spatial memory representations, as shown by studies where learning in a visual motion detection task was facilitated for audio-visual as opposed to visual-only training occurring repeatedly over a five-day period (see Seitz, Kim & Shams, 2006). Taken together, the above studies argue that the configuration of cross-modal stimuli is incidentally learnt over time during encoding and contributes to a visuo-spatial representation that guides visuospatial search during recall. In the L. Smith et al., (2020) study, the authors investigated whether this facilitation would hold in a visual search task for a stimulus that was previously associated with a distinctive head movement (recall from introduction that a brief pulse of GVS acts to simulate a natural head movement, see Fitzpatrick & Day, 2004). More specifically, the authors questioned whether implicit information about head position could assist memory processes by shaping the broader context (i.e., the visuo-spatial representation) that the individual stimulus was encoded in (L. Smith et al., 2020). A visual search paradigm was used, in which participants were first encoded with objects at random locations on a

computerized grid. Unknown to participants, the appearance of a pre-determined object was paired with a brief, sub-sensory GVS signal, whereas control objects were presented to them in the absence of GVS. Participants' memory was subsequently tested when they were instructed to find the target-object in an array of stimuli. The authors reported that searches were faster when targets were presented in that grid location where the GVS-paired visual stimulus had appeared during the encoding phase. These results indicate that when subjects return to a familiar scene, visual judgments are facilitated for those targets that appear at the location previously associated with the vestibular input (L. Smith et al., 2020). These data provided preliminary evidence that task-irrelevant but temporally coincident vestibular signals can guide visual search in subsequent encounters by possibly enriching the concurrent encoding of the visual stimulus which in turn is stored in memory more effectively and is retrieved more quickly (L. Smith et al., 2020).

The insights gained from the above study inform or advance upon reports that have argued a generalized arousal effect on cognitive processes following vestibular stimulation or suggestions that the facilitation observed could be alluded purely to attentional shift (Bächtold et al., 2001; Brandt et al., 2005; Dilda et al., 2012; Ghaheri et al., 2014; Ghahraman et al., 2016; L. Smith et al., 2020; Wilkinson et al., 2008). It is true that a cognitive advantage following vestibular stimulation has been previously reported in visuospatial paradigms. For example, Bächtold et al., (2001) showed that visual memory recall for locations of objects could be enhanced if vestibular stimulation in the form of water-based caloric vestibular stimulation (CVS) was applied during encoding of said locations. Similarly, Wilkinson et al., (2008) showed that participants who had received GVS while learning the names of several faces, recalled detailed about faces more quickly than those who received sham stimulation. These studies concluded that vestibular stimulation improved visual memory by facilitating cerebral blood flow to the brain structures responsible for these spatial cognitive processes (Bächtold et al., 2001) or the advantage seen was due to a generalized enhancement in arousal that led to non-specific cognitive gains (Wilkinson et al., 2008). Although informative, these studies aimed to

purely enhance performance via artificial vestibular stimulation (L. Smith et al., 2020) rather than cast light into the underpinning mechanisms of action. Secondly, the protocols followed discharged prolonged waveforms of GVS during stimulation which translate to a real-world equivalent of the head constantly rotating along the same head movement vector and therefore do not resemble real-life conditions (Angelaki & Cullen, 2008; L. Smith et al., 2020). In addition, applying GVS continuously makes it difficult to pinpoint which aspects of the spatial learning and memory processes are influenced by the vestibular input (i.e., encoding, retention or retrieval). Furthermore, these experimental paradigms probed cross-modal interactions in which multiple visual stimuli were presented during stimulation (Bächtold et al., 2001; Wilkinson et al., 2008,), instead of aiming for a unique vestibular-visual pairing (L. Smith et al., 2020). Indeed, an experimental paradigm that presents multiple visual stimuli during a simulated head movement that lasts minutes at a time makes it difficult to establish how vestibular signals affect encoding of individual stimuli, which are often used as landmarks to guide visual navigation (Iaria, Bogod, Fox & Barton, 2009). By addressing the above shortcoming, L. Smith et al., (2020) showed that temporally co-incident vestibular input can facilitate implicit memory for locations in subsequent encounters and that much briefer periods of stimulation (instead of prolonged protocols carried out in other studies) could also be of benefit and are worth investigating further.

Although the above study was the first to show that vestibular sensory information can facilitate subsequent visual judgements via a form of specific cross-modal integration, further research is needed to replicate the effect under different experimental protocols to ensure it is not paradigm-specific and in turn establish and confirm the pervasiveness of the GVS prime. Another limitation of the above study is that only immediate effects were investigated. Ultimately, enhancing memory for spatial representations could provide the basis to develop non-invasive approaches to remediate spatial memory deficits in people suffering from amnesia. However, to better utilize the GVS priming advantage, its longevity needs to be further defined. Previous studies in hemi-spatial neglect patients for example have shown that vestibular

stimulation improves attention and quality of life up to 4 weeks post stimulation (Wilkinson et al., 2014). Beyond furthering our understanding about how vestibular cues influence visuospatial memory, establishing both the pervasiveness and endurance of the GVS prime in spatial memory is of vital importance when attempting to understand the therapeutic applications of this method to amnestic conditions.

The following sections will describe the methods and results from three independent experiments which paired the onset of a spatial location with a unique sub-sensory GVS pulse to further our understanding of the psychological account behind the integration of temporally coincident vestibular cues in visuospatial memory processes by shedding light into the previously addressed limitations. Studies in this chapter aimed to firstly replicate the effect seen in the aforementioned study (L. Smith et al., 2020) in different paradigms in order to establish whether the paradigm independent GVS priming advantage has an omnibus effect (Experiments 1 and 2). In addition, the same experiments attempted to investigate the longevity of the GVS advantage by testing at different intervals post stimulation (Experiment 1 tested 30minutes after the initial stimulation, Experiment 2 tested additional timepoints of 2hours and 24hours after initial stimulation). Lastly, Experiment 3 tested whether the GVS prime would hold in a paradigm that incorporated a dynamic element resembling more closely real-life settings. The results obtained here confirm previously shown results that recall of a visual target location is facilitated if the initial encoding of the visual location is accompanied by a temporally coincident vestibular signal, supporting a specific role of the vestibular inputs in visuospatial memory (L. Smith et al., 2020). The information obtained could help identify more specific conditions in which coincident vestibular signals facilitate visual memory and thereof help us better understand in which way these signals are used. In addition, by replicating the GVS prime in two different paradigms, the pervasiveness of the priming advantage could be established.

Experiment 1: Establishing the omnibus effect of GVS priming

This first study in this chapter aimed to specifically replicate the effect previously seen by

investigating whether salient vestibular signals presented incidentally with visual stimuli can be used by visual memory to enrich or individuate one visual memory event from another (L. Smith et al., 2020). An entirely different paradigm and novel stimuli were used. The experimental procedure involved a similar visual search task, which consisted of a circular display of Gabor patches as stimuli, which are sinusoidal gratings frequently used in visual studies (Durrie & McMinn, 2007). Gabor patches can be experimentally manipulated across two elements (frequency and orientation, see K. Kristjánsson, 2006) and given that they can be distinguished by their frequency/orientation and are free of semantic association, the GVS signal is expected to be interacting with perceptual rather than semantic memory processes. This was primarily the rationale for choosing different stimuli to the previously used animal-like "Fribbles" (Barry, Griffith, De Rossi & Hermans, 2014; L. Smith et al., 2020). In addition, given the complexity of "Fribbles'', they may be complex for use with older population studies as they differ in many elements, including various attachments and colours.

Several other simplifications were adopted to customize the experimental paradigm. Firstly, the stimulation parameters were adopted in the current study. L. Smith et al., (2020) based their stimulation parameters associated with the facilitation of implicit memory after repetitive exposure. The authors showed a GVS priming advantage after using 39 GVS pulses per participant across the span of the experiment (3 pulses per block for 13 blocks, L. Smith et al,. 2020). Recall that if our hypothesis were true, then a single GVS pulse (akin to a single head movement) should be sufficient to influence spatial memory. However, since the GVS signal is artificial and may not convey a meaningful head movement, the prime may be less effective and need to be administered more than once to exert effect. Clarifying this would be beneficial to establish protocols for patient studies, as lengthy experimental paradigms could result to patient fatigue. For this reason, in the experiment, the number of GVS pulses was reduced from 39 to 18 (3 pulses per each of the six blocks). Secondly, the current study aimed to define the longevity of GVS priming by testing participant's performance not only immediately after priming but also

30 minutes after stimulation. This interval was chosen based on evidence that this is sufficient time to allow for long-term potentiation (LTP), an increase in synaptic strength induced by repetitive stimulation of presynaptic terminals which leads to synaptic plasticity and underlies memory function in the human hippocampus (Huang, 1998).

It was predicted that if vestibular signals can enhance visual memories, then a visual stimulus that is co-incidentally associated with the brief, sub-sensory vestibular input will be recalled faster than a control stimulus that is presented to participants in the absence of stimulation. If vestibular inputs enhance specific aspects of the object representation (object or spatial properties for example) then a main effect of Location or Image will be observed respectively. Finally, if all objects are responded to with the same accuracy and reaction time, this would indicate that GVS has a broader beneficial effect that is not specific to location or object properties (L. Smith et al., 2020). Given that additional vestibular inputs were not administered beyond the initial detection task (see Figure 2.1), it was examined whether the same effect predicted in Part I would also hold in Part II of the study.

Method (1)

Participants

A total of 39 individuals took part in this study. Participants were recruited via the University of Kent's Research Participation Scheme (RPS) and were undergraduate students who participated in return for six course credits. Prior to taking part in the study, all participants were asked to give their written informed consent after being given a detailed description of the study. The research was approved by the University of Kent's Psychology research ethics committee and all participants were treated in line with the guidelines provided by the British Psychological Society (BPS).

Stimuli

The stimuli included in this paradigm were Gabor patches (see K. Kristjánsson, 2006). The Gabor patches varied in two dimensions; the *orientation* of the sinusoid making up the Gabor (left, right, horizontal, vertical) and the *spatial frequency* of the sinusoid (high or low) which was defined by the distance between the lines that compose of the Gabor stimulus. A total of 8 Gabor patches were used in each array, positioned in 8 pre-determined locations, forming a circular display (see Figure 2.3). Using the aforementioned two-featured objects allowed to have absolute control on the differences between the stimuli within the array, which could be experimentally manipulated in a way that certain sets of objects that contain common features were selected for use in the same trial (K. Kristjansson, 2006). This was particularly useful because in this paradigm distractors were introduced, which differed from the trial target object in one of the features (orientation or spatial frequency, see Figure 2.3) and served to increase task difficulty. Given that the current experiment only contained 8 objects within the array, the risk of participants using explicit strategies to memorize key targets in pre-determined locations was high (Hout & Goldinger, 2010). To exclude this possibility, each target was primed in a pre-determined location during the learning phase but was presented in each of the 8 locations during the search tasks, including the key location (see below).

Design

A within-participants factorial design was used with each participant completing six trial blocks of a single experimental session, each comprised of an encoding phase (detection task) where object-location associations were incidentally learnt and a recall phase (search task), where memory for these associations was indirectly tested (Figure 2.1).

To counteract object properties or pre-determined locations themselves influencing performance during recall (due to the possibility of bias for more memorable objects or locations), four different stimulus arrays were created in total, with different Gabor images placed in various pre-determined locations across arrays, so that the target Gabor object paired

with GVS or placed on the Control location differed across arrays. In addition, the positions of the stimuli on the circular display were carefully selected so that both Control and GVS Gabor images and pre-determined locations were counterbalanced within each experiment and across experiments (for example, a Gabor patch paired with GVS in one array was used as a control in another). Participants were randomly assigned to one of the four arrays and data sets were combined before final analysis (see below). Stimuli were displayed on a white background of a 15inch computer screen.

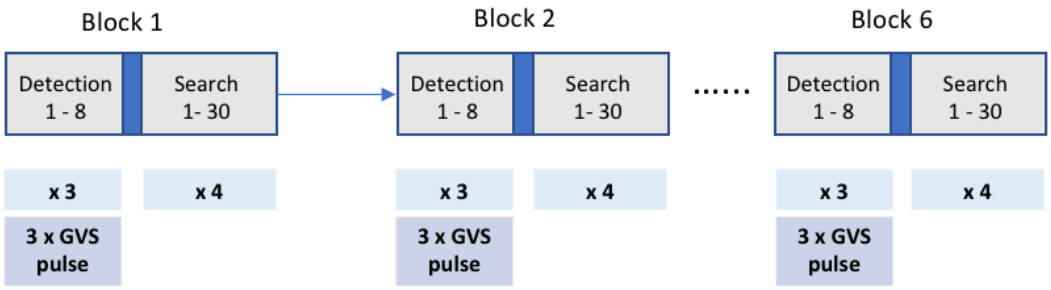

Figure 2.1. Schematic diagram of the experimental procedure summarizing trial structure in both detection and search tasks in Part 1 of Experiment 1. Three repetitions of the detection task were presented (therefore 3 GVS pulses in the GVS) and four repetitions of the search task. Six blocks were used in total. A total of 18 pulses of GVS were administered throughout the course of the experiment. Part II consisted of the search sections only from each of the six blocks.

Stimulation protocol

Participants were seated in a comfortable chair in an isolated testing lab. A padded chin rest was used to keep participants' head position constant to minimize movement during the experiment (this way natural vestibular stimulation arising from head movements during the task was kept to a minimum so that controlled stimulation of the vestibular system could be achieved by using the GVS device). Free movement was permitted during several allocated breaks to minimize discomfort. The experiment was designed and recorded using PsychoPy (University of Nottingham). The GVS stimulation protocol and the research design followed are described in detail below.

Bilateral bipolar current was discharged to match the onset of the target-location

association during the detection task only. All stimulation was performed by galvanic vestibular stimulation units (neuroConn DC-Stimulator) using the configuration of anode left and cathode right, previously shown to lead to greater visual memory improvement (see Rorsman et al., 1999; Wilkinson et al., 2008). Surrounding skin was first cleansed with an alcohol swab and exfoliating gel was applied to ensure complete electrical contact with the electrodes. Bilateral bipolar current was discharged at the onset of the target object-location association (achieved through a PsychoPy function that triggers electrical currents and enables simultaneous pairing of an object stimulus with a GVS signal). The current was delivered using a pair of 5.1 x 10.2 self-adhesive, disposable electrodes (Covidien, Uni-Patch Inc.) placed over the mastoids behind the ears. An impedance check was performed prior to the study to verify complete electrical contact. Each pulse lasted for 1000ms to accompany the onset of the key-image that was paired with the GVS signal. Stimulation occurred at 0.25 - 0.3 mA. The amplitude of the stimulation was chosen based on previous studies that showed it induces a behavioural and electrophysiological response yet remains sub-sensory so it does not elicit conscious sensation such as itching or illusory head movement (see Dilda et al., 2012; L. Smith et al., 2020; Wilkinson et al., 2012).

Threshold testing was conducted prior to the experiment to ensure participants received sub-sensory stimulation. Direct current stimulation occurred between 0.25-0.3mA while participants kept their eyes closed. GVS stimulation perception was first assessed for each participant at 0.3mA and if perceived, was adjusted to 0.25mA. In addition, a questionnaire (Appendix A) was used to estimate the perceived intensity of the stimulation and any sensations it evoked upon completion of the study. Participants who reported to have perceived the stimulation (N=6) were excluded from the final analysis, since their performance could be associated with somatosensory responses rather than vestibular inputs (these participants did not report perceiving the stimulation during the thresholding process however noticed it during the experiment).

In addition to the above exclusions, three participants were further excluded from the

study due to equipment failure. Three additional participants requested to withdraw from the study after reporting that they couldn't tell apart the Gabor images as the lines that determine spatial frequency were blurring into one (this may have had happened due to the experiment being too long, see below). Following the aforementioned exclusions, the final analysis was conducted on 27 participants for part I of the study and N = 26 for part II as one participant did not attend the follow-up testing session.

Procedure

In order to test memory indirectly, the experiment was disguised as a "Detection task" in which participants undertook a visual search task as they were asked to identify the target object on a computer screen as quickly and as accurately as possible. The experiment lasted 1.5hours, with the follow-up part lasting approximately 40 min. Participants were asked to return exactly 30min after the completed the first part of the study to be tested again on 6 blocks of the recall phase – the encoding phase where stimulation occurred was omitted in this second part of the study - in a first attempt to establish whether the GVS effect holds 30min after last stimulation (Part II). Participants were debriefed and informed about the real aims of the study upon completion of both parts of the experiment.

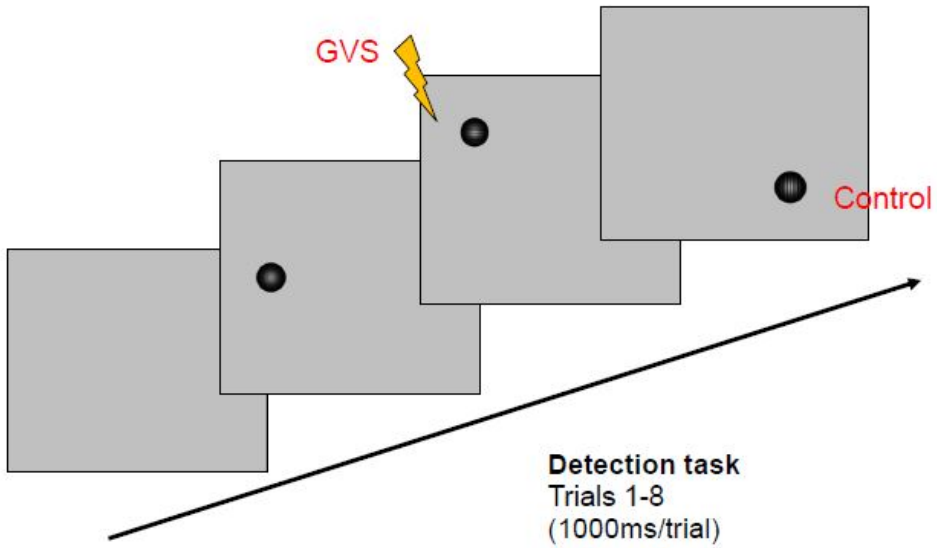

Figure 2.2. Trial structure in detection task. A single Gabor patch was shown in each trial and participants were asked to respond by pressing the spacebar every time they saw an object on the

screen. A sub-sensory GVS pulse was only released alongside one Gabor patch during this task. The Control image was also shown during this task. Three repetitions of this task occurred so a total of 24 trails were included in this task (with different interval ISI so that their appearance is not anticipated).

***Detection task*.** This part of the experiment served to encode participants with the Gabor patches in set locations on the circular display and it was during this task that the pairing with the vestibular pulse occurred. Each trial begun with an empty grey screen with a fixation central cross and was followed by the consecutive display of single Gabor patches, each presented for 1000ms (see Figure 2.2). Gabor patches were presented in a different location (each one presented in a pre-determined location so that object-location association occurs) and three repetitions took place. Participants were instructed to detect the appearance of the Gabor object and respond with the spacebar as quickly as possible, a feature included to ensure participants were attending to the stimuli presented. Overall, this phase consisted of 8 Gabor patches presented three times each, resulting in 24 trials overall (shown in randomised order with ISI interval ranging from 5-8s so that object's appearance is not anticipated). Three block repetitions were implemented and given that only one object was paired with GVS, three GVS pulses were discharged in each of the six blocks, leading to a total of 18 pulses released over the course of the experiment.

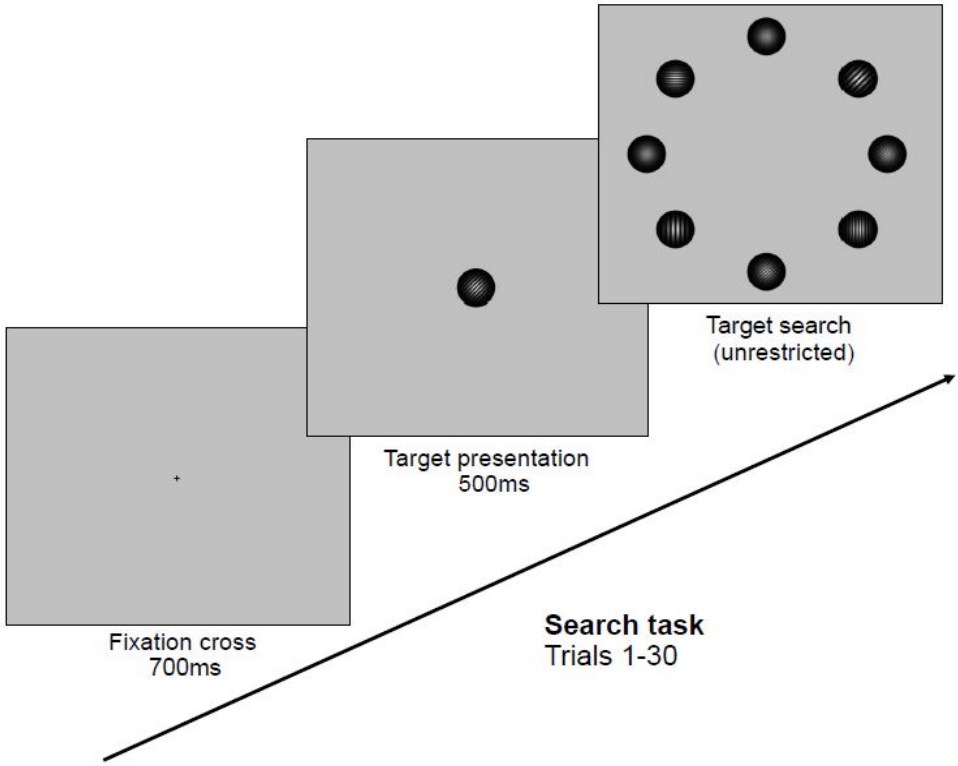

Figure 2.3. Trial structure in search task. Participants were presented with the target image and were requested to actively search and identify it in the display using the mouse. Four repetitions of this task occurred so there were 120 trials during the search task.

Search task. This part of the experiment followed each encoding phase and served to test participants' implicit memory for the encoded objects. Each trial began with the presentation of a fixation cross in the centre of the screen for 700ms, immediately replaced with a single Gabor patch for 500ms. This target object was either an 'Old' Gabor patch image that the participants were encoded with during the detection task or a 'New' image that only appeared during this recall phase. This was immediately followed by a display of all eight Gabor patches. In each trial, participants were instructed to actively search for and detect the object that they were just presented with and click on the target-object as quickly and as accurately as possible. Participants were given unlimited time to respond but they were restricted by accuracy, meaning they had to click on the correct target in order to continue to the next trial. Targets were always present in all trials and this feature was included to ensure engagement throughout the study. Only the first estimation of the target was accounted for in the accuracy measure. The recall phase consisted of 30 trials in total presented in a randomised order.

From all trials included in the experiment, six that contained the key images were the focus of the study and were the trials included in the final analysis. The Gabor image that was presented alongside the GVS stimulation (hereafter mentioned as GVS Image) was shown on the same pre-determined location of the display as during the encoding phase (hereafter mentioned as GVS location-GVS image trial). A Control image, which was also presented during encoding, was tested in its original location (Control location - Control image trial and in the location that was associated with GVS during encoding (Control image - GVS location trial). On another trial of the recall phase, the GVS Image was shown on the Control location, in which participants were primed with the Control image during the encoding phase but not the GVS image (GVS image -Control location trial). Finally, a new image (not presented during encoding) was shown in a similar fashion, resulting in the New image - GVS location and New image – Control location trials respectively. The remaining trials were added to disguise the nature of the paradigm as a detection task rather than a paradigm that tests participant's implicit memory. In addition, more trials meant that participants were less likely to memorize the key comparison stimuli, therefore less likely to use explicit strategies (see Hout & Goldinger, 2010).

These six key comparison trials were included for the reasons described below. By contrasting the GVS image - GVS location and Control image - Control location trials, it could be assessed whether encoding an object while simultaneously administering a salient GVS pulse facilitates implicit memory for this object compared to another image presented in a control location and encoded in the absence of GVS. Furthermore, given that vestibular signals could enhance implicit memory by enhancing different properties of the object-location association, by using these comparisons, it could be explored which aspects of the memory representation might be facilitated when the multisensory encoding (visual stimulus in the presence of the vestibular input) occurs (L. Smith et al., 2020). For instance, vestibular signals could enhance implicit memory by differentially affecting only the object properties. If this were the case, then the image that is paired with GVS is expected to be responded to quicker than the other two images

(New image and Control image), regardless of the location (GVS or Control). Another way that the vestibular signals could affect implicit memory is by differentiating objects only in a location-specific manner. For example, all objects that are presented in the GVS location, regardless of their identity (i.e., regardless of whether they are a GVS, Control or New image), would be responded to faster than when presented in the Control location. However, if all the above were true, then an interaction effect would be seen which would suggest that vestibular signals differentiate one visual memory from another by providing both location and object-identity information. Finally, if all objects are responded to the same across the measures tested, this would indicate that GVS has a more broad-scale arousal effect that is not specific to location or object properties.

Results (1)

Data analysis

As noted above, participants were not instructed to consciously recollect previously shown object-location associations, to the contrary, memory was tested implicitly. For this reason, RTs were the main focus of this study. Accuracy data was also measured as a secondary dependent variable but was expected to reach ceiling levels due to the expected low difficulty-level of the task.

All correct trials (key and non-key trials) were included in the initial analysis, collapsed across all four arrays. Extreme outliers ($p<.001$) were first removed from the dataset using a Z-score correction, following this process: a grand mean was first calculated including all correct trials, then subtracted from the reaction time of the individual trial and finally divided by the grand standard deviation which again included all correct trials. Z-scores greater than 2.5SD were excluded from the final analysis.

Analysis first determined whether implicit memory was present in the recall phase (see (Manelis, Hanson & Hanson, 2011) by comparing correct filtered RTs from trials from stimuli

that were presented during the detection part of the study (old stimuli) and these that appeared only in the recall phase, hence were new to the participant (new stimuli). Responses to old objects were quicker (*M=1578.42ms*) than responses to objects that were new to the participants (*M=1704.53ms*); this difference reached statistical significance [$t(52) = -2.42$, $p=.019$], indicating that search performance is facilitated due to priming thereby confirming implicit memory effects (Manelis et al., 2011).

All further analyses were conducted upon correct key comparison trials only. The independent variables were Location (GVS or Control) and Image (GVS, Control or New). A RM ANOVA 3 (Image – GVS, Control, New) x 2 (Location – GVS or Control) analysis was conducted.

Results – Part I

Reaction Time. Neither Location nor Image reached significance; $F(1, 26) = 2.69$, $p=.11$, $\eta_p^2 = .094$ for Location and $F(2, 52) = 3.01$, $p=.06$, $\eta_p^2 = .104$ for Image (see Figure 2.4). The two-way interaction between Image and Location [$F(2, 52) = .521$, $p=.59$, $\eta_p^2 = .020$] also failed to reach statistical significance.

Accuracy. As expected, accuracy data for the key comparison trials showed ceiling effects in all groups (all conditions close to 90%, see Figure 2.5). The main effect of Location failed to reach significance [$F(1,26) = 0.061$, $p=.806$, $\eta_p^2 = .002$], whereas the main effect of Image was marginally significant [$F(2,52) = 3.165$, $p=.053$, $\eta_p^2 = .109$], which derived from a difference between the GVS ($M = .894$) and the New ($M = .836$) Image. The two-way interaction did not reach statistical significance [$F(1.56, 40.48) = .348$, $p=.655$, $\eta_p^2 = .013$].

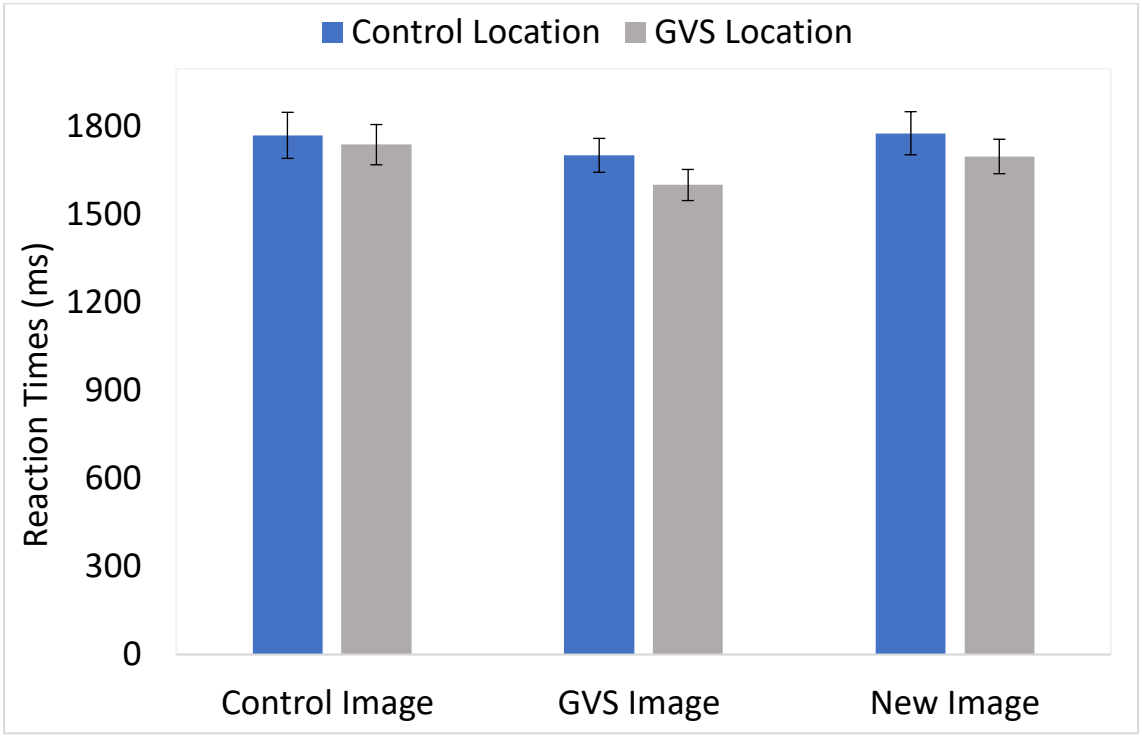

Figure 2.4. Combined reaction times for the 6 key comparisons in all four arrays in Part I of the study. A trend favouring the GVS location was found, however this did not reach significance. Error bars represent standard error of the mean.

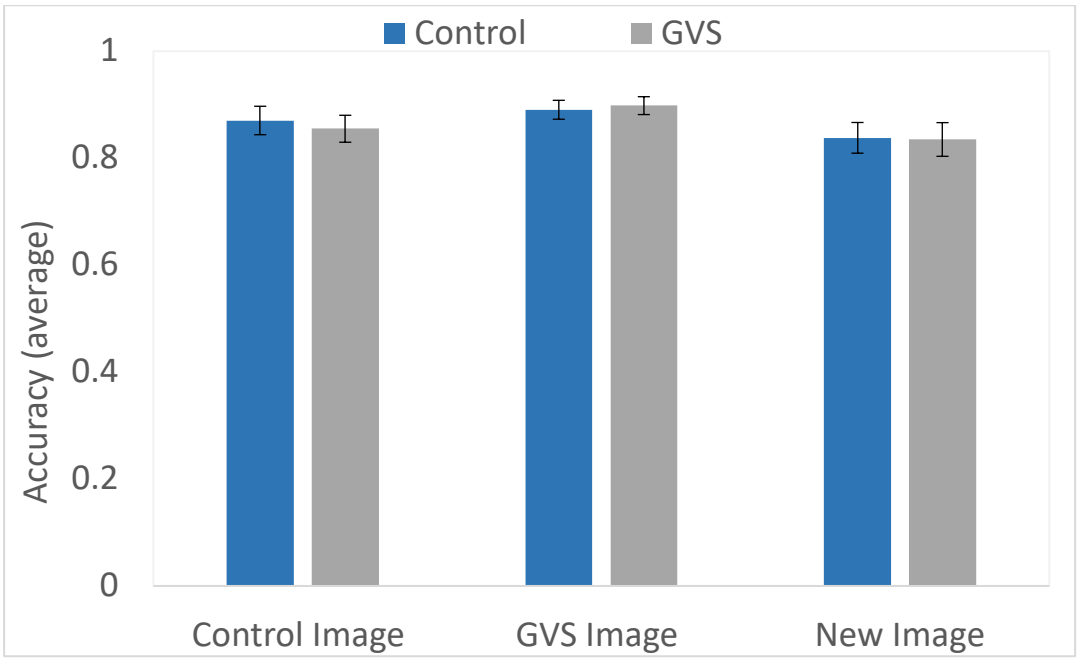

Figure 2.5. Average accuracy for the 6 key comparisons in all four arrays in Part I of the study. No significant effects were found. Error bars represent standard error of the mean.

Results – Part II (tested 30min post completion of Part I)

Reaction Times. The main effect of Image failed to reach statistical significance; [$F(1.34, 33.42) = 2.20$, $p=.14$, $\eta_p^2 = .081$] however the main effect of Location [$F(1, 25) = 6.12$, $p=.02$, $\eta_p^2 = .197$] revealed shorter RTs towards targets presented in GVS location (M = 1558ms) compared to the Control location (M = 1683ms), see Figure 2.6. The two-way interaction between Image and Location [$F(2, 50) = .046$, $p=.96$, $\eta_p^2 = .002$] also failed to reach statistical significance.

Accuracy. Similar to part I, accuracy data showed ceiling effects in all groups (see Figure 2.7). The main effect of Location failed to reach statistical significance [$F(1,25) = 0.209$, $p=.65$, $\eta_p^2 = .008$], whereas the main effect of Image was found significant [$F(2,50) = 4.243$, $p=.02$, $\eta_p^2 = .145$]. The main effect of Image derived from a difference between the GVS (*Mean* =.913) and the New (*Mean* =.831) Image (Figure 2.7). The two-way interaction also failed to reach statistical significance [$F(2,50) = 0.279$, $p=.758$, $\eta_p^2 = .011$].

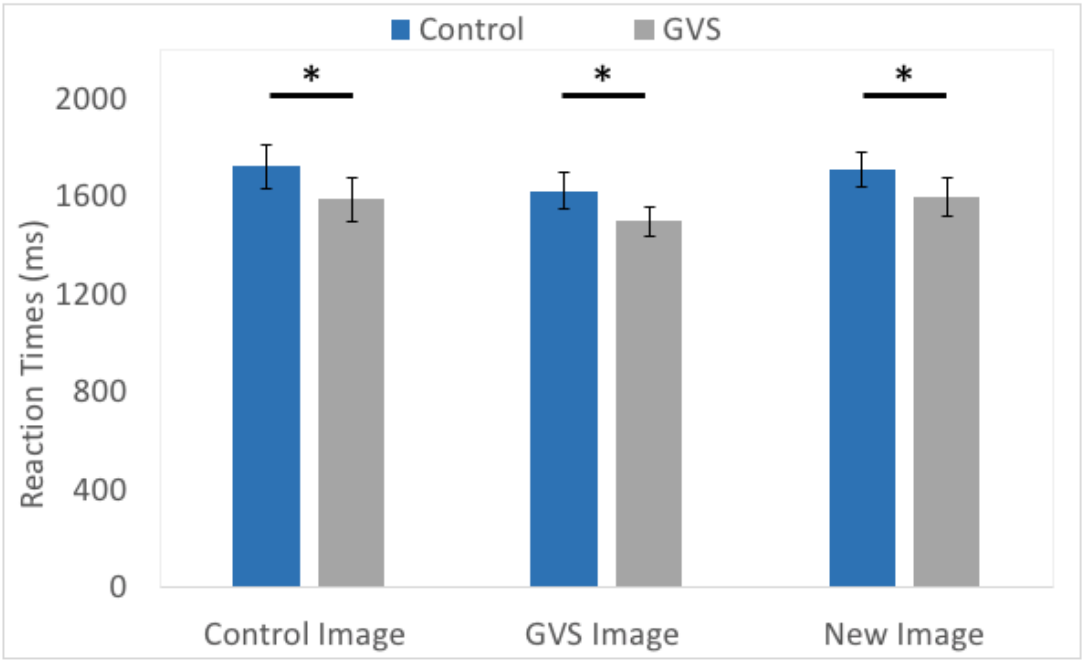

Figure 2.6. Combined reaction times for the 6 key comparisons in all four arrays from the second part of the study where participants were tested 30min after completing the first part (part II). A main effect of Location was found significant (p=.02), no other significant effects were found. Error bars represent standard error of the mean.

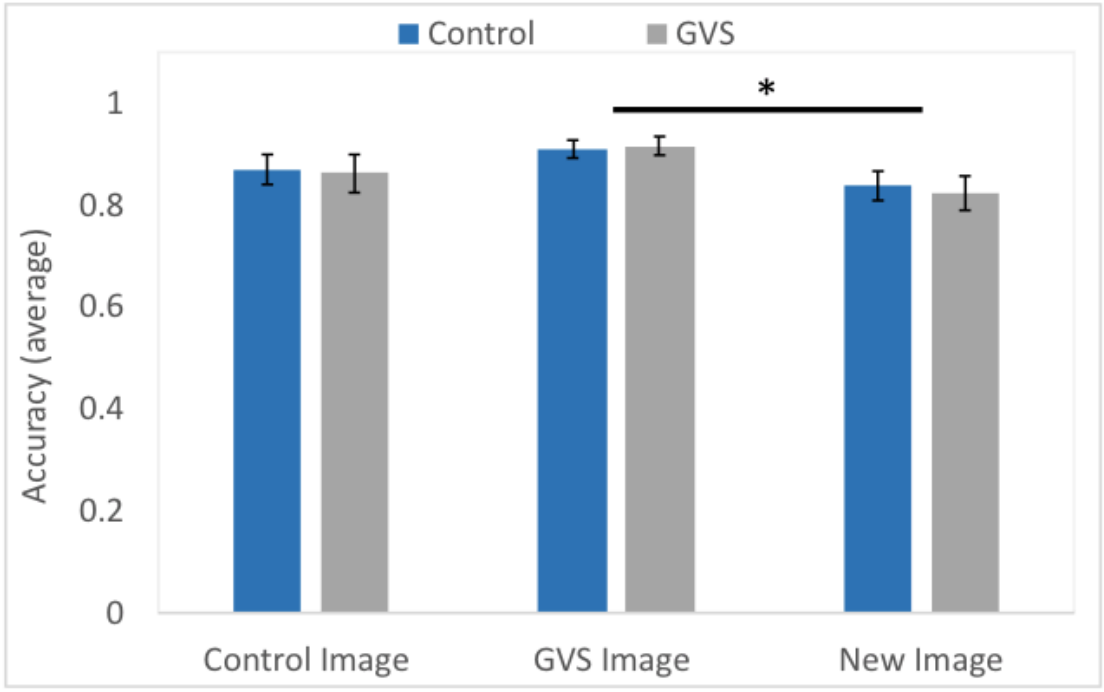

Figure 2.7. Average accuracy for the 6 key comparisons in all four arrays from data collected 30min after completing the first part (Part II). A main effect of Image was found significant (p=.02) between the GVS image and the New image, no other significant effects were found. Error bars represent standard error of the mean.

Discussion (1)

Over the last three decades research has demonstrated that vestibular sensory inputs are important for spatial learning and memory and artificially stimulating the vestibular system via GVS can modulate visuospatial memory. Existing literature suggests that visual memory is facilitated when a stimulus from a different sensory modality is encoded at the same time as the visual event (Driver & Spence, 1998). A recent study investigating whether vestibular signals could enhance memory in a similar way showed that a stimulus that was incidentally encoded alongside a vestibular input was processed more efficiently relative to unpaired controls (L. Smith et al., 2020). The present study aimed to further these findings in an attempt to establish the omnibus effect of the GVS advantage as well as its longevity. By means of a visual search paradigm using Gabor patches as stimuli, it was tested whether participants' responses would be quicker for a pre-determined target that appears in a spatial location that had previously been

paired with a unique vestibular signal, as provided by a brief, sub-sensory pulse of GVS. This was tested immediately after stimulation (Part I) as well as 30 minutes post completion of the initial task (Part II), an interval chosen as proof of principle in an attempt to investigate its lastingness. It was predicted that search would be facilitated for only those visual stimuli that were accompanied by a salient vestibular pulse during encoding.

Results from Part I of this experiment failed to replicate immediate priming effects in RTs or Accuracy. Although descriptive statistics showed that Gabor patches presented in the pre-determined spatial location associated with GVS during the encoding phase were found overall quicker than control objects that were encoded in the absence of stimulation, this difference failed to reach statistical significance (see Figure 2.4 and 2.5). A statistically significant difference was seen however when participants were tested 30 minutes following the initial stimulation (Part II, see Figure 2.6). The advantage was only seen in the *RT* measure, whereas *accuracy* remained consistently high in both parts of the experiment (approximately 80-90% confirming previous studies, see L. Smith et al., 2020), with no statistical effects reaching significance except from a main effect of Image between the GVS and the New image. In the next paragraphs, these results are discussed in more detail; first I interpret the effect seen in Part II of the study, then the lack of effect is discussed and suggestions for further studies are made.

The fact that any image (Control, GVS, New) that appeared in the GVS-paired location was responded to quicker than the Control location in Part II, confirms that GVS highlights the pre-determined visuospatial location that was paired with in such a way that search for any image appearing in that spatial location was facilitated. The specificity of the effect suggests that the location at which the GVS prime occurred was implicitly retained in visual memory so that the identification of any target appearing at the location was subsequently enhanced. These data suggest that vestibular signals are indeed used to enrich unimodal visual representations of space and would be consistent with the idea that GVS interacts with visual memory in a specific rather than generic manner. In particular, if GVS merely up-regulated all processing then search for

both spatial and object properties would have been facilitated, rather than just the spatial properties of the primed object-location association. These results provide initial evidence that the use of the vestibular sensory information in a more specific and direct manner (Bottini & Gandola, 2015) with visual memory processes being particularly receptive to the vestibular sensory input (L. Smith et al., 2010).

Since several studies have shown that the vestibular system plays a role in object-recognition memory (Hitier et al., 2014) it would not have been unexpected if recall for the object paired with GVS were facilitated as well. The present results however suggest that the GVS advantage is limited to spatial properties with an enhancement of non-spatial aspects not supported from the data. This lack of a main effect of Image is consistent with previous studies (L. Smith et al., 2020). A difference was found in *accuracy* between the New and GVS images (see Figure 2.7), however this was independent of location and seems to be due to object properties; participants found the New image more difficult to identify than the GVS image. Carefully assessing stimuli for object-properties that make them more distinct or less difficult than others in visual display could potentially eradicate this undesirable complication from future studies.

The location-specific effect seen in Part II is not surprising since the vestibular system provides input about one's position in space (Angelaki & Cullen, 2008) and self-motion and positional information contained within vestibular signals is likely to be particularly relevant for spatial aspects of visual memory. One could argue that a visual-vestibular methodological interaction as the one investigated here would be expected to lead to facilitation of object properties as well as spatial aspects, however an advantage in favour of object-location associations was not supported from the data, as the two-way interaction was not significant. It is possible that if the object properties were relevant to space and navigation, for example they were larger and more prominent and were used as landmarks to guide navigation, they may have been more relevant to vestibular input, which may have led to an additional effect of Image.

Indeed, the aforementioned studies implicating a role of the vestibular system in object-recognition memory following vestibular stimulation attribute its implication to place cell activation, which is responsive to both spatial and non-spatial (e.g., geometric and behavioural) aspects of the environment (see Hitier et al., 2014). An alternative explanation is that vestibular signals carry solely spatial information relevant to where the body and head is positioned relatively to space that informs and enriches visual representations of space in a similar manner with place cells or head direction cells in cognitive mapping (Brandt et al., 2017; Jacob et al., 2014).

Contrary to predictions and the results obtained in L. Smith et al., (2020), there was no statistical significance in RTs between Gabor patches presented in the GVS or Control location when participants were testing for an immediate GVS advantage (absence of Location effect, see Figure 2.4 and 2.5). One possible explanation for the lack of effect is that neuro-plastic changes in synaptic strength could only be achieved after a certain period of time following GVS administration. Recall that additional pulses of GVS were not administered in Part II, only the test blocks were conducted, therefore the significant effect seen in Part II is not a result of additional stimulation. Alternatively, neuro-plastic changes in synaptic strength could only be achieved after at least a certain number of GVS pulses were administered in order to improve neural communication associated with the control and storage of information in short-term memory processes (Reinhart & Nguyen, 2019). Individual block analysis of Part I (see Appendix B, part A) showed that the obtained results could be interpreted in two ways i) the GVS prime was possibly established already from block 1 and was maintained throughout the blocks (all but the last one, which could be attributed to fatigue, see below) but the magnitude of the effect could only be revealed 30min after stimulation (see Figure 2.6), or ii) that the difference reached statistical significance only after block 5, therefore after 15 pulses of GVS were administered, implying that a strong GVS advantage may be a result of accumulative stimulation. Both these interpretations would suggest a carry-over effect from Part I, which, given that it was present in

all blocks of Part II (see Appendix B, part B), led to statistically significant results in Part II. Given that the previous visual search study (Smith et al., 2020) administered a higher number of GVS pulses (39 instead of 18) and managed to detect an effect immediately after stimulation, future studies could consider increasing the number of GVS signals incorporated into the paradigm to enhance recall for spatial locations.

Another potential explanation for the lack of effect in Part I may be that the presence of distractors may have caused interference leading to prolonged RTs (DeSimone, Everling & Heath, 2015; Hout & Goldinger, 2010). Recall that in the present task, each of the Gabor stimuli was placed on the circular search display in the presence of a distractor (objects that differed from the target object in one of the features, orientation or spatial frequency, see Methods section), in an attempt to increase the overall difficulty of the task given that only eight stimuli consisted the display in total. However, studies have shown that visual search is affected if distractor objects that share common elements with the target-object are present on the visual display (see DeSimone et al., 2015; Hout & Goldinger, 2010; Á. Kristjánsson & Campana, 2010). Since in this experiment, the search for Location (implicit) is associated with the search for Image (explicit), if the search for Image demands a higher cognitive load due to the difficulty of identifying the right target-image, then the search for Location may also be delayed. This conflict may have resulted in delayed RT responses as participants had to decide which of the two images (the real target or the distractor) was the correct target-object. Indeed, prolonged RTs (average = 1675ms compared to 1363ms in the previous visual search experiment even if the array of this last experiment consisted of 12 images, see L. Smith et al., 2020) reflected that participants did not ignore the distracting non-targets. Consequently, the implicit effect of Location may be lost or diluted, and any advantage caused by the GVS signal will not be revealed or not result in significant results in this case in Part I. However, it may lead to significant differences being revealed with additional practice or familiarity with the Gabor patches as participants carry on through the experiment, with results therefore reaching

significance in part II. Note that if one follows this argument, accuracy measures can still reach high levels while interference occurs, as participants can still be correct after delayed RTs. Future research should consider the stimuli composing the visual search display more carefully and evaluate the necessity of including distractors in upcoming experimental paradigms.

In addition, future studies could include shorter experimental protocols to eliminate fatigue effects, as in the present study participants reported that the Gabor patches stimuli were becoming blurrier as they were progressing through the experiment and that eventually they couldn't tell them apart. This may have resulted from the experiment being too long (1.5hrs) and participants being seated in front of a screen for all this time (breaks were incorporated only between blocks). This may also explain the lack of effect in the last block of Part I (Figure 2.5). Future studies should aim to reduce the visual overload by addressing this shortcoming.

To summarize, Experiment 1 failed to replicate immediate priming effects previously seen in a similar visual search study. A statistically significant difference was only when participants were tested again 30 minutes after completion of the first part of the experiment. The advantage seen in Part II suggests that GVS specifically influences the spatial element of the item representation that is associated with during encoding, with subsequent visual searches being facilitated for that spatial location, when subjects return to the same 2-D visual scene. The current results suggest that the GVS prime may not be paradigm-specific, since it can be replicated under different experimental conditions and participants. However, future studies should address why immediate effects of this GVS advantage were absent. Several reasons that could potentially play a role are fatigue effects, interference effects or the number of GVS signals incorporated at the priming phase of the experiment and are all addressed in the next experiment.

Experiment 2: A simplified Gabor patches paradigm incorporating additional GVS signals

Experiment 1 aimed to test whether the GVS advantage previously seen in an implicit memory task (L. Smith et al., 2020) will hold in an entirely new paradigm that uses different

stimuli and is developed keeping in mind patient needs. Results failed to replicate immediate priming effects however, when participants were tested 30 min following completion of Part I, previously obtained results that GVS specifically influences the spatial element of a stimulus representation were confirmed. Several limitations were believed to have restricted the GVS prime from facilitating visual search which would subsequently lead to strong immediate effects in accuracy and RT measures. These limitations were addressed in Experiment 2. More specifically, the length of the task was modified and the number of GVS pulses administered was increased. Given that participants reported tiredness and blurriness while conducting the previous experiment, which probably resulted from the lengthy exposure to Gabor patches, the overall number of repetitions in each block was reduced in half (two instead of four repetitions, see schematic diagrams of the experimental procedure on Figure 2.1 and 2.10). However, in an attempt to increase the overall number of GVS signals administered throughout the experiment, six repetitions of the detection task were used. This meant that participants received 6 GVS pulses in each block, resulting in a total of 36 GVS pulses throughout the experiment (Figure 2.10). This resembles more closely the number of pulses used previously (Smith et al., 2020).

In addition, special care was taken to include Gabor stimuli that were easier to identify, in an attempt to resolve the interference effects identified in Experiment 1. Given that visual search is affected if distractor objects that share common elements with the target-object are present on the visual display (see DeSimone et al., 2015; Hout & Goldinger, 2010; Á. Kristjánsson & Campana, 2010), stimulus manipulations ensured that all Gabor patches differed in both within-feature elements (both spatial frequency and orientation) instead of restricting changes to one feature per stimulus, as in Experiment 1. Furthermore, similar to Experiment 1, the effect was tested 30 minutes (Part II) as well as 2 hours (Part III) after completion of the first part of the study, in an attempt to replicate the 30-minute delayed effect seen in previous experiment and establish the longevity of the GVS advantage.

The sections that follow explain in more detail how these changes were implemented. As

per previous experiment, it was predicted that Gabor images presented in the spatial location co-incidentally encoded with a brief, subsensory GVS will be recalled more quickly than images presented to participants in a control location.

Method (2)

Participants

A total of 25 individuals took part in this study (study terminated early due to stimuli limitations, see below). Recruitment took place as previously described and participants who took part in Experiment 1 were not permitted to participate in this study.

Procedure and GVS stimulation protocol

All stimulation was performed by galvanic vestibular stimulation units and procedure followed was as described in Experiment 1. As noted above, a total of 36 pulses of GVS were administered throughout the detection phases (see Figure 2.8). GVS thresholding took place to ensure participants received sub-sensory stimulation and perception was also assessed at the end of the experiment using the same questionnaire as per previous experiment (Appendix A) to identify those participants who perceived the stimulation during the experiment (N =1). Four additional participants requested to withdraw from the study after reporting that they couldn't tell apart the Gabor images as the lines that determine spatial frequency were blurring into one. The final analysis was conducted on 20 participants.

Four arrays were included here as per previous experiment and were counterbalanced across participants. To deter participants from using explicit strategies when detecting the targets, all targets were used in all potential locations of the circular arrays, as previously described in Experiment 1. In an attempt to establish the longevity of the effect, this experiment tested participants 30min after completion of Part I (similarly to Experiment 1) but also 2hr following completion of Part I (Part II) as well as the following day (24hr – Part III). The experiment lasted

for approximately 1hr and each follow-up section 20-30min.

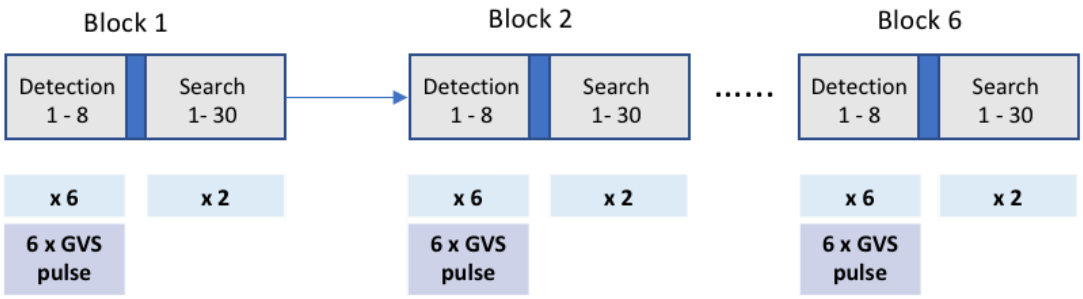

Figure 2.8. Schematic diagram of the experimental procedure summarizing trial structure in both detection and search tasks in Part I of Experiment 2. Six repetitions of the detection task were presented and only two repetitions of the search task. Six blocks were used in total. A total of 36 pulses of GVS were administered throughout the experiment. Subsequent test phases consisted of the search sections only from each of the six blocks.

Results (2)

Data analysis

As per previous experiment, RTs were the main focus of this study. Outliers were removed as previously described. Analysis first determined whether implicit memory was present in the recall phase by comparing correct filtered RTs from trials from stimuli that were presented during the detection part of the study (old stimuli) and these that appeared only in the recall phase, hence were new to the participant (new stimuli). Responses to old objects were slightly faster (*M=1501.6ms*) than responses to objects that were new to the participants (*M=1556.7ms*); this difference however did not reach statistical significance [$t(38) = -.840$, $p=.415$], indicating that priming effects were not present in this experiment and that search performance was not facilitated due to priming. This is concerning as priming effects in experiments that test implicit memory are expected to be present as they indicate implicit memory effects (see Manelis et al., 2011) and could have possibly occurred due to complications with object properties, as discussed below.

All further analyses were conducted upon the key trials, as previously mentioned. Data from all four arrays were combined and all further analysis was performed on correct key comparison trials only for the reaction times measure. The independent variables were Location

(GVS or Control) and Image (GVS, Control or New). A RM ANOVA 3 (Image – GVS, Control, New) x 2 (Location – GVS or Control) analysis was conducted.

Results – Part I

Reaction Times. Neither Location nor Image reached statistical significance; $F(1, 19) = .300$, $p=.59$, $\eta_p^2 = .016$ for Location and $F(2, 38) = 2.50$, $p=.10$, $\eta_p^2 = .116$ for Image (see Figure 2.9). The two-way interaction between Image and Location [$F(2, 38) = .110$, $p=.89$, $\eta_p^2 = .006$] also failed to reach statistical significance.

Accuracy. As expected, accuracy data for the key comparison trials showed ceiling effects in all groups (see Figure 2.10). Main effect of Location was not found statistically significant [$F(1,19) = .305$, $p=.587$, $\eta_p^2 = .016$], whereas the main effect of Image was significant [$F(1.29.24.51) = 7.114$, $p= .01$, $\eta_p^2 = .272$], which derived from a difference between the GVS (*Mean* =.940) and the New (*Mean* =.840) Image ($p= .009$). The two-way interaction failed to reach statistical significance [$F(1.51, 28.8) = .689$, $p = .508$, $\eta_p^2 = .035$].

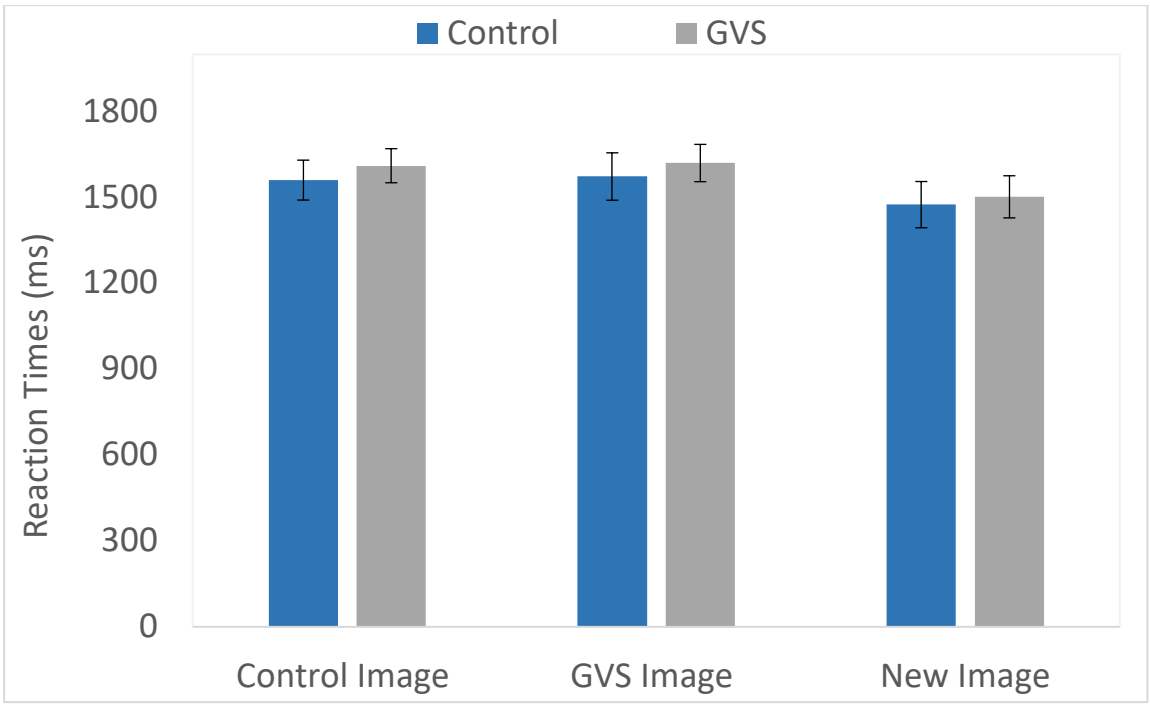

Figure 2.9. Combined reaction times for the 6 key comparisons in all four arrays in part I of the study. No significant effects were found. Error bars represent standard error of the mean.

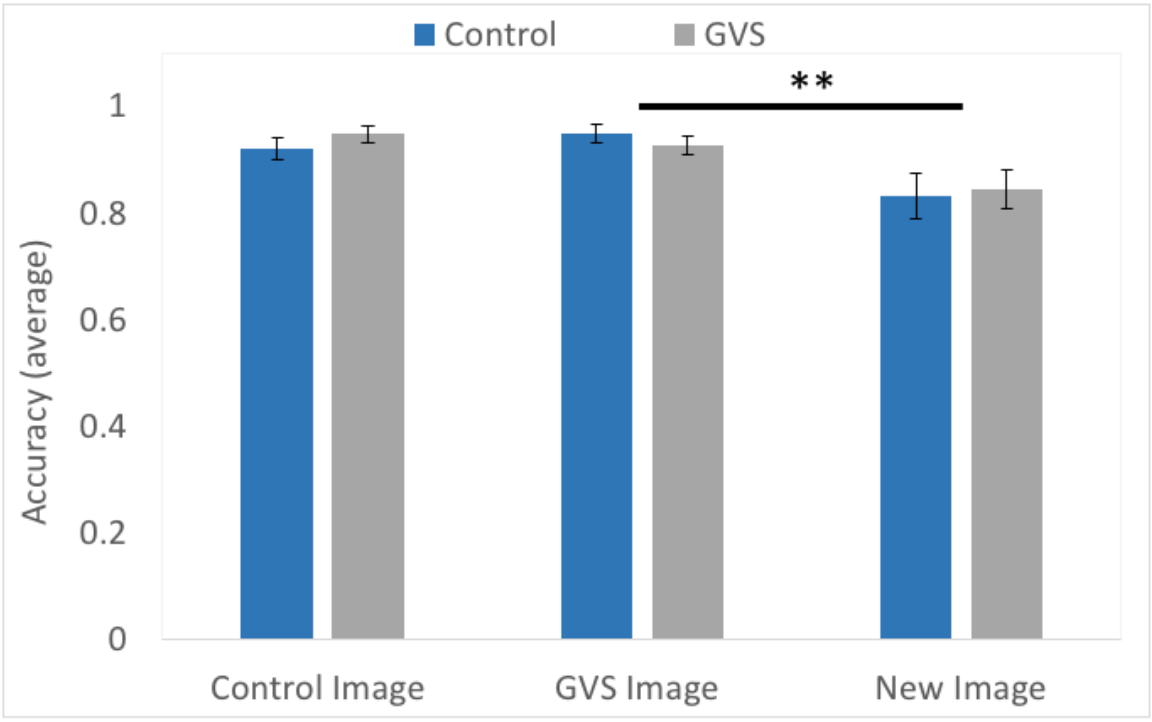

Figure 2.10. Average accuracy for the 6 key comparisons in all four arrays the first. A main effect of Image was found significant (p=.009), deriving from a difference between the GVS and the New image. No other significant effects were found. Error bars represent standard error of the mean.

Results – Part II (tested 30min post completion of Part I)

Reaction Times. The main effect of Location was not significant $F(1, 19) = .062$, $p = .81$, $\eta_p^2 = .003$ but a main effect of Image reached significance $F(2, 38) = 6.61$, $p = .003$, $\eta_p^2 = .25$, whereby RTs were shorter for the New image (M =1351ms) than the GVS image (M = 1518ms). The two-way interaction between Image and Location [$F(2, 38) = 3.692$, $p = .034$, $\eta_p^2 = .163$] was also found statistically significant. Post-hoc analysis revealed this significant difference derived from the Control ($p = .012$) and New Image ($p = .006$), when presented in the Control location (see Figure 2.11).

Accuracy. As expected, accuracy data for the key comparison trials reached high levels in all groups (see Figure 2.12). The main effect of Location [$F(1,19) = .011$, $p = .919$, $\eta_p^2 = .001$] , the main effect of Image [$F(2, 38) = 2.663$, $p = .08$, $\eta_p^2 = .123$] and the two-way interaction [$F(2, 38) = .784$, $p = .464$, $\eta_p^2 = .040$] failed to reach statistical significance.

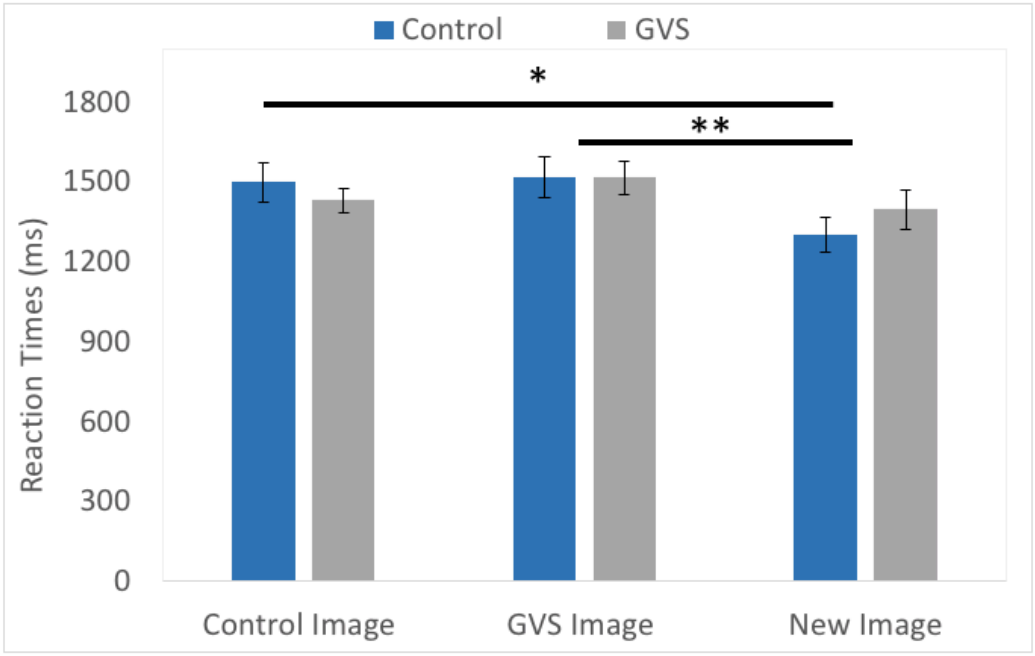

Figure 2.11. Combined reaction times for the 6 key comparisons in all four arrays. The main effect of Location was significant due to RTs being significantly faster for the New image compared to the GVS (p =.003). The two-way interaction between Image and Location was also significant due to a difference between the Control and New Image (p =.03), when presented in the Control location. Error bars represent standard error of the mean.

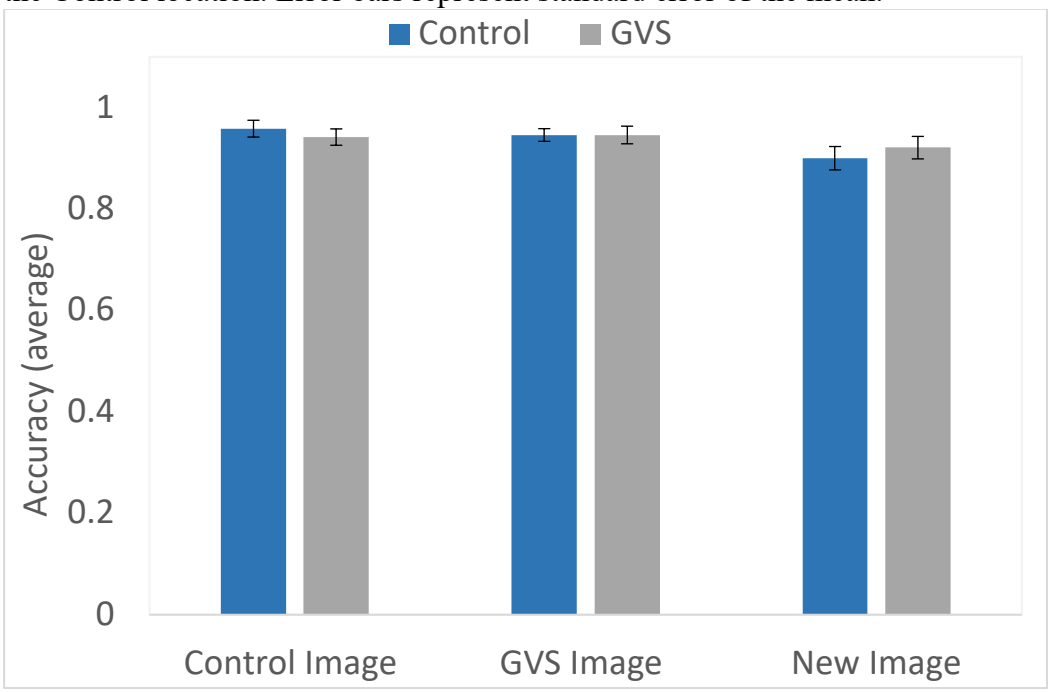

Figure 2.12. Combined accuracy scores for the 6 key comparisons in all four arrays. No significant effects were found. Error bars represent standard error of the mean.

Comparable results were seen for the last part of the study (Part III), tested the next day after the participants completed part I and II of the experiment (all p>.05, data not shown due to space constraints).

Discussion (2)

The current paradigm was an attempt to improve features of Experiment 1 in order to eliminate distractor and fatigue effects. The level of difficulty was amended by means of simplified stimuli and the task length was shortened, while the amount of GVS pulses administered was increased. It was predicted that immediate effects would be found whereby responses to Gabor patches that were temporally paired with the artificial vestibular input during encoding would be recalled more quickly in subsequent encounters of Part II (tested 30 minutes after initial completion of first part) and Part III (tested 2 hours after initial completion of first part) of the experiment. Contrary to predictions, these changes failed to yield similar results to those seen in my previous studies (Part II of Experiment 1 and L. Smith et al., 2020). The significant effects seen in the first part of the study were more accurate responses for the GVS than the New image (see Figure 2.10). When participants were tested 30 minutes later (Part II), a difference was also detected in RTs for these two images, with significantly shorter responses for the New than the GVS image, regardless of whether they were placed in the Control or GVS location (see Figure 2.11). Furthermore, participants responded more quickly to the Control than the New Image, when presented in the Control location (see Figure 2.11). In the paragraphs that follow, possible methodological limitations that may have contributed to the lack of Location effect seen in previous studies are expanded upon.

Overall RTs in the current experiment were shorter (M = 1524.25) than in Experiment 1 (M = 1675.02), which indicates that the current version was indeed simplified and that the objects selected as part of the visual search display did not cause conflict in target selection judgements. It seems however that prominent object-property effects were present in this dataset which may have masked a GVS facilitatory effect. In part I of this study, RTs for the New image were overall faster compared to RTs for the GVS and Control images (see Figure 2.9), suggesting that the New image was far easier to recognize and respond to in the display. Given

that this image is new, participants were expected to show less familiarity to it compared to the images that they previously encountered (Control, GVS) during the priming phase (priming effects, see Manelis et al., 2011). This unexpected result implies that in the present experiment the New images were more memorable. A closer look into the response patterns to these stimuli within each array individually provides further support to this interpretation (data not shown). Object-property effects that favour one stimulus over another may have also contributed to the lack of priming effects, as the difference between RTs for new and old objects did not reach statistical significance (see data analysis section). Accordingly, it is possible that my over-simplification of the stimuli leads to explicit memory strategies being employed by participants and future studies should address these limitations.

Moreover, reports of blurriness and visual problems were increased in this study compared to the last, with participants reporting during debrief that the Gabor patches were indistinct and that the lines that defined spatial frequency started “blurring into one” as they carried on with the experiment. Undeniably, this could be attributed to the longer priming phase and could suggest that the extended length of the priming phase may have led to the lack of effect due to tiredness and fatigue. It is worth mentioning at this point that participants reported they found the priming phase too long and showed lack of engagement, which probably led to them using the response button during the detection task without really attending to the objects on the screen and could further explain the aforementioned lack of priming and lack of effect. Future studies should take into consideration visual and cognitive load in the proposed study design, but also ensure that the experimental protocol of the priming phase is engaging so that encoding is facilitated.

The above methodological constraints and limitations make it difficult to interpret whether GVS indeed facilitated visual spatial encoding but the effect couldn’t be revealed because the experimental conditions masked the effect. Recall that the detection task was much lengthier compared to previous experiments (it was presented to the participants six times instead

of three as in Experiment 1) to enable participants to receive twice the amount of GVS inputs (see Figure 2.8). It is possible that the GVS advantage could be replicated in future paradigms that incorporate an increasing the number of GVS signals while trying to shorten the length of the detection task in an attempt to limit visual overload (believed to have masked the effect). However, the time constraints of this PhD restricted a step-by-step methodological approach whereby only one paradigm alteration was implemented in each experiment. In addition, such experimental designs would still need to address the issues of the visual overload causing blurred vision due to continuous exposure to the Gabor patches. Recall that beyond furthering our understanding of how vestibular inputs inform spatial memory processes, ultimately the studies reported here aimed to constrain therapeutic applications of vestibular stimulation on amnestic populations and choosing user-friendly stimuli that would be also suitable for clinical populations may be highly beneficial for future paradigms. For these reasons, future studies could use paradigms that are not based on complex associations that rely on stimuli properties that entail both their object-properties and its location (see Manelis et al., 2011 for an example). Rather, further work should opt for experimental designs that focus solely on spatial aspects of stimuli, therefore eliminating the potential interference effects caused by the stimulus properties. An approach of this type would make sense given that the L. Smith et al., (2020) visual search study showed that GVS influenced solely spatial properties of the primed location, whereas object-properties of the image coincidentally presented in that primed location remained unaffected by the artificial vestibular pulse. Indeed, the paradigm implemented in the next (and last) experiment in this chapter was specific to testing spatial locations based to this approach.

Experiment 3: Developing a paradigm that solely tests spatial aspects of stimuli

Experiment 1 partially verified previous reports that vestibular signals preferentially affect spatial aspects of an object, and that object identities are not affected. Experiment 2 failed to show such an advantage, however methodological issues may have prevented such results from being detected. The manipulations performed in the two previous experiments focused on

the non-spatial attributes of the stimuli which, in hindsight, may have been misplaced given evidence that GVS interacts most strongly with spatial stimulus features (i.e., L. Smith et al., 2020, Experiment 1 of this thesis). Following this line of thought, the paradigm used in Experiment 3 did not rely on a visual search task or object-location associations and instead used a different experimental paradigm that probed only visual-spatial processing. While this shift limits direct comparisons with the rest of the experiments presented in this chapter, these changes were believed to be necessary to determine whether a more robust effect of visual-vestibular interactions could be found.

A potential paradigm that would suit such needs is the computerised version of the Morris Mater Maze Task (MWMT) which has been extensively used in animal (Vorhees & Williams, 2014) and human studies (Brandt et al., 2005; Dobbels et al., 2020; D. A. Hamilton et al., 2002) to directly test memory for spatial locations and is considered the golden standard test for hippocampal-dependent spatial learning and memory. In this task, subjects are trained to locate a hidden escape platform that is submerged in a circular pool of opaque water. Local cues are not present, and subjects learn the location of the hidden platform based on distal cues that are placed in the surrounding area of the pool. Once place learning for the platform has occurred, even if subjects are asked to begin from different starting positions, they could still take a direct path to the hidden platform using the external cues as reference points. The theoretical basis of this task rests on the notion that spatial memory and perception are relative; that is the location of an object is remembered relative to a point of reference (a prominent object in the environment) or a reference frame, rather than its absolute position, which entails remembering the exact coordinates of the object's location (Taylor & Tversky, 1996). Subjects construct a ‘cognitive map’, which is a mental representation of the landmarks and paths in the environment and are able to reach the target platform by any route available, not just the one used during learning (see Iaria et al., 2009), therefore testing place learning and spatial memory specifically. A similar paradigm could be used to test memory for spatial location, with memory load for object

properties significantly reduced.

After reviewing the place learning literature, a suitable 2- dimensional experimental paradigm was identified which could be adapted for the present study. Fitting, Wedell and Allen (2009) tested memory for spatial location while participants navigated within a spatial circular display on a computer screen. The task involved a learning phase, during which participants were encouraged to explore a circular area starting from four different positions until they find a hidden platform. No local cues were present to facilitate place learning for the hidden platform, only visual cues situated outside the circular area. A test phase then followed, in which participant's memory for the hidden platform was tested. In order to resemble more closely a real-world environment which is dynamically changing, a navigational component was incorporated into the test phase of this virtual spatial task, whereby the orientation of the visual display was varied in three different ways relatively to the subject so that four different orientations were included overall (0º, 90º, 180º and 270º). This manipulation intended to encourage subjects not to depend on egocentric (self-to-object) cues to find the hidden platform, rather to rely on allocentric (object-to-object) encoding of the spatial location of the hidden platform relatively to the external visual cues (Fitting et al., 2009; Taylor & Tversky, 1996).

The same paradigm was implemented in the current study, which methodologically differed from the other two studies described in this chapter in three fundamental aspects. Firstly, the current paradigm is not a visual search task and the target in Experiment 3 is not present on the display; on the contrary, participants are expected to retrieve the hidden platform's location from memory in the test trials, clearly testing memory for spatial location (i.e., spatial memory, see Fitting et al., 2009). This simplification also ensured that no distractors were present to generate object-based interference as the one seen in previous experiment. Secondly, the structure of the paradigm was changed so that participants did not conduct six blocks one after another, only two blocks were used (other than the practice trials), one in which GVS was administered upon reaching the target platform during place learning and the second one

whereby the platform was presented to them in the absence of stimulation and served as control. Not only did this help shorten the experiment overall to only 30 minutes, given that lengthy experimental blocks contributed to fatigue and cognitive load in previous experiments, but also allowed me to increase the number of GVS signals administered without increasing the experimental trials significantly. Last but not least, contrary to Experiments 1 and 2 where objects were tested in absolute locations, the three display orientation manipulations (90º, 180º and 270º) included in the test phase of the current design tested relative spatial (allocentric) processing. Details of how these changes were implemented in the current paradigm are provided on the Methods section.

Recall that the construction of cognitive maps is a multimodal process that requires the integration of spatial information from different modalities, including vestibular cues (Wolbers & Hegarty, 2010). Since the vestibular system provides information regarding the spatial aspects of visual representations (Experiment 1 and L. Smith et al., 2020), I hypothesised that if vestibular signals are used by visual memory to mark the location of an object in space relative to cues in the environment, then the beneficial effect of GVS seen in part II of Experiment 1 would not only be seen when the exact same scene is presented during the testing phase, but would also hold across display manipulations. More specifically, a GVS effect only seen during the upright condition (0º orientation condition) would suggest that vestibular signals assist in coding the absolute spatial location of an item representation and would confirm results seen in Experiment 1. If the effect holds following manipulations in display orientations (90º, 180º and 270º), that would indicate that GVS signals are used to code the position of the object relative to cues in the environment, therefore enhancing allocentric spatial processing. These results would be consistent with previous studies which have shown that a GVS-advantage was found present for objects displayed in the position that is associated with GVS during the encoding phase but was tested in a 90-degree inverted grid during the recall phase, whereby the target appeared in a new location represented by new co-ordinates but its position relatively to the cues on the grid

remained the same (L. Smith et al., 2020). Such results would i) further our understanding of how vestibular signals interact and influence memory for visual representations of space and ii) inform therapeutic applications of GVS that aim to remediate spatial memory deficits in clinical populations whose allocentric representations of space are severely affected (Diersch & Wolbers, 2019; Gazova et al., 2013; Harris, Wiener & Wolbers, 2012; J. M. Wiener, de Condappa, Harris & Wolbers, 2013)

To recap, it was predicted that participants will be more accurate and faster at identifying the target platform that was paired with GVS compared to the one that was presented in the absence of stimulation both when the display was presented to them in the same orientation and in a varied orientation. The methods and experimental paradigm implemented to test these hypotheses are explained in detail below.

Pilot studies

Two pilot studies preceded the main experiment and, in an attempt to keep this chapter concise, only their key-points are summarised here. Apart from serving to resolve technical issues while setting up the paradigm, the pilot studies also helped to indicate the optimum number of external cues that were needed to facilitate navigation to the hidden platform and at the same time still maintain a level of difficulty so that the task is engaging to participants; it is well established within the spatial memory literature that the number of cues present influences place learning with more visual cues contributing to better perceiving exact locations (Fitting et al., 2009). Given that participants' performance in the original version of this paradigm achieved ceiling levels, in order to increase task difficulty and make the task more engaging, one could decrease the number of visual cues present in the visual scene. However, additional cues also served to better perceive the display orientation manipulations (Fitting et al., 2009). Since in this study, participants were not provided with visual feedback as to where the platform was located until the end of the block, it was of vital importance to investigate during the pilot studies how to

achieve balance between making sure that participants perceived any scene manipulations made and at the same time maintaining a level of difficulty so that participants remain engaged. The solution to this challenge was to manipulate the field around the search area by introducing a background image across the circular area which split the whole visual display into two different sections (green and blue section, see Figure 2.14) and provided substantial cues that the visual field changed orientation.

In addition, the number of trials (and subsequently GVS pulses administered) during the learning phase had to be established to ensure that sufficient learning has taken place prior to testing memory for that location. Recall that a careful examination of block analysis in Experiment 1 revealed that a difference between the RTs from GVS and Control trials was already established from Block 1 (see Appendix B, part A). Taking into consideration that a substantial increase in GVS pulses in Experiment 2 did not lead to replicating previously seen results (from Experiment 1), instead of using numerous repetition blocks in which participants received stimulation, then proceeded into the test phase, followed by more stimulation and testing, in the current study, a more straightforward approach was chosen whereby participants received stimulation at the beginning of the block (continuously in one trial after the other instead of only one pulse per block). Eight pulses of GVS were administered given that four pulses did not lead to a significant effect in one of the pilot studies. This meant that the learning phase was adapted from Fitting et al., (2009) to consist of eight learning trials (see Methods section below for more details).

Methods (3)

Participants

A total of 56 individuals took part in this study. Recruitment and request of ethics approval were followed as previously described. Participants who took part in Experiment 1 and 2 and previous pilot studies were not permitted to participate in this study.

Procedure

All participants attempted to navigate to the location of the hidden platform that were located within a circular field in each block. The target platform represented the escape platform in the conventional Morris water maze task. Each experimental session consisted of one practice block and two test blocks (GVS or Control, see Figure 2.13). Each practice and test block contained a learning phase, in which participants learned the location of the hidden platform starting from eight different positions followed by a test phase that consisted of 48 test trials (12 repetitions of 8 starting points x 4 conditions, 1x upright and 3x whereby display orientation was varied: 90º, 180º and 270º). In each block, only one platform was the target, which, during the learning phase, was either accompanied by a brief burst of GVS (GVS platform) or presented in the absence of stimulation (Control platform). Instructions in the learning phase encouraged participants to explore the circular area until they find the hidden platform. They were asked to pick up and move an arrow image within the circular area continuously in search of the one hidden target platform, which became apparent only when they hovered over it with the mouse. This ensured they engaged with the task and replaced the response button used in Experiment 1 and 2 where participants were asked to press the spacebar as soon as they detected the stimulus on the screen during the priming phase. In the GVS trials, participants received stimulation as soon as the mouse reached the hidden platform and the platform became apparent. To ensure that participants learnt the locations of the platforms, the orientation of the display was not varied in the learning phase. Given that the learning trials were eight in total (one for each starting point), eight pulses of GVS were administered.

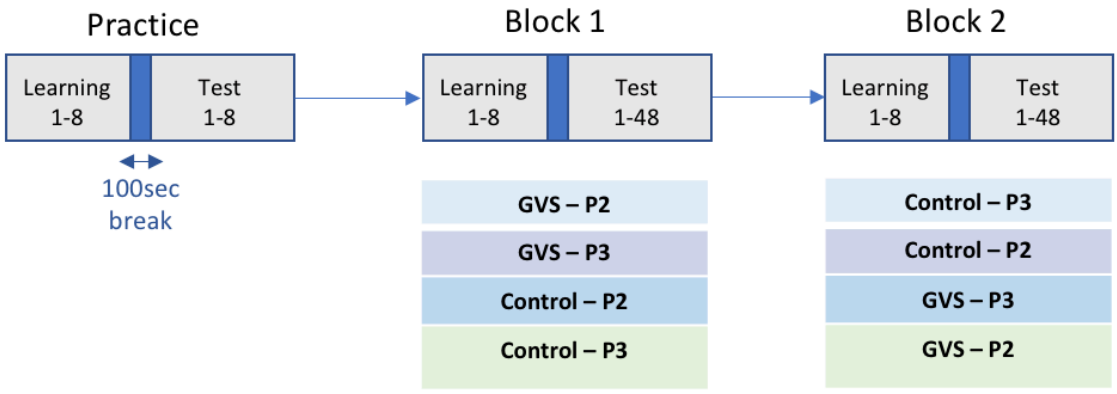

Figure 2.13. Schematic diagram of the experimental procedure summarizing trial structure in Experiment 3. Each participant completed a practice block (consisting of 8 learning and 8 test trials), followed by two test blocks (consisting of 8 learning trials and 48 test trials). The colored tables show the allocation of participants in four different groups. If one assumes P1 was the practice platform, P2 and P3 platforms were associated with GVS or Control blocks in a way that half of the participants completed the paradigm having associated the P3 platform with GVS and half of them the P2 platform with GVS, in order to eliminate bias (see methods section for coordinates). In addition, half of the participants completed the GVS block first and half of them second to limit practice effects.

Following a break of 100sec, participants were introduced to the test phase. Here, the platform was again hidden and participant's memory for its location was tested. During this phase, the orientation of the platform location was varied, and three different orientations were included (90º, 180º and 270º). However, the exact location of the target platform relatively to the external cues remained unchanged (see Figure 2.14). Three cues were inserted externally of the circular area, as shown in Figure 2.14. Platform locations were strategically positioned whereby bias due to spatial configurations was eliminated (for example, platforms were not positioned in areas where participants could form mental geometric shapes between the platform and external cues which would subsequently favour memorising platform locations). Participants were expected to rely on these external cues to help them navigate within the circular area and find the target locations. The external cues were deliberately created in bright shades that were highly distinguishable from each other and could be used as landmarks. The platform's location remained hidden during the test phase and no visual feedback was provided to participants about the platform's location until the completion of the block. In order to make the task more engaging, a score was included at the end of each round, which provided feedback on their

performance. The score was accompanied by a visual representation of the location of the hidden target and the location of participant's estimations of where the target was in all four conditions, upright and the three conditions where the display manipulations took place.

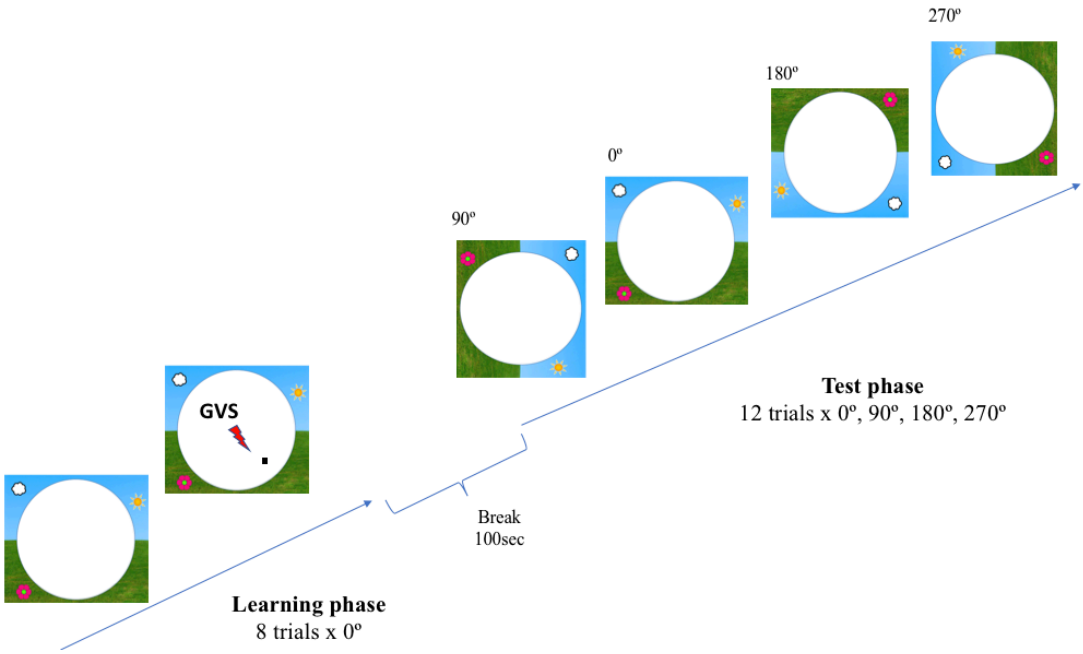

Figure 2.14. Schematic diagram of experimental session in each block. In the learning phase, participants were instructed to move the cursor over the circular area until they found the hidden platform. Upon reaching the target platform in the GVS block, a brief pulse of GVS was administered, whereas in the Control block, the platform was presented in the absence of stimulation. Participants' memory for location was tested in the same scene in the test phase, however here the orientation of the array was manipulated. Three blocks were completed in total (Practice, GVS and Control).

The procedures described above were illustrated to the participant during a practice block, which was conducted at the beginning of the experiment and served to provide elaborate verbal feedback on participant's performance to ensure the task was understood. Participants were given explicit instructions to conduct the experiment as fast as possible and as accurately as possible, without compromising one for the other (i.e., be really fast but risk clicking in the wrong location). This was already practiced during the learning phase in which participants were encouraged to practice moving directly to where they estimated the target was located. By the end of the practice block, participants reported they were clear on how to conduct the experiment. In addition to counterbalancing the location of the platforms (see Figure 2.13), half of the participants conducted trials in the Control location first and half the GVS location first, in

order to eliminate practice effects (see Figure 2.13). No explicit clarifications were given about the display orientation manipulations and all trials (learning and test trials) were randomized. In total, participants completed 24 (8 starting points x 3 platforms – practice, GVS, Control) trials for the learning phase and 144 (48 test trials x 3 platforms) for the test phase. The experiment lasted 20 - 30 minutes.

Materials

Participants were tested individually and were seated in a comfortable chair in an isolated testing lab with instructions presented on a 15-in computer monitor. A padded chin rest was used to keep participants' head position constant to minimize movement during the experiment. The visual display consisted of a circular area which was presented on a grey background. The three external cues were anchored in the following positions in x, y coordinates: sun 27, 3 ; ball 3, 27; cloud 3, 3. Two of the external cues were equally distant from each platform and the third one was exactly in the middle, so that they create an equilateral triangle. Their location was constrained so that participants could not take a straight trajectory toward a visual cue from any starting location and find the platform. An invisible grid with 31 rows at the y coordinate and 31 columns at x coordinate divided the background area and was used to track participants' path and calculate the number of moves (which was the number of grid squares) participants made while navigating within the circular area.

The starting point varied across eight different positions (North, South, West and East plus the in-between points) and was illustrated with an arrow image. Each trial started with the cursor in the middle of the circular area. Participants were initially instructed to move the cursor to the starting position, click once with the left mouse button to engage the arrow image to their mouse movements, then navigate the circular area until they discover the hidden platform, which became only visible once they hovered over it with the arrow image/mouse cursor. The hidden platform was always a black square, which depending on the round, was either the GVS or the

Control platform. The x, y coordinates for the GVS platform were 9, 23 (P2) and the Control 21, 7 (P3, vice versa for the counterbalanced group, see Figure 2.13). They were then asked to click again with the left of the mouse inside that target square, which consequently dropped the arrow image inside the target location square. The locations of two platforms were counterbalanced so that the distance was the same from all starting points between the two platforms, not to affect the measures of RTs or the number of moves made. The end of each trial was followed by a dynamic checkerboard effect of black and white, which covered the whole background grid area, to avoid providing participants with cues of the key locations. The next trial then followed with the cursor positioned in the middle of the screen.

GVS Stimulation Protocol

All stimulation was performed by galvanic vestibular stimulation units (neuroConn DC-Stimulator) using the bilateral bipolar configuration of anode left and cathode right, as previously described. A single pulse lasting 1000ms was discharged when participants hovered the arrow image over the hidden target platform for the first time, to ensure that the association between the vestibular input and the visual location of the target platform happened when participants were first exposed to this location (exposure to the target location paired with GVS only happens in the presence of GVS). As with previous experiments, thresholding was included in this experiment to ensure that the stimulation was not perceived by participants and was conducted prior to the experiment using a blinding technique, as previously described. Stimulation occurred between 0.25 - 0.3 mA; GVS stimulation was first assessed for each participant at 0.3mA and if perceived, was adjusted to 0.25mA. Participants who still noticed the stimulation during this step were excluded from the study. GVS perception was also enquired at the end of the experiment using a questionnaire (as per previous experiment). Two participants reported perceiving the stimulation and therefore was excluded from the study based on this criterion and two additional participants were excluded due to technical issues (final N=52).

Data Analysis

Measures of *RT* and *accuracy* were included in the data analysis, as well as the measure of *moves made,* which counted the number of background grid squares participants crossed to reach the target platform. Furthermore, given that accuracy in the pilot studies was low since participants could not see the target platform and that they were not given confirmation on the target's location in between trials, it was important to include a measure that would provide an indication of how far from the actual target participants estimated the target platform to be. This *distance from target* variable was measured in cm.

Prior to statistical analysis, the following filters were applied to exclude trials from unengaged participants who did not follow instructions of a direct route to the target. (1) Given that from any starting point, the actual number of square grids participants had to cross to get to the target platform ranged from 3 to 20, any trials less than 3 moves were excluded on the assumption of accidental clicks. (2) Any trial in which participants who took longer than 30 moves to reach the platform was assumed to have been performed contrary to instructions, which were to use the most direct route possible. The 30-move cut-off was established in the pilot studies in which participants took on average of 16 moves to get to the target and was increased to a cut-off of 30 moves to allow for slight deviation in the display orientation conditions. An automated cut-off of no more than 100 moves was included, however no trial exceeded 100 moves. In addition, in the pilot studies, participants' scores of *distance from the target* averaged 2cm, therefore participants with average score of more than 3cm throughout all trial conditions were excluded from the study, on the assumption of lack of engagement (N=4). For all other participants (final N = 49), place learning was verified in screenshots of learning trials, in which all participants moved directly towards the platform from the second learning trial onwards.

The difference between GVS and Control trials in each condition was tested using paired t-tests, when data set followed a normal distribution, or a Wilcoxon Signed Ranks test for paired samples, when the data set was positively skewed (*RTs* and *distance from target*). For the

distance from the target measure for example, it was expected that most scores would be closer to 0, which represented participants estimating the target platform correctly (therefore zero distance from the target), therefore it was assumed that the median will be a more robust indicator of central tendency and less sensitive to outliers, since extreme scores were present for some participants. For this reason, a modified z-score was used instead of a standard z-score. To calculate modified z-scores, the median was subtracted from each participant's score and then divided by the standard value of 1.486*MAD, where MAD stands for Mean Absolute Deviation (Pham-Gia & Hung, 2001). Any resulting modified z-scores that were greater than 2.5 were removed from further analysis. *RTs* and *moves made* were calculated on accurate trials only.

Results (3)

Accuracy. Participants estimated significantly more accurately the location of the GVS-paired platform (M = 0.028, SD = 0.20) compared to the Control platform (M = 0.018, SD = 0.28) when the 2-D scene was presented to them in the same orientation as during learning (see Figure 2.15), as indicated by a paired t-test; $t(48) = -2.33$, $p = .023$. No significant differences were found in the trials where the display orientation manipulation took place (all paired t-tests $p > .05$).

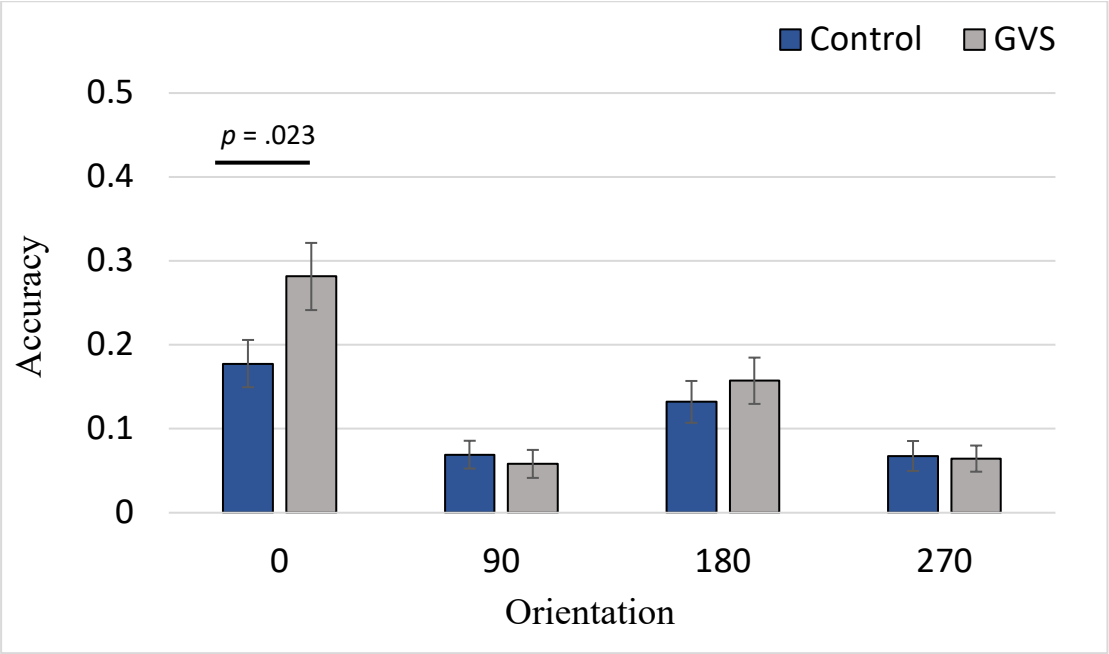

Figure 2.15. Accuracy measures in all conditions participants were tested in. Participants were significantly more accurate for the GVS platform than Control one when the 2-D display was presented in the same orientation as during learning. No other significant differences were found. Error bars represent standard error of the mean.

Reaction Time. Descriptive statistics suggested that participants found the GVS platform slightly faster in the upright condition (*Mdn* = 3.52), compared to the Control trials (*Mdn* = 3.41). In addition, less dispersion in scores for GVS trials in all conditions was observed (see Figure 2.16), however, no significant differences were found (all Wilcoxon paired tests $p > 0.05$).

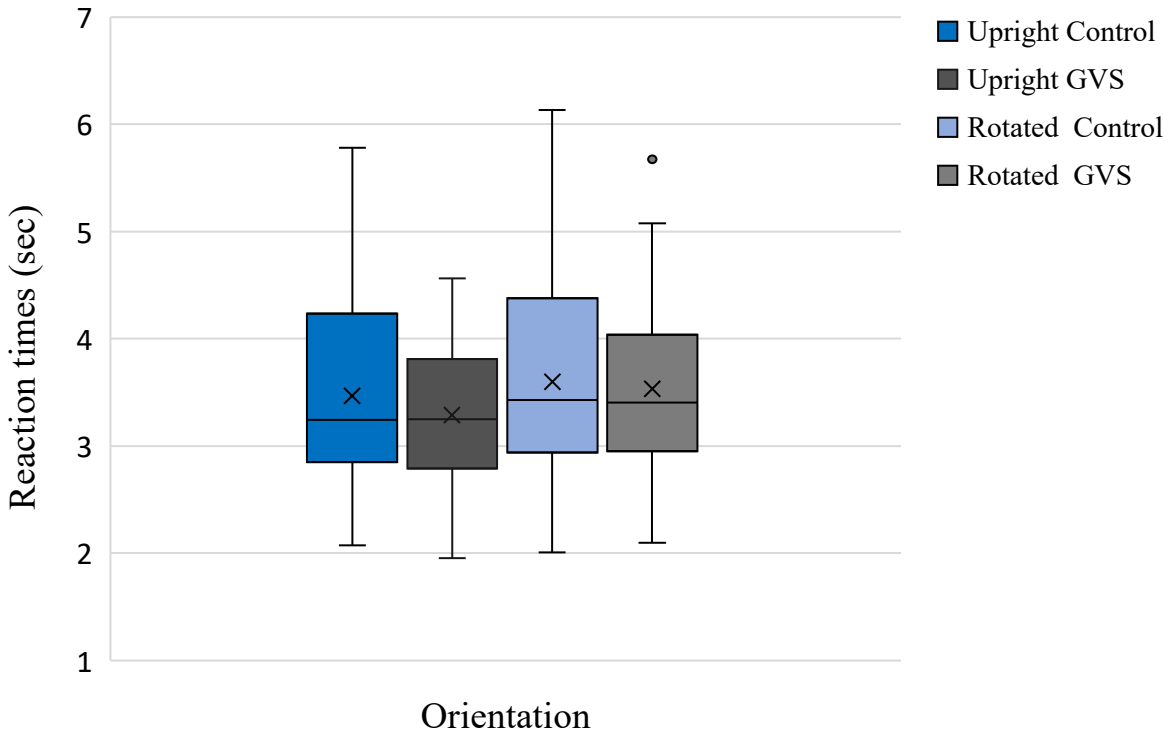

Figure 2.16. Reaction times for all conditions tested. Trials from 90º, 180º, 270º display orientation conditions were combined into one group for simplification, as no differences in RTs were detected within each orientation group. Although values were less dispersed in the GVS trials compared to the Control one in both groups, and slightly faster in the upright condition, these differences did not reach statistical significance. Middle line of the box represents the median, x the mean. Whiskers represent the minimum and maximum value within the group, and the dots the outliers.

Distance from target. Participants' estimations of the GVS location were significantly closer (*Mdn* = .99) than the ones for the Control location (*Mdn* = 1.10) in the upright condition (see Figure 2.17), as indicated by a Wilcoxon Signed Ranks test for related samples (*T = 356, Z = -2.20, p=.028*). This difference however did not remain significant when accurate trials were excluded (*T* = 426, *Z* = -1.25, *p*=.21). No significant differences were found in trials where display orientation manipulations took place (in all paired tests, *p > 0.05*).

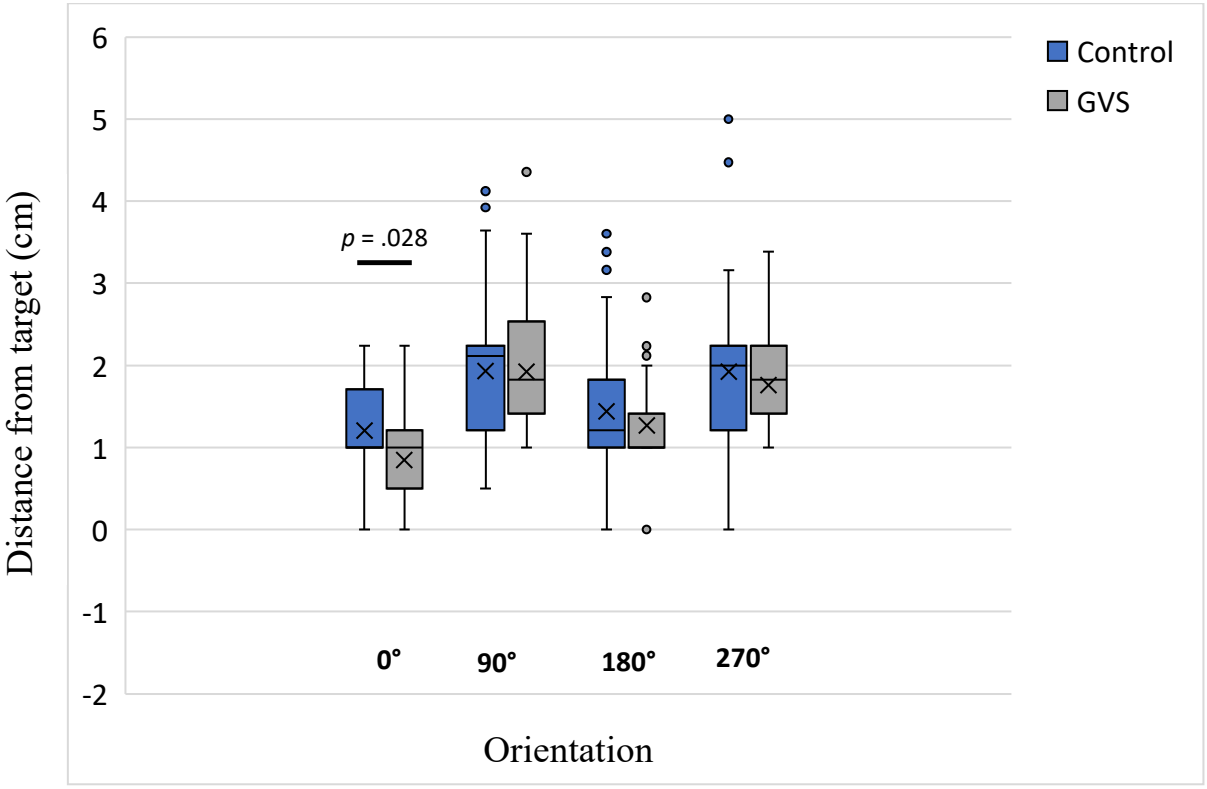

Figure 2.17. Scores for the *distance from target* measure for all conditions tested. Although values were less dispersed in the GVS trials overall, significant differences were only found in the upright condition. Middle line of the box represents the median, x the mean. Whiskers represent minimum (0 equals to reaching the target) and maximum value within each group and the dots the outliers. Includes accurate trials.

Moves made. Participants made fewer moves to reach the GVS platform in both the upright (GVS *M*= 13.89, Control *M* = 15.07), and rotated (GVS *M*= 15.14, Control *M* = 15.64) conditions (see Figure 2.18), however this difference between the two platforms did not reach significance in none of the groups tested (in all paired t-tests, $p < .05$).

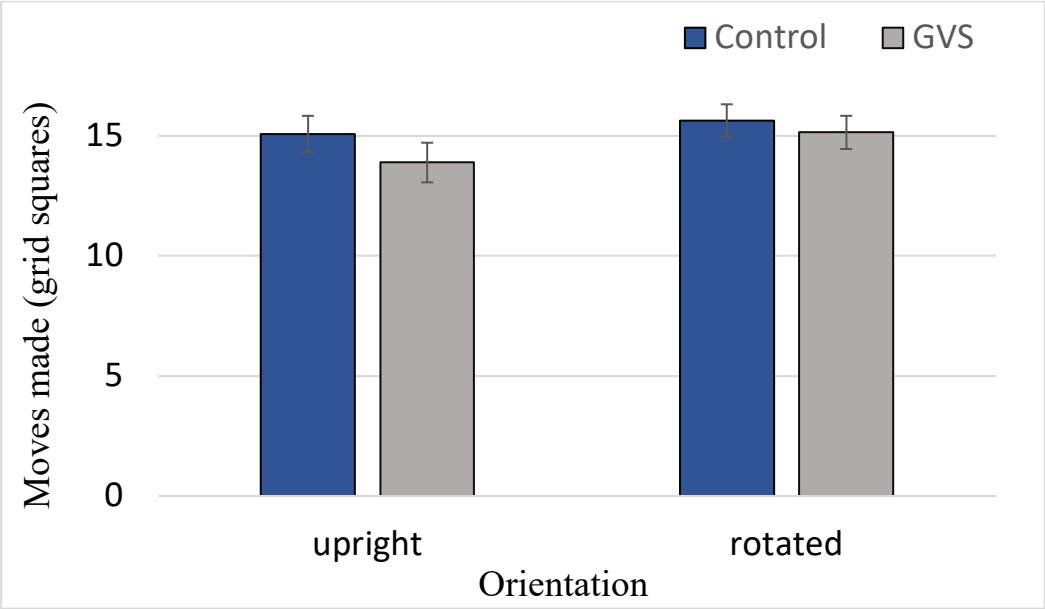

Figure 2.18. Moves made in all conditions participants were tested in (measured in grid squares). Overall, participants made less moves to get to the GVS location in both upright and rotated conditions. No significant differences were found in the moves made in either condition. Trails were collapsed across rotated conditions for simplification. Error bars represent standard error of the mean.

Discussion (3)

Experiment 3 was designed to examine whether the GVS priming advantage identified in Experiment 1 would hold in a paradigm that minimises the possibility for spatial bias to be affected by object identity. A navigational component was incorporated in this spatial task by including three display orientation manipulations (90º, 180º and 270º) on the theoretical basis that spatial memory and perception are relative; that is the location of an object is remembered relative to a point of reference such as prominent objects in the environment (Taylor & Tversky, 1996). This addition meant that during recall participants were presented with the same 2-D scene they encountered during encoding however in some trials that scene was presented at the same orientation as during learning and in others the display orientation changed relatively to the participant. In all trials however the exact position of the target platform relative to other objects on the screen remained the same. By including this manipulation during recall it was examined whether vestibular signals assisted in encoding the position of the object relative to the external visual cues in the environment as opposed to just encoding its absolute location. I predicted that

recall would be facilitated for that spatial location that was paired with a unique sub-sensory pulse of GVS during place learning i) when the encoded 2-D scene is presented in the same orientation as well as ii) when the display orientation varied.

Consistent with the first hypothesis, the results from the upright condition indicated that participants were significantly more accurate at finding the exact location of that target platform that was accompanied by the temporally coincident vestibular input during learning. These results are consistent with the trend seen in part I of Experiment 1 and the statistically significant difference in participant's responses for faster recognition of GVS-paired stimuli compared to these presented in the absence of stimulation seen in part II of Experiment 1. This outcome also replicates previous reports that have shown a similar GVS priming advantage confirming the cross-modal interplay mechanism (Smith et al., 2020). Recall that both these previous studies used a visual discrimination task in which participants were asked to identify the target within a visual display of possible targets present. In the current paradigm however, participants had to retrieve the target location entirely from memory and with no target – distracter discrimination taking place. Experiment 3 hence confirmed previous evidence that unimodal visual representations of space are enhanced by temporally coincident vestibular input and helps to further establish the pervasiveness of the GVS prime which is shown in the current experiment to extend to paradigms specific to spatial memory. Interestingly, this effect was found after a short stimulation protocol (recall that only one round of 8 pulses of GVS were administered) in a much shorter paradigm compared to Experiment 1 and 2.

Contrary to prediction, responses for the target platform paired with the GVS input were not facilitated (see Figure 2.16), although RTs were slightly shorter for the GVS trials. A potential explanation for the lack of effect in participants' reaction time responses could be the fact that participants were engaging more actively in the current paradigm. Recall that participants were instructed to click on the image indicating the starting point, drag that across the circular area and click on the exact location they estimated the target platform to be. This

may have prevented any reaction time advantage from being revealed. The fact that the paradigm was manually demanding may also be the reason why the GVS prime was revealed in previous experiments in RTs whereas in the current experiment it was found in accuracy measures.

Contrary to the hypothesis, the current paradigm failed to reveal a GVS advantage when display rotation took place, whereby accuracy and RT performance were similar for both target platforms. This indicated that spatial memory was facilitated by the vestibular input only when the same exactly scene as during encoding was presented to participants. These results are consistent with the encoding specificity principle in which memory retrieval is optimal when visual cues at recall match these at encoding (Tulving & Thomson, 1973), with the original spatial configuration and orientation important for subsequent visual memory retrieval (Sun & Gordon, 2010). Indeed, changes in display orientations cause rise in errors of judgement in tests of spatial perception and working memory (Harris, Stone, O'Bryant, Proulx & Johnson, 2000), which increase as the degrees of orientation increase (Fitting et al., 2009; G. R. Harris et al., 2000). Recall that participants encoded spatial locations during the learning phase in the upright condition only, and various display orientations were then assessed during the test phase, to enforce retrieval within allocentric spatial reference frames. The fact that the learning of the key locations was limited to the upright condition, however, may have elicited a strong self-based encoding of spatial representations, which was carried onto the other conditions throughout the experiment. This is indicated from participants' estimations of the target platform being far from the actual target platform, as shown by the *distance from target* measure (see Figure 2.17), showing that participants did not transfer the learning of the original spatial configuration onto the trials where orientation manipulations took place. The current results are inconsistent with previous studies that have shown that GVS encoding is relative to other objects on the visual display (L. Smith et al., 2020), however the display manipulation on this latter study was restricted to only one change of orientation (90º), which could possibly still have allowed self-based encoding to have an effect (e.g., if target location is encoded on the left, is tested on the

right relatively to the participant when the display is rotated by 90º). Future studies should address these limitations during the encoding phase (see further discussion on the next section).

Despite the above limitations, Experiment 3 confirmed previous reports of vestibular inputs being exploited by visual memory to enhance and individuate one visual event from another. The current study is the first account that have shown improvement specific to spatial memory retrieval in a spatial navigation task following coincidental vestibular-visual cross-modal encoding. This effect was replicated after a short stimulation protocol and a relatively low number of vestibular inputs, however future studies should address whether the GVS advantage will hold when display rotations occur, as this would resemble more closely real-life conditions whereby spatial configurations (e.g., spatial relationships) between targets or landmarks and one's body change as one moves in space. Further research could also explore whether clinical populations who suffer from spatial memory deficits would benefit from the effect shown here. Further discussion of the main findings from Experiments 1-3 is provided below.

Chapter Summary and Discussion

The current chapter mainly explored whether salient vestibular signals that are presented incidentally with visual stimuli can be used by visual memory to individuate one visual memory event from another. Three experiments were conducted using an experimental design that explored whether a spatial location encoded with a salient GVS signal (cross-modal encoding) was processed faster in a subsequent recall test than other locations which were encoded without stimulation (uni-sensory encoding). The first two were based on an object-location association task and the third experiment tested spatial learning specifically via a 2-D virtual water maze task.

Summary of results

Experiment 1 examined whether memory retrieval is facilitated for a visual stimulus that is paired with a temporally coincident vestibular input during encoding. A novel visual search

task was used with Gabor patches as stimuli and participants' recall was tested immediately as well as 30min post stimulation, in an attempt to establish the longevity of the predicted effect. Results from immediate recall indicated a trend with faster responses to Gabor patches encoded in the presence of GVS compared to control objects that were encoded in the absence of stimulation. Interestingly, any image (Control, GVS, New) that appeared in the GVS-paired location was responded to faster suggesting that vestibular inputs highlight the pre-determined visuospatial location that were paired with in such a way that search for any image appearing in that spatial location is facilitated. Given that the advantage seen only reached significance 30min post stimulation, Experiment 2 tried to uncover an effect by increasing the length of the encoding phase, in order to incorporate a larger number of GVS pulses. This study failed to replicate the previously seen GVS advantage of Experiment 1, however priming effects were not present and stimulus properties seemed to have interfered with the search for location, which implies the lack of a facilitation in memory retrieval may have resulted from these methodological limitations. Furthermore, fatigue and tiredness were frequently reported by participants, which may have also been additional factors for the lack of effect. The methodological limitations of Experiment 2 were addressed in Experiment 3, which tested spatial aspects of the primed location while limiting task reliance on object properties. The paradigm used was specifically designed to test spatial memory within a computerized environment and aimed to eliminate any interference from object identity by encouraging the encoding of objects relatively to the spatial configuration on the display during space learning. In the recall phase, the visual display was tested either in the original or in three different orientations. Results showed that participants were more accurate at finding the exact location of the target platform paired with GVS during space learning. However, contrary to hypothesis, vestibular inputs did not seem to facilitate memory retrieval when the same scene was presented at a different orientation other than the original one. Although these results suggest that the GVS advantage does not hold when testing relative locations of objects in space, given that a previous study showed a similar facilitation (see Smith

et al., 2020), further studies should investigate whether the paradigm provided appropriate cues for an effect to be revealed when display orientation varied (see next sections for further discussion).

Together Experiments 1 and 3 replicated previous preliminary data and provided strong evidence that temporally coincident vestibular inputs interact with visual processes to enhance spatial aspects of stimuli and enrich visual representations of space. The effect was shown in two independent paradigms, a visual search and spatial memory specific tasks, confirming the pervasiveness of the GVS prime and providing the first account to date that vestibular inputs enhance spatial memory specific representations. Experiment 3 further assisted in providing evidence that shorter stimulation protocols are sufficient for an effect to be revealed.

Theoretical mechanism

A key aim of this chapter was to help define the psychological mechanism behind vestibular-spatial memory interactions, as to date, limited research has been conducted on whether visual memory processes make use of vestibular inputs and how (L. Smith et al., 2020). My results confirm and advance previous findings of specific enhancement (Brandt et al., 2005; Kremmyda et al., 2016; Schautzer et al., 2003; L. Smith et al., 2020). Both Experiment 1 and 3 provide theoretical insights about the integration of vestibular inputs into representations of space by suggesting that GVS highlights spatial aspects of the primed location. In addition, the results obtained here suggest that GVS signals help individuate one visual event from another, and although in the last experiment this effect did not seem to hold in more dynamic environments, several experimental constraints could have limited a GVS advantage from being revealed. The specificity of the effect suggests that the location at which the GVS prime occurred was implicitly retained in visual memory so that the identification of any target appearing at the location was subsequently enhanced. These data indicate that vestibular signals are indeed used to enrich spatial aspects of unimodal visual representations in a similar way to other sensory

modalities in the cross-modal literature whereby memory retrieval for a visual event is facilitated if accompanied by a temporally coincident auditory or tactile stimulus during encoding (Driver & Spence, 2000; Lacey et al., 2011; Lehmann & Murray, 2005).

The aforementioned effects could inform previous studies that have shown enhancement towards multiple stimuli after continuous vestibular stimulation and, partly as a consequence, have invoked an account based on general cognitive arousal (Bächtold et al., 2001; Brandt et al., 2005; Dilda et al., 2012; Ghaheri et al., 2014; Ghahraman et al., 2016; Wilkinson et al., 2008). The experimental designs of paradigms used in Experiments 1 and 2 could allow for the conclusions that, if vestibular input merely upregulated all processing, then discharging temporally coincident vestibular signals alongside an object-location association would have facilitated search for the object properties of that stimulus as well as the spatial properties. The present results however suggest that, in addition to the generic account previously mentioned, vestibular signals contribute specific information to spatial memory processes. An effect of Image was not found following vestibular stimulation, only an effect of Location, suggesting that only specific signal content was incorporated into visuospatial processes. It is possible that a generic arousal response following vestibular stimulation could be elicited as well as a specific account which is presented in the current studies. One is inclined to believe that additional GVS pulses used in the current experiments failed to instigate an arousing response due to the short protocol used or due to the sub-sensory stimulation administered, which is less likely to elicit attentional arousal effects (L. Smith et al., 2020). Longer protocols of supra-threshold GVS stimulation, such as the unnaturally long vestibular inputs applied in the aforementioned studies above, or a different stimulation configuration (left ear CVS, anodal GVS to left mastoid) would perhaps have led to generic arousal instead of specific effects.

The results obtained in this chapter are consistent with previous findings of specific visuospatial facilitation in visual search paradigms following coincident brief pulses of galvanic stimulation (L. Smith et al., 2020). In addition, similar facilitation effects have been found within

individual somatosensory sub-modality pathways in which temporally coincident vestibular signals have been shown to increase sensitivity to both mechanical and electrical stimuli (Ferrè, Day, Bottini & Haggard, 2013; Ferrè, Kaliuzhna, Heberlin, Haggard & Blanke, 2014). Furthermore, face recognition tasks (Wilkinson et al., 2008) or visual recognition paradigms engaging spatial and verbal cognitive processes have also shown amelioration following increased vestibular input (Bächtold et al., 2001). The latter studies however have shown effects during vestibular stimulation instead of informing subsequent judgements (visual target identification) or spatial memory processes (memory retrieval for a fine-grain spatial location) as shown in the present studies. In addition, their experimental paradigms are based on multiple stimuli instead of carefully linking individual head movements to individual visual stimuli, therefore failing to address the specific hypothesis here about the potential for vestibular inputs in helping index discrete visual events (L. Smith et al., 2020).

The preceding discussion highlighted the imperative gains the experiments in this chapter offered to further the theoretical understanding between vestibular and spatial memory interactions. The insights gained here however are clouded by several ambiguities, which are discussed in the next paragraphs.

Limitations

It should be noted that although GVS is considered to simulate a natural head movement, the content provided by the visual and vestibular inputs is incongruent, i.e., GVS induces an illusory head movement however visual and proprioceptive inputs indicate the head is stationary (Palla & Lenggenhager, 2014). This mismatch could enhance the visual event by amplifying the salience of the vestibular input which in turn would make the GVS-paired visual representation more memorable (L. Smith et al., 2020). Furthermore, GVS involves unnatural peripheral stimulation and activates brain regions which are not activated by natural vestibular stimulation (Ferrè et al., 2014). Future studies should address whether the current findings would be

replicated by stimulating the vestibular system under conditions in which visual and vestibular interactions naturally occur (L. Smith et al., 2020).

Moreover, the conditions necessary to obtain the GVS prime remain still ambiguous. The advantage seen in the current studies may be attentional in nature (only obtained when participants are attending to that particular spatial location), pre-attentional (whereby any salient stimulus that happened to coincide with the GVS pulse but did not catch attention contributed to the GVS advantage, such as background grid in Experiments 1 and 2 or additional cues on the visual display in Experiment 3). Furthermore, the GVS advantage may require voluntary hand movement as in all experiments participants were instructed to either press a response button when attending to the target object or click on the grid square as soon as they detected the target platform. Future studies would need to determine if the effect is contingent upon these motor responses. Using GVS simultaneously with other methods, such as eye-tracking for example, while limiting motor responses, could assist with shedding light onto these ambiguities (Crawford, Deveraux, Higham & Kelly, 2015).

Further limitations apply to the experimental paradigm itself. Recall that Experiment 3 failed to produce the priming effect when the display was presented in different orientations than the one from the original encoding. As previously mentioned in the corresponding chapter section, one potential reason for the lack of effect could have been that participants encoded and learnt spatial configurations in the upright condition, which may have encouraged encoding target locations relatively to the body axes of the self (self-based or egocentric cues, see Abekawa et al., 2018). However, the display orientation conditions were included to test allocentric retrieval, meaning that these trials encouraged object-to-object instead of body-to-object (or self-based) associations. One could speculate that given that vestibular inputs contribute information about the body's position and orientation within space (Abekawa et al., 2018; Ferrè et al., 2013), it is possible that vestibular inputs were not exploited by visual memory for the rotated (allocentric) conditions in this 2-D experiment. Indeed, Brandt and Dieterich

(2016) have suggested that vestibular inputs only contribute to egocentric spatial representations in 2-D environments, supporting this potential explanation. Future experimental paradigms that incorporate 3-dimentional (3-D) environments could potentially clarify the above limitation.

Another limitation of the experimental paradigm is that subjects may have found it difficult to identify previously encoded objects in a spatial array after the array itself has changed orientation, which in turn lead to the lack of effect. Indeed, changes in display orientations cause rise in errors of judgement in tests of spatial perception and working memory (G. R. Harris et al., 2000), which increase as the degrees of orientation increase (Fitting et al., 2009; G. R. Harris et al., 2000). Interestingly, this is not the case when participants physically change their perspective when they move relatively to the array (Kozhevnikov & Hegarty, 2001; Simons & Wang, 1998). As with the limitation above, this could be potentially resolved if the paradigm incorporated simultaneous changes in participants' perspective as the display orientations took place, such as immersive environments in virtual reality for example, whereby spatial representations are updated as one moves in space. An additional suggestion would be for future paradigms to include prominent objects in the environmental design that participants are reliant upon for spatial navigation, to further aid orientation and spatial memory.

Another ambiguity of the experimental design is that it is not known whether the GVS advantage seen in the upright condition was a result of encoding established on self-based cues (i.e., target platform is located on the top left relatively to the static participant) or allocentric cues (i.e., target platform is next to the respective external visual cue within the visual display) or possibly a combination of both. Indeed, given the fine-grain nature of the spatial memory tested in Experiment 3, it would not be unreasonable to speculate that high *accuracy* and perhaps the '*distance from the target'* scores in the upright condition were achieved by additional reliance on the spatial relations of visual cues externally of the arena and the platform. Future studies dissociating these two components could help further characterize the GVS prime in terms of whether the advantage relies on self-based or object-to-object spatial configurations.

Taken together, the above observations imply that the absence of a GVS advantage in the trials where display orientation varied may have resulted from a) the relatively high error rate in the rotated conditions, and/or b) a strong self-based encoding strategy induced by only applying GVS in the upright orientation. Addressing these limitations would facilitate further understanding of how GVS helps visual memory to individuate one memory from another in more dynamic environments. Further investigations could ensure that i) the task incorporates an immersive, more realistic, environment whereby participants' perspective is constantly updated as they move in space, and ii) GVS signals are integrated during allocentric encoding.

Conclusion

This chapter has provided evidence that vestibular inputs guide processes involved in visual search and visual spatial navigation. The evidence suggests that the information derived from the vestibular system can be used in a very specific manner to individuate one visual memory from another. The effects were however dependent on specific experimental conditions, and the next chapter seeks to establish the robustness of these effects in dynamic, more realistic environments.

Chapter 3

Introduction

The previous chapter provided evidence of an interaction between vestibular inputs and processes involved in visual search and spatial navigation. The enhancement following vestibular stimulation provides specific spatial information that helps individuate one visual memory from another. The last experiment in the previous chapter however included several methodological constraints that may have limited the GVS effect from generalising across fixed to variable viewpoints. To explore this possibility, the current chapter describes a further navigational study that was conducted in a virtual, dynamic environment in which viewpoint constantly changed. Ultimately, the rationale for performing these navigational studies stems from an interest in the amelioration of neurological disorders using galvanic vestibular stimulation. Therefore, it is considered of foremost importance to further characterize the GVS prime and understand the functional basis of such manipulations in normative subjects before continuing to investigate how these procedures would benefit clinical populations. Given the overwhelming reports in elderly adults with spatial memory deficits who reportedly ignore allocentric spatial representations (Diersch & Wolbers, 2019; Gazova et al., 2013; M. Harris et al., 2012; J. M. Wiener et al., 2013), results obtained from the current investigation could potentially inform therapeutic protocols to enhance allocentric encoding during navigation using vestibular stimulation.

Recall that the paradigm in Chapter 2 tested memory for location while participants navigated within a virtual swimming pool on a computer screen. Starting from eight different points, they learnt to navigate to the location of the hidden platform in the presence of visual cues placed outside the arena. Participants encoded spatial locations of hidden platforms during the learning phase in the upright condition only, however various display orientations (0º, 90º, 180º and 270º) were later assessed during the test phase. This manipulation was incorporated in the spatial task as a navigational component that encouraged retrieval within allocentric spatial

reference frames. By rotating the spatial display when testing recall for the location of the hidden platform, it was examined whether vestibular signals assisted in encoding the position of the hidden platform relative to the external visual cues in the environment. However, as discussed in Chapter 2, several methodological constraints clouded the results showing an absence of a GVS advantage in the rotated conditions (these are discussed in detail in chapter 2 and therefore only summarised here briefly); 1) The spatial layout was learnt during the practice phase in the upright orientation only, which, in turn, may have resulted in a strong self-based encoding strategy that limited the scope of vestibular priming and only benefitted later judgements when the same orientation was used. 2) The cognitive load of having to mentally rotate displays to utilise allocentric information – illustrated by a relatively high error rate in the rotated conditions - may have over-shadowed an allocentric benefit that was only revealed as an upright advantage.

Future investigations would have to ensure that a test environment is created whereby 1) GVS signals are integrated during allocentric encoding in a more realistic environment whereby participants are exposed to all orientations during the learning phase and 2) participants' perspective is constantly updated as they move in space which in turn is expected to reduce the need for mental rotations. Recall that self-based representations describe the surrounding environment as perceived from an individual's location, according to where they are currently in space relatively to other objects in the external environment (Jeannerod & Biguer, 1987). In a non-immersive environment (e.g., previous 2-D paradigm) the orientation of the visual field varied, but participants held an external viewpoint of these rotated scenes (i.e., screen display orientation varied but participant's position remained still experiencing the rotations externally therefore not being part of the rotated field or unable to change position to adjust the field of view accordingly). Indeed, when comparing 2- and 3-dimensional immersive environments, studies show that immersion is necessary to provide the participant with adequate stimuli for the formation of self-based reference frames (Kozhevnikov & Hegarty, 2001). I therefore hypothesised that an immersive environment which generates a first-person perspective at all

times whereby participants can constantly update their point of view as they move in space would be more appropriate to test the integration of vestibular inputs in spatial learning. Finding a paradigm that would allow to address these limitations could potentially lead to replicating the GVS advantage within allocentric spatial reference frames.

Furthermore, the last experiment in Chapter 2 left an additional question unclear; that is, whether the GVS prime influences egocentric or allocentric reference frames or possibly both. Recall that allocentric spatial representations rely on object-to-object spatial configurations and involve the encoding of information about the location of an object relatively to other objects in space (e.g., in the previous experiment, target platform is located next to the red external cue) whereas in egocentric spatial representations, the location of an object is encoded relatively to the body axes of the self (e.g., target platform is up and to the participant's right, or down and to their left, see Kozhevnikov & Hegarty, 2001). If the effect is only observed in the upright condition, one could infer that vestibular cues are integrated in spatial learning using egocentric representations of space. If vestibular signals are used by visual memory to mark the location of an object in space relative to cues in the environment, then the beneficial effect of GVS would still hold when objects are presented in the rotated conditions during the testing phase, confirming the role of GVS in allocentric representations. Given that the effect was absent in the rotated trials, it could be inferred that GVS does not influence allocentric representations of space. However, given the aforementioned methodological limitations, the previously obtained results limited such interpretation.

The above considerations led to a search for a more suitable paradigm that would help dissociate allocentric and egocentric encoding, as well as create an immersive environment in which participants constantly hold a first-person view of their surroundings. To that end, a virtual Morris Water Maze (MWM) task was used to test spatial learning in a virtual reality (VR) paradigm. Recall that in a typical MWM experiment, rodents are placed inside a swimming pool filled with opaque water, which also contains a submerged escape platform (Morris, 1981).

Rodents are released from different starting points around the perimeter of the pool and in their attempt to find a way out, they swim towards different directions and encounter the hidden platform. Soon they learn to navigate taking a direct path to the platform based upon a constellation of distal visual cues, even if local cues are absent. It is expected that spatial learning occurs after a few trials so that rodents would travel to the platform in less time than the time they took in the initial trials and animals who have mastered this would persist looking for the platform's location even if the platform is removed or external cues are reduced in number (D. A. Hamilton et al., 2002). More recently, virtual versions (VR) of MWM have been used directly on human subjects to test human place learning (Hamilton et al., 2002), investigate age differences in place navigation (Driscoll, Hamilton, Yeo, Brooks & Sutherland, 2005) or in the formation of cognitive maps (Iaria et al., 2009), and test which brain areas are involved during different spatial orientation strategies (Iaria, Petrides, Dagher, Pike & Bohbot, 2003). Of relevance to this study, it has been shown that virtual place learning engages similar brain areas involved in real-life navigation (Hilliard et al., 2019; Iaria et al., 2003, 2009; Maguire et al., 1997) which suggests it may be a suitable methodology to investigate our hypothesis. VR technology has gained enormous ground as it provides interactive tools that immerse the user in a rich, multimodal 3-D word using computer-generated environments while maintaining a great degree of control over the parameters of the environment compared to the real word (Diersch & Wolbers, 2019). In addition, applications can be easily adjusted for each experimental condition and scenarios that are too expensive in the real world can be recreated cost-effectively in a virtual environment and with relative ease while maintaining ecological validity (Tsirlin, Dupierrix, Chokron, Coquillart & Ohlmann, 2009, Diersch & Wolbers, 2019). VR has been suggested as a rehabilitation tool for vestibular abnormalities such as vestibulo-oculomotor and vestibulo-spinal functions (Alpini et al., 1998), balance control (Mao, Chen, Li & Huang, 2014), unilateral spatial neglect (Tsirlin et al., 2009) or chronic bilateral vestibular failure (Schautzer et al., 2003) and could be a promising tool for individuals who suffer from spatial representation or

spatial memory deficits linked to vestibular loss (Driver & Halligan, 1991; Previc, 2013).

The virtual version of the MWM used in this chapter was created based on the virtual paradigm described by Hamilton et al., (2002), see Methods section for more details. While holding a first-person visual perspective, participants were encouraged to navigate within the virtual swimming pool in search of the hidden platform. Healthy subjects were randomized across two tasks; the first task required participants to reach the hidden target from eight different starting points in the presence of four prominent landmarks, therefore testing allocentric representation of space and spatial memory in the context of encouraging participants to develop a cognitive map of the landmarks and paths in the virtual environment. The second task instead prompted participants to use the distance from a single landmark as a reference and over-learn the habitual route of navigating towards the hidden platform with no distal or proximal cues present in the environment, using the starting point as their only reference and making choices in respect to body motion (known as path integration), therefore testing egocentric encoding. In each task, half of participants received stimulation when they reached the hidden target platform (GVS group) and the other half performed the experiment in the absence of stimulation (Control group). Following a short break, participant's memory for the platform location was tested while the platform remained hidden.

Since it is not known whether vestibular signals conveyed through GVS can be equally harnessed by ego- and allocentric processes, the aim of the present chapter was to address this uncertainty by using the aforementioned paradigm that would create environments to encourage participants to use the two main orientation strategies mentioned above. Recall from Chapter 2 that the construction of cognitive maps is a multimodal process that requires the integration of spatial information from different sensory modalities; visual, somatosensory, proprioceptive, auditory, and of course vestibular cues (Bottini & Gandola, 2015; Wolbers & Hegarty, 2010). These sensory inputs can provide information that is coded either in allocentric or egocentric representations of space (Colombo et al., 2017). When learning to navigate in a new

environment, one may adopt different strategies. For example, learning a route between two fixed positions, which becomes habitual after practice, is known to be reliant on procedural memory dependent on the striatum (Iaria et al., 2003). Orienting ourselves based on prominent landmarks in our surroundings, on the other hand, is believed to take place in the hippocampal complex, where cognitive maps enhance spatial memory by storing information regarding landmarks and routes used to navigate in that environment, so that trajectories to key locations can be instantly re-calculated when the path is obstructed or the starting point changes (O'Keefe & Nadel, 1979; Save & Poucet, 2009). Given that vestibular cortical projection areas have been shown to involve brain regions responsible for spatial memory and navigation and the construction of cognitive maps (Hitier et al., 2014; Lopez et al., 2012; Suzuki et al., 2001; Vitte et al., 1996) with both the hippocampus and the striatum receiving such projections, I hypothesized that both egocentric and allocentric representations of space will be influenced by vestibular input.

Materials and Methods

Participants

A total of 16 individuals took part in this study. Participants were recruited via the University of Kent's Research Participation Scheme (RPS) and were undergraduate students who participated in return for course credits. Prior to taking part in the study, all participants were asked to give their written informed consent after being given a detailed description of the study. The research was approved by the University of Kent's Psychology research ethics committee and all participants were treated in line with the guidelines provided by the British Psychological Society (BPS). Individuals with history of neurological disorders such as brain injury and seizures, impaired vision, or with prior experience with our experiments were not permitted to take part in this study. Participants completed the study in two days and were counterbalanced in

the order they conducted the egocentric and allocentric experimental tasks (see more details below). One participant did not follow up for the second part of the study, resulting in a total of 15 participants in the egocentric condition.

GVS Stimulation Protocol

All stimulation was performed by galvanic vestibular stimulation units (neuroConn DC-Stimulator) using the bilateral bipolar configuration of anode left and cathode right, as previously described. A single pulse lasting 1000ms was discharged when participants reached the target platform for the first time using the joystick. A total of eight pulses was administered per participant per experiment (see *Procedure* section for more details). As with previous experiments, thresholding was included in this experiment to ensure that the stimulation was not perceived by participants and was conducted prior to the experiment using a blinding technique, during which participants' eyes were kept closed using an elasticated headband. Direct current stimulation occurred between 0.25 - 0.3 mA; GVS stimulation was first assessed for each participant at 0.3mA and if perceived, was adjusted to 0.25mA. Participants who still noticed the stimulation during this step were excluded from the study (N = 6). GVS perception was also enquired at the end of the experiment using a questionnaire (as per previous experiment) and participants who reported perceiving the stimulation were excluded from the study (N=1).

Materials

Participants were seated in a comfortable chair in an isolated testing lab, wearing an Oculus Guest VR headset and using a Logitech Extreme 3D Pro-Precision Joystick. A padded chin rest was used to keep participants' head position fixed and minimize movement throughout the experiment. The experimental paradigm was run using Vizard (version 6) and instructions were presented to participants on a 15-in computer monitor as well as verbally to ensure full comprehension. Participants were asked to navigate to a target platform located in a circular

swimming pool within a square floor-plan virtual reality environment. This target platform remained hidden unless participants hovered over it with the joystick during the learning phase (see below) and represents the escape platform in the conventional Morris water maze task. Figure 3.1 depicts a schematic layout of the virtual environment in the allocentric condition. Opaque blue water was used to create the surface of the pool and help conceal the platform. The pool was surrounded by a circular wall which extended approximately 10% of the pool diameter above the surface, similarly to Hamilton et al., (2002) and four distal walls created a square floor-plan virtual environment.

In the allocentric condition, four distal cues were placed between the distal walls and the swimming pool and were the only visual features in this environment. The cues were real-life objects (rock, sculpture, umpire chair and water temple), were made prominent by the way of bright colouring, rich texture and size (see Figure 3.1 and 3.4A), were highly distinguishable from each other and were used to disambiguate the spatial locations of the platforms. Only one cue was placed in front of each distal wall and their position was fixed and carefully determined prior to testing so that it is off the centre of the pool and that participants couldn't follow a straight path towards a peripheral cue from any of the starting locations and find the platform using peripheral cues as a spatial guiding reference. As in similar experiments, the platforms, when visible, occupied approximately 2% of the pool area and extended half of the pool wall height above the surface water. The location of each platform was fixed relatively to the visual peripheral cues. In each block, the platform was placed in three different fixed locations that were predetermined prior to testing (one for the practice round, one for the GVS location and one for the Control). The GVS and Control platform locations were chosen carefully prior to testing so that their distance from each starting position was counterbalanced. This step was vital in order to avoid reaction time, speed and path length measures being affected by experimental variability between conditions. Eight starting positions were used in total, all fixed at the inner edge of the swimming pool and predetermined prior to testing (see Figure 3.1 and 3.2).

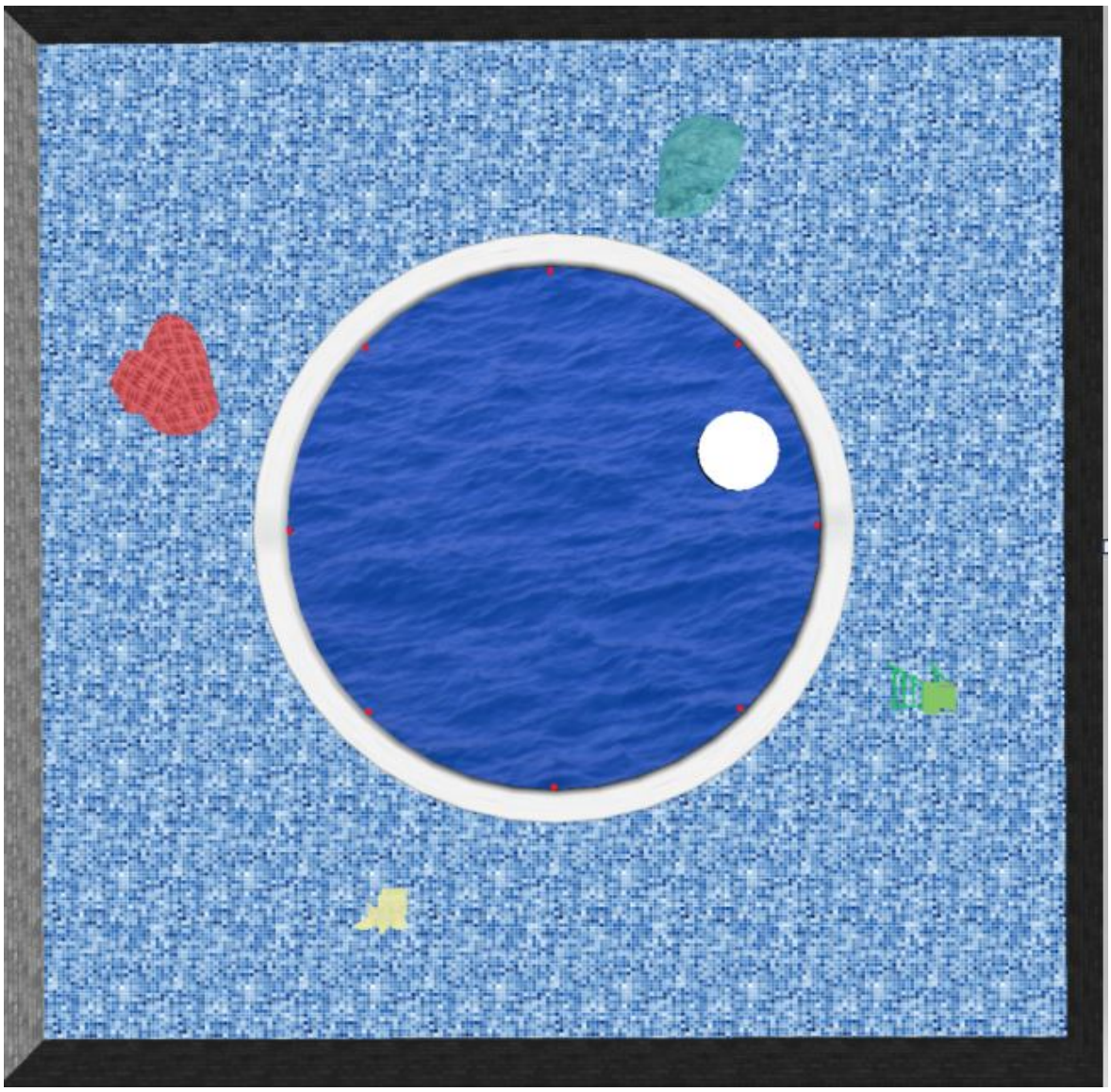

Figure 3.1. Birds eye layout of the virtual reality environment for the allocentric condition. The round white platform is located within the round swimming pool, which is surrounded by the pool wall. The four prominent objects surrounding the swimming pool are the visual cues located off-center and away from all direct paths that participants may take when beginning from each starting position. The difference with the egocentric condition was that external cues were not present and there was only one starting position in the test trials instead of eight in the allocentric condition, as shown in Figure 3.3.

Considering all the counterbalancing points presented above, participants were randomly assigned to four groups (see Figure 3.5), with half of them conducting the experiment with the GVS platform in Block 1 and the other half in Block 2, to limit practice/order effects. In addition, in half of the participants, the P2 position was associated with GVS and in the rest of them the P3 position was the GVS platform, to eliminate any experimental variability that may occur, however the positions were symmetrical as shown in Figure 3.2, therefore this was

included as an additional measure. Furthermore, participants were counterbalanced in the order they conducted the egocentric and allocentric experimental conditions.

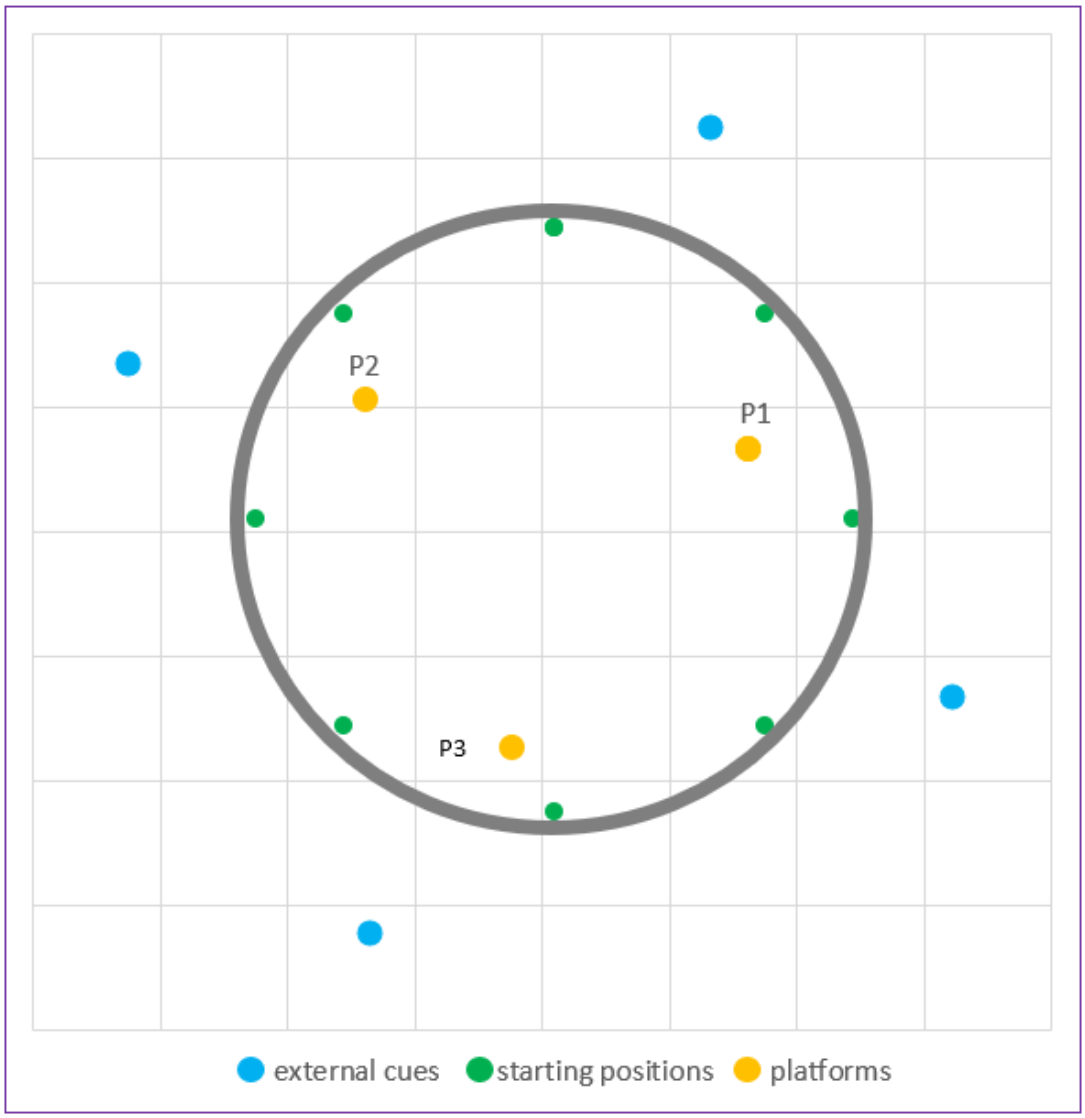

Figure 3.2. An approximate schematic diagram of the virtual reality environment in the allocentric condition. P1, P2 and P3 represent the locations of the platforms for each block. P1 was always the practice platform in all experiments. P2 and P3 were the GVS and Control platforms as their position was easier to counterbalance between participants. In each block, participants began the trial pseudo-randomly without replacement (in the same repetition) from each of the eight different starting points (indicated in green) and navigated the swimming pool based on four external cues placed outside the pool (blue dots).

In the egocentric condition, participants began the trials from the same fixed starting position and were expected to navigate to the target platform relying on egocentric cues (e.g., straight ahead and to my left/right). No external objects were included in this experimental set-up (see Figure 3.3 and 3.4B) and only one starting position per block was permitted. As with the

allocentric condition, no explicit information was provided to participants regarding starting point, spatial references etc. The same counterbalancing rules applied here, and participants formed four groups, similarly to the allocentric condition (see Figure 3.5).

A first-person view of the virtual environment was displayed throughout the experiment, with a field of view of 45 degrees. Participant's position was always slightly above the surface of the water. Navigation was controlled using a joystick which enabled forward, backward, left and right movement. Given that participants' heads were resting on a headrest during testing, they were given sufficient time to practice familiarising themselves with movements of the joystick that replaced movements of the head when navigating in space during a practice block. All participants confirmed they were comfortable with this, any behaviour that did not follow instructions was corrected during the practice block therefore prior to the testing phase. When participants found the platform during the learning phase, the platform became apparent and extended half of the pool wall height above the surface water and stayed there for 4sec, to provide participants with adequate time to notice the surroundings and for the stimulation to occur. Stimulation followed the protocol described above and only occurred when participants reached the GVS platform. A post-experiment questionnaire assessed participant's perception of stimulation and these who perceived the stimulation was excluded from the study. No time limit was applied to the experiment, as many participants during the pilot study experienced nausea, therefore participants had no restrictions on time when exploring the swimming pool during the learning phase or when reaching the platform during the test phase (see more details below).

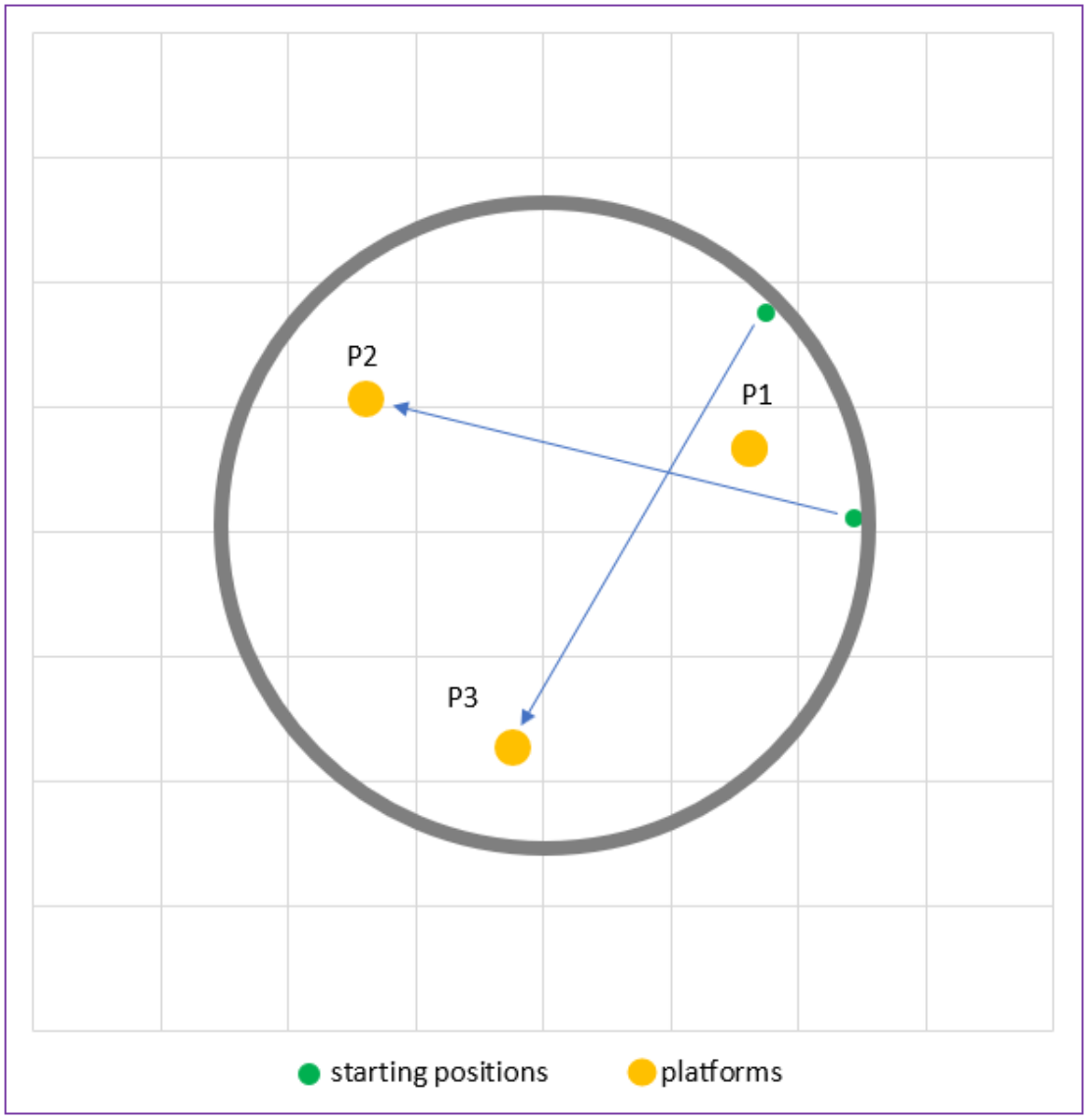

Figure 3.3. An approximate schematic diagram of the virtual reality environment in the egocentric condition. P1, P2 and P3 represent the locations of the platforms for each block. As with allocentric condition, P1 was used as the practice platform. P2 and P3 were the GVS and Control platforms counterbalanced between participants. In each block, participants began the trial from the same starting point and navigated the swimming pool based on egocentric cues (e.g., straight ahead and to my right, left), as no external cues were available to them (their path is shown with the blue arrow for each platform).

An invisible grid with 8 rows at the y coordinate and 8 columns at x coordinate divided the square floor plan of the virtual environment (see Figure 3.2). In the allocentric condition, the four external cues were anchored in the following fixed positions in x, y coordinates: 26.79, 64.67; 64.67, -26.79; -26.79, -64.67 and -64.67, 26.79. Starting locations were chosen pseudo-randomly in each trial, based on the compass points and the equal spaces in between. The

starting location x, y coordinates were the following: 2, 48.9; 35.16, 35.16; 48.9, 2; 35.16, -31.16; 2, -44.9; -31.16, -31.16; -44.9, 2; -31.16, 35.16. The locations of the platforms were also fixed relatively to the external cues and were the following in x, y coordinates: 32.36, 13.39; -4.57, -34.7 and -27.80, 21.26. Participants started the trial facing the centre of the pool, instead of the pool wall as in other similar virtual Morris Water Maze task versions (see Hamilton et al. 2002) in order to minimize turning movements due to nausea reports during the pilot study. In the egocentric condition, platforms were fixed in the same positions as above and only two starting positions were used, with the following x, y coordinates: 2, 48.9; 35.16, 35.16.

Procedure

All participants were tested individually. Each experimental session consisted of one practice block and two test blocks. Each block included a learning phase, in which participants learned the location of the hidden platform, followed by a test phase that consisted of 8 test trials in the practice block (8 starting points with no repetition) and 32 test trials (8 starting points x 4 repetition) in each of the two blocks. Platform locations were fixed within the same block and changed only when participants were moved onto the next block. During the learning phase, participants pseudo-randomly began from one of the eight starting positions starting (in the allocentric condition) or one starting position (in the egocentric condition) and were encouraged to explore the swimming pool until they find the platform. They were asked to use a joystick and move within the circular area continuously in search of the one hidden target platform, which became apparent only when they hovered over it with the joystick. Once they moved themselves over the hidden platform, the platform rose underneath them and extended half of the pool wall height above the surface water. The appearance of the platform was either accompanied by a brief burst of GVS (GVS platform) or presented in the absence of stimulation (Control platform). In the case of the GVS platform, stimulation was simultaneous with participants first reaching the platform and the platform becoming apparent. Given that the learning trials were eight in

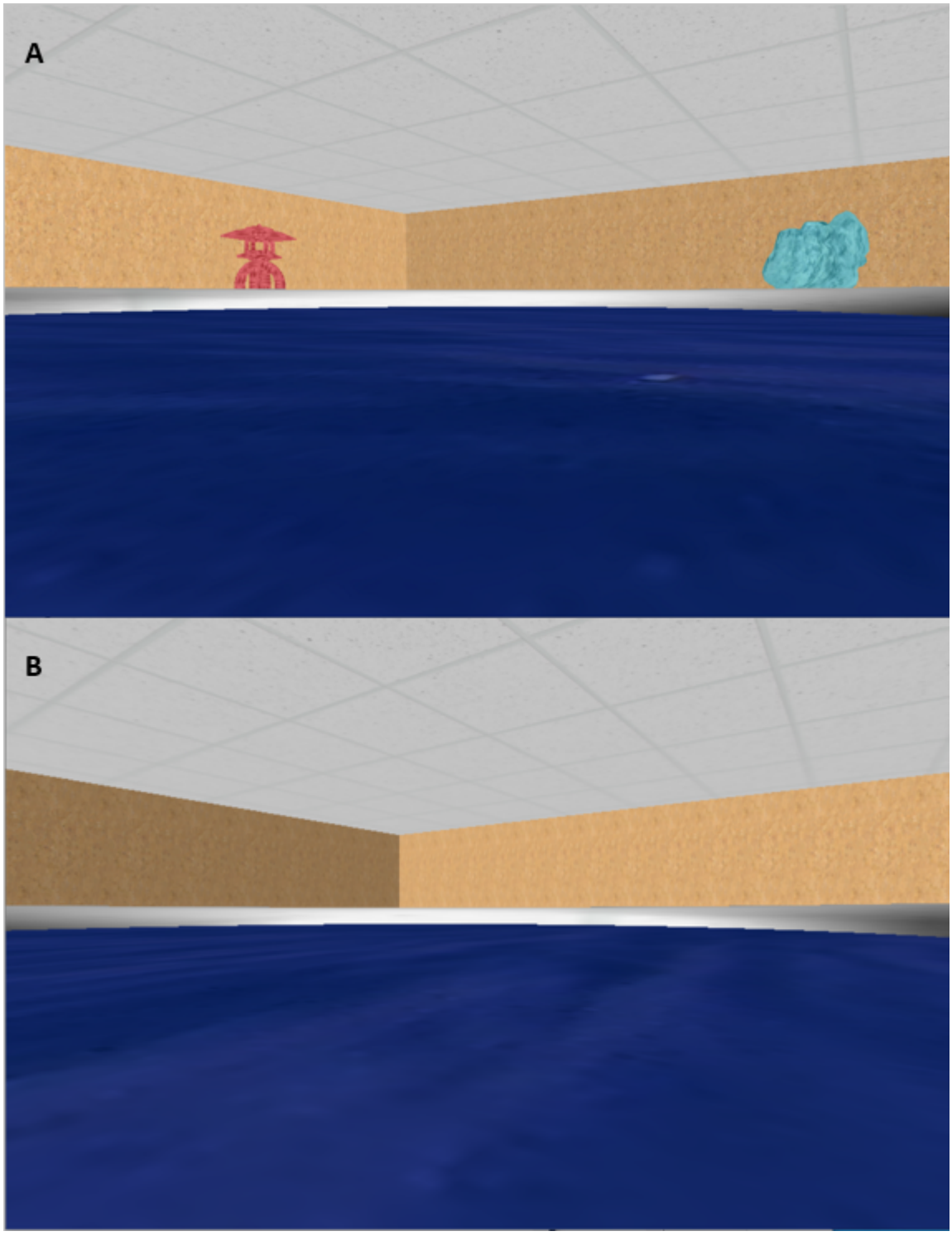

Figure 3.4. Screenshots of the allocentric (A) and egocentric (B) experimental conditions demonstrating participant's perspective in the virtual reality task. A first-person view of the environment was displayed throughout the experiment. In the allocentric condition, external cues were used to disambiguate platform locations whereas in the egocentric condition, participants based their navigation on egocentric cues (e.g., straight ahead and to my right, left) instead. See more details in the Procedure section.

total (one for each starting point), eight pulses of GVS were administered in total. Platforms

stayed risen for 4 seconds, allowing time for stimulation and giving participants the opportunity to explore the surroundings and learn where they are in space relatively to the external cues. No explicit instructions were given to look around the swimming pool, this was expected to happen as a natural process of spatial learning (see Iaria et al., 2009). The reduced time of 4 seconds while on the platform compared to the 10 second waiting time in similar paradigms (see Hamilton et al., 2002) was chosen due to the fact that participants used the joystick, which for a full rotation in the virtual environment took only 4 seconds to complete, using moderate speed, therefore it was assumed that this timeframe was sufficient for them to get a well-rounded understanding of their position in space. Following this short delay, the participant was moved onto the next starting point for the next trial, where they were instructed to practice moving directly towards the platform using the shortest route possible in the remaining seven trials (see Figure 3.4).

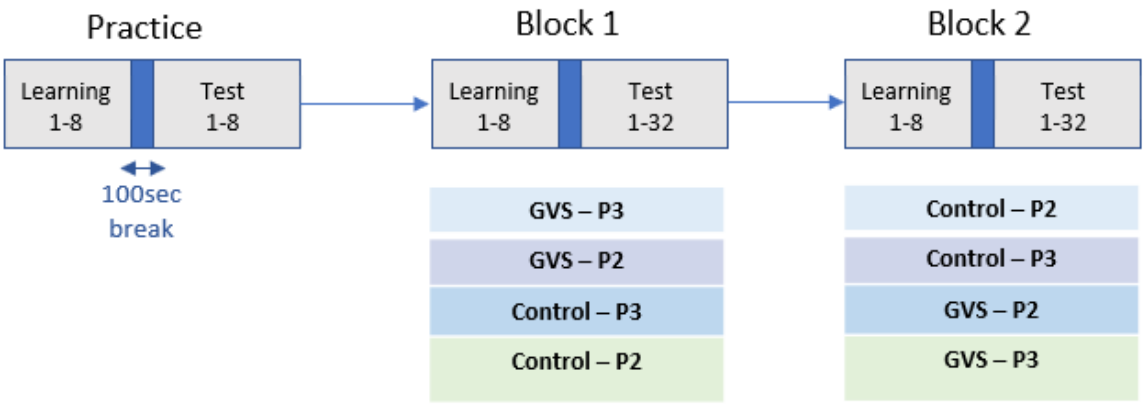

Figure 3.5. Schematic representation of the paradigm used in this experimental set-up for both the egocentric and allocentric conditions. Each participant completed a practice block (consisting of 8 learning and 8 test trials), followed by two test blocks (consisting of 8 learning trials and 32 test trials). The colored tables show the allocation of participants in four different groups (the same concept was applied in both the allocentric and egocentric conditions). P1 was always the practice platform (see Figure 3.1, 3.2 and 3.3), whereas P2 and P3 platforms were associated with GVS or Control blocks in a way that half of the participants completed the paradigm having associated the P3 platform with GVS and half of them the P2 platform with GVS, in order to eliminate bias. In addition, half of the participants completed the GVS block first and half of them second to limit practice effects. Furthermore, participants were also counterbalanced in their order of completing the egocentric and allocentric conditions, with half of them completing the egocentric condition on day 1 and half of them on day 2. Rest between blocks was allowed, due to frequent nausea reports.

Following a break of 100sec, participants were introduced to the test phase, consisting of 8 trials in total for the practice round and 32 trials for the test rounds. Here, the platform was again hidden and participant's memory for its location was tested. Instructions encouraged participants to move directly onto the position where they estimated the platform was located and to click using the joystick. Participants were not instructed to move to the platform as soon as possible, due to the nausea reports during the pilot study. Instead, they were instructed to be as accurate as possible. In a similar fashion to the learning phase, participants were expected to rely on the external cues (in the allocentric condition) or egocentric cues (egocentric condition) to help them navigate to the hidden platform. The difference in the test phase is the platform did not become apparent when participants reached the area it was located, contrary to the learning phase. Participants had to rely on their confidence in moving onto the correct position and carry on the next trial, upon clicking onto where they estimated the platform was located. Participants did not receive visual feedback that they found the platform. No information regarding the number of starting points, useful strategies or any other features of the experimental design were made known to participants.

As mentioned above, participants completed a practice block prior to moving onto the test phase to ensure they were comfortable with the task, they had a thorough understanding of what they are asked to do and to provide us with an opportunity to elaborate and provide verbal feedback on their performance. By the end of the practice block, all participants were clear on how to conduct the experiment and as shown by the practice trial analysis, they achieved spatial learning (see Figure 3.7 - 3.9). In total, participants completed 24 (8 starting points x 3 platforms – practice, GVS, Control) trials for the learning phase and 72 (32 test trials x 2 test platforms plus 8 test trials for the practice platform) for the test phase. Participants conducted the experiments with no time restrictions and experiments lasted approximately 50-60 minutes, depending on performance.

Data Analysis

The following measures were considered:

Accuracy: test trials were considered accurate when participants reached any part of the platform and clicked using the joystick, which, according to the instructions, meant that was the exact position they estimated the target platform was positioned. Accuracy was one of our main measures as in the previous 2-D experiment, we observed a significant difference between estimations of GVS and Control locations. We expected accuracy for the GVS platform to be significantly higher than the Control platform.

***Target proximity*:** was included as an additional measure to *Accuracy* to counteract for accuracy scores being at ceiling or floor levels (for example, in previous 2-D experiment the task was cognitively demanding). This measure counted - in cm - how far the participants clicked away from the center of the target platform and helped understand how far from the actual target participants estimated the hidden platform to be. We expected closer target proximity for the GVS platform.

Latency: this measure replaced RTs in previous experiments, and it represents the typical escape latency measure in the Morris Water Maze task, which indicates the time it takes for the subject to find the platform. In our task, it is measured in seconds and it represents the time participants took to reach the platform. This is different to the *RTs* that we have previously reported in that RTs would represent the time the participants took to move from their starting point to the platform and click using the joystick to indicate the position of the platform. The reasons we decided that *latency* was a more suitable measure at this instance were twofold: firstly, the reports of nausea suggested not to instruct participants to navigate to the platform as quickly as they could, and secondly, because during the pilot study, participants were seen to take their time when reaching the target and trying to position themselves according to the external cues around them, rendering *RT* measures not suitable for analysis of duration of spatial processing in this instance. In theory, latency would be quicker for the GVS platform, however,

given the technical considerations above, we did not anticipate a difference between the two groups. Given the exploratory nature of the experiment however, this measure was included in our analysis, in case it was informative.

Strategy analysis*:* The behavioral analysis used in this study was based on Gehring, Luksys, Sandi & Vasilaki (2015) and Vouros et al., (2018) who have reported stereotypical animal behaviors when using the Morris Water Maze task. In the following analysis we show that the behaviors participants adapted in the paradigm tested here are very similar to the behaviors of rodents in the conventional MWM task (Gehring et al., 2015; Vouros et al., 2018). The reason why we did not use swim path classifications from human studies in this analysis is because they are very limited and they only report general strategies without being comprehensive and analyzing trajectories in great detail (see Kallai, Makany, Karadi & Jacobs, 2005 for example).

Participant's trajectories were analyzed using the open-source RODA software downloaded from the github depository (https://github.com/Rodent-DataAnalytics/mwm-ml-gen) which uses a series of graphical user interfaces in MATLAB to analyse trajectory data. Author's instructions were followed for each step of the data preparation (for more details, see Getting Started · RodentDataAnalytics/mwm-ml-gen Wiki · GitHub). In brief, raw data were first transformed so that each file contained the participants id, the recorded *Time* value and x, y coordinates to indicate the *Location* of each participant in the virtual environment. The four groups of participants were entered into the software as per instructions for Day 1, Trials 32 together with the following details: Trial timeout – 100000 (sec), Centre (X,Y) – (2,2), Arena radius (47), Platform (X,Y) – (-25.8,23.3) for P2 platform and (-2.6,-32.7) for P3 platform, Platform radius (cm) – 7.07. The analysis was carried out twice, as the software allows analysis for only one platform at a time.

Practice trials were analyzed in segments as they were relatively long, and several strategies were seen within the same trajectory. Length of segments was 100cm each – this is

higher than the author's recommendation of 63cm, but it was more suitable to our data as, given that our environment is a virtual one instead of a real-life swimming pool, trajectories were expected to be overall shorter. On the contrary, test trials were analyzed in trajectories, as, expectedly, following the eight practice trials, participants had a very good understanding of where they were in space and where the platform was situated, so their trajectory was overall shorter (as indicated by comparing Figures 3.7- 3.9, average trajectory path is only 62cm in the test trials compared to 80cm in the practice trials). The swim path classifications were labelled as follows (see Figure 3.6 for visual aids):

Direct Finding (DF): participants choose a straightforward path to the target platform. DF trials are typically all accurate.

Approaching target (AT): participants adjust their path towards the target platform. Both slight and more sudden adjustments in movement were assigned to this behavior. These trials are also typically accurate.

Thigmotaxis (TT): participants move exclusively on the periphery of the swimming pool and movement towards the center is limited. This is a typical behavior in animal trials as rodents attempt to escape when trying to climb the wall, and surprisingly several participants adopted this strategy, especially during practice trials, probably because they remembered the platform to be around the edge of the pool. This strategy would rarely lead to a successful trial.

Scanning (SC): participants randomly search different areas of the pool without manifesting any specific understanding of where the target platform might be or without focusing on specific areas. This strategy would rarely lead to a successful trial.

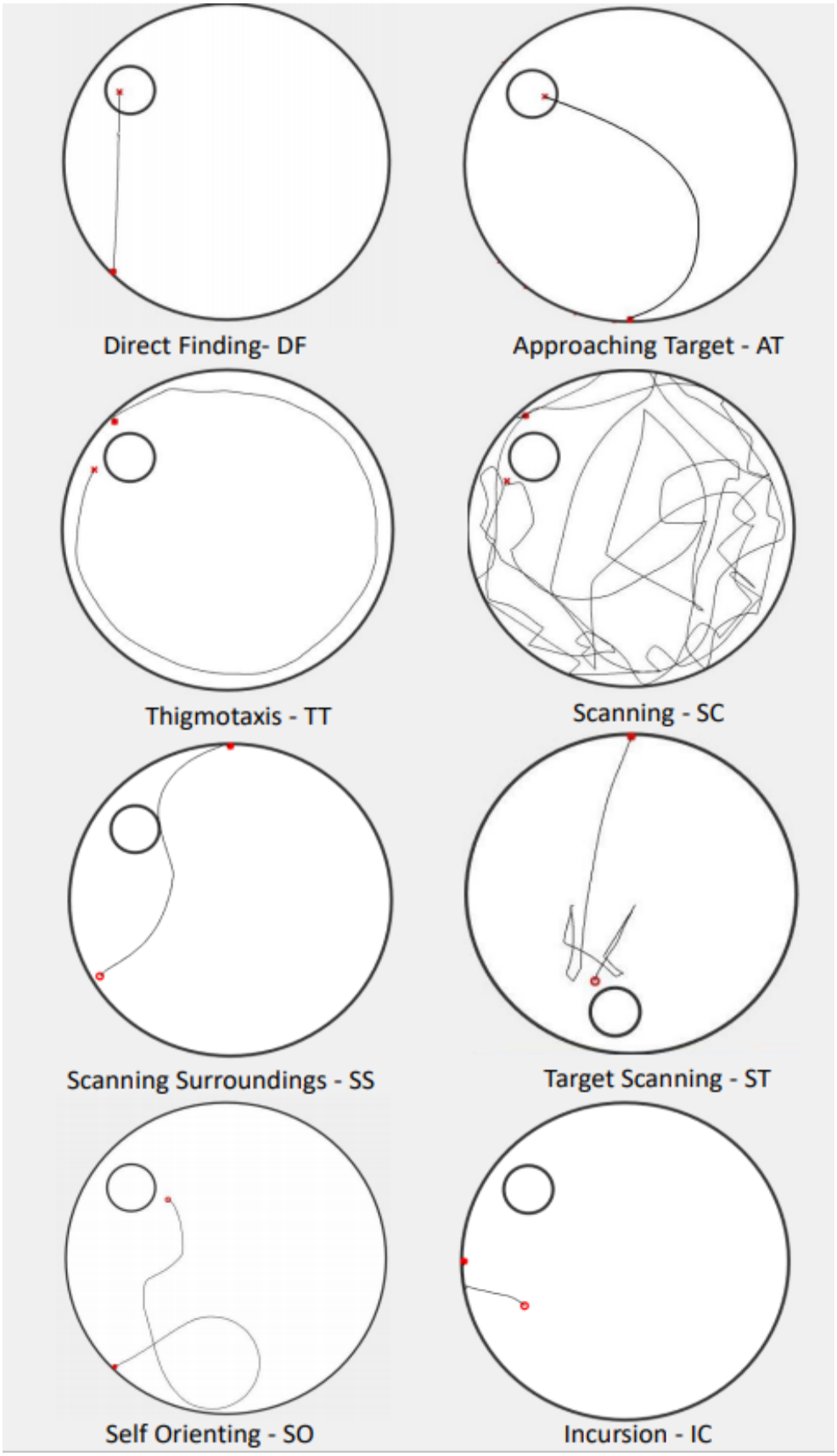

Figure 3.6. List of strategies seen in participant's trajectories as they moved from the starting position to the target platform in the virtual Morris Water Maze task. Solid red dot represents the starting point.

Scanning surroundings (SS): this behavior is typically shown when participants move very close to the target platform but continue their path further than its actual position. This strategy would rarely lead to a successful trial.

Target scanning (ST): participants are actively looking for the target platform in areas very close to it.

Self-Orienting (SO): this strategy occurs when participants perform a loop inside the swimming pool to orient themselves.

Incursion (IC): participants begin to move away from the periphery of the swimming pool and move towards the center. This strategy would rarely lead to a successful trial.

Data preparation: To establish the effectiveness of our counterbalancing measures, data-checks were first completed to ensure there were no performance differences due to the order in which experimental blocks were completed (GVS or Control platform completed first) or the location assigned to the GVS or Control platform. No counterbalancing differences in accuracy were found [$F(3,11) = 0.78$, $p = .53$, $\eta^2 = .18$].

The following section details the results found, starting with the analysis of the practice data. Accuracy, target proximity and escape latency measures from the test phase are reported next. After each participant's mean scores were calculated for each measure, the data was combined and if it followed a normal distribution ($p > .05$ in the Shapiro-Wilk test of normality), a RM repeated measures analysis was performed to statistically test the difference between the GVS and the Control groups. Escape latency was calculated in a similar manner to RT analysis, see page 45.

Results - Practice phase

All datapoints from the practice phase from both conditions (egocentric and allocentric) were combined to test whether spatial learning took place in the dataset and therefore confirm that test trials would be reliable for further analysis. Visual inspection of the length of the path

participants took to reach the platform (see Figure 3.7) showed that some participants took up to four trials to learn the exact location of the platform. Descriptive statistics showed that the path length in the later trials (see Figure 3.7, trials 5-8) was shorter compared to the first ones (see Figure 3.7, trials 1-4), with overall *Mean* = 54.59cm for trials 5-8 and *Mean* =106.38cm for trials 1-4, indicating that the necessary pre-condition of place learning had been met for both GVS and Control platforms. As expected, a similar trend was seen when escape latency was analysed showing quicker routes to the target location in later trials (*Mean* = 12.52 sec in trials 5-8 versus *Mean* = 21.37 sec in trials 1-4, data not shown). A quick examination of strategies used by participants in the practice trials showed that SC, AT and TT were used considerably more by participants in the first four trials (see Figure 3.8) whereas DF and AT were the predominant strategies used in the later trials (trials 5-8, see Figure 3.9), comprising of approximately 84% of overall trials, again confirming spatial learning.

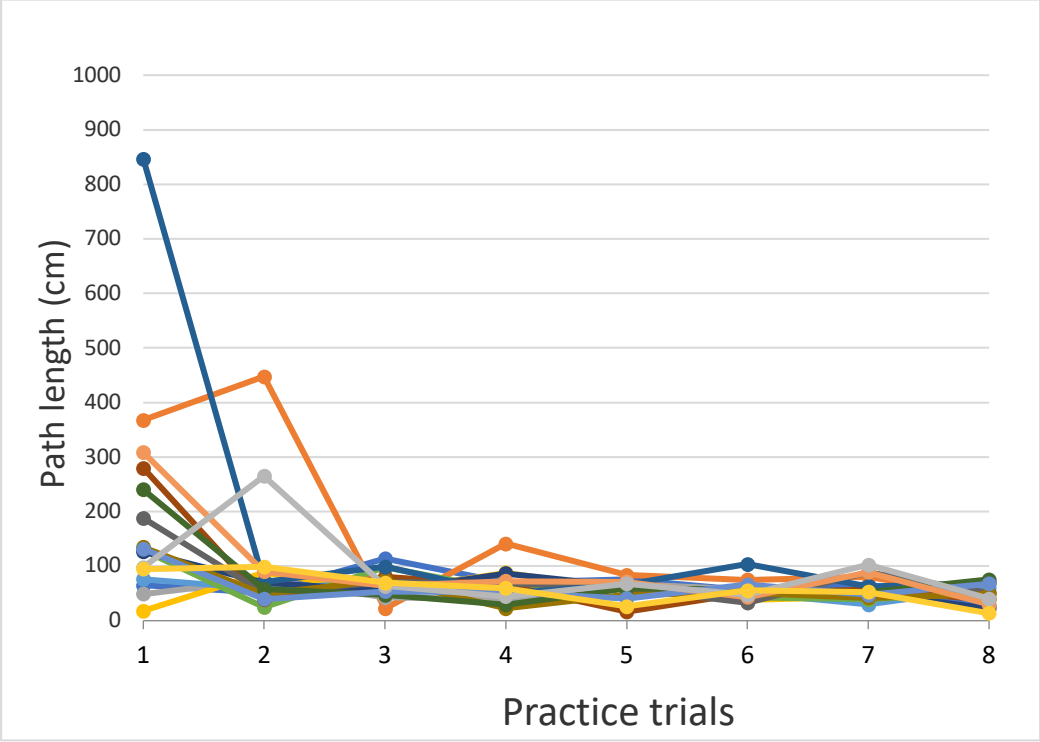

Figure 3.7. Path length for each participant on each of the 8 practice trials for each condition. The route that participants took to reach the target platform was shorter at the end trials compared to the initial trials, which indicates that place learning occurred. Each line shows scores for each participant tested. Given that this is the practice phase, and the platform became visible when participants moved onto it, all trials shown here are accurate.

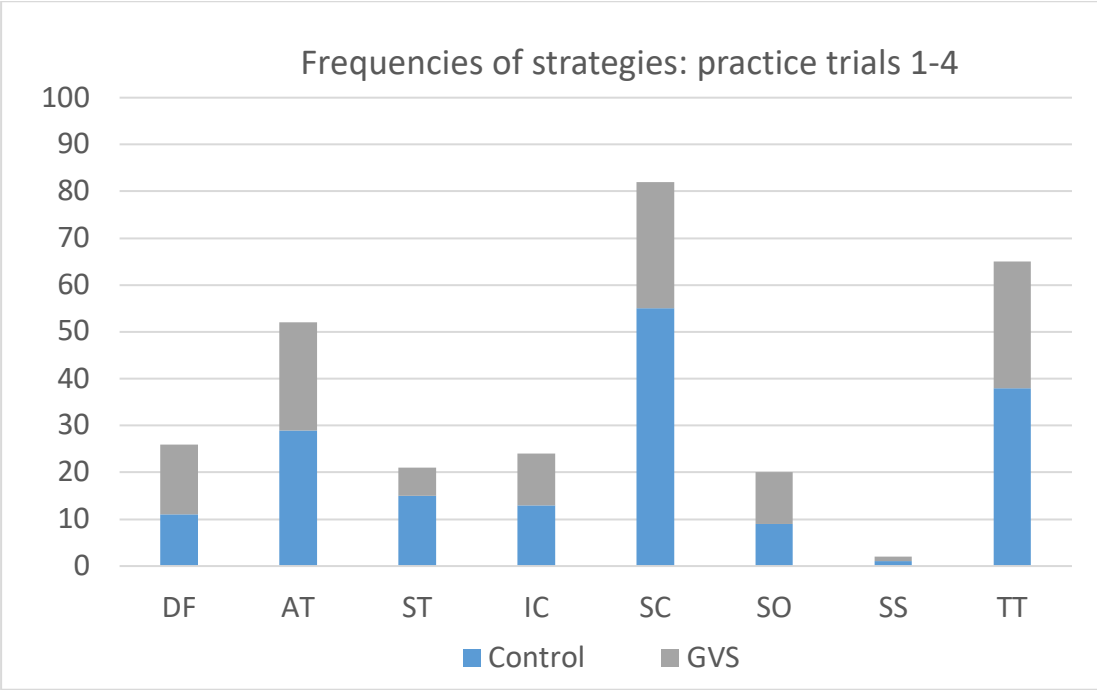

Figure 3.8. Frequencies of strategies used by participants in trials 1-4 during the practice phase. Given that trials 1-4 showed considerable variability (see Figure 3.7), we analysed these trials on their own. This showed that the Scanning (SC), Target scanning (ST) and Thigmotaxis (TT) strategies seen in previous graph were mostly used in the initial four trials by participants when looking for the Control platform, whereas Self-Orienting (SO) was more prominent when searching for the GVS platform. As with previous graph, this represents accurate trials.

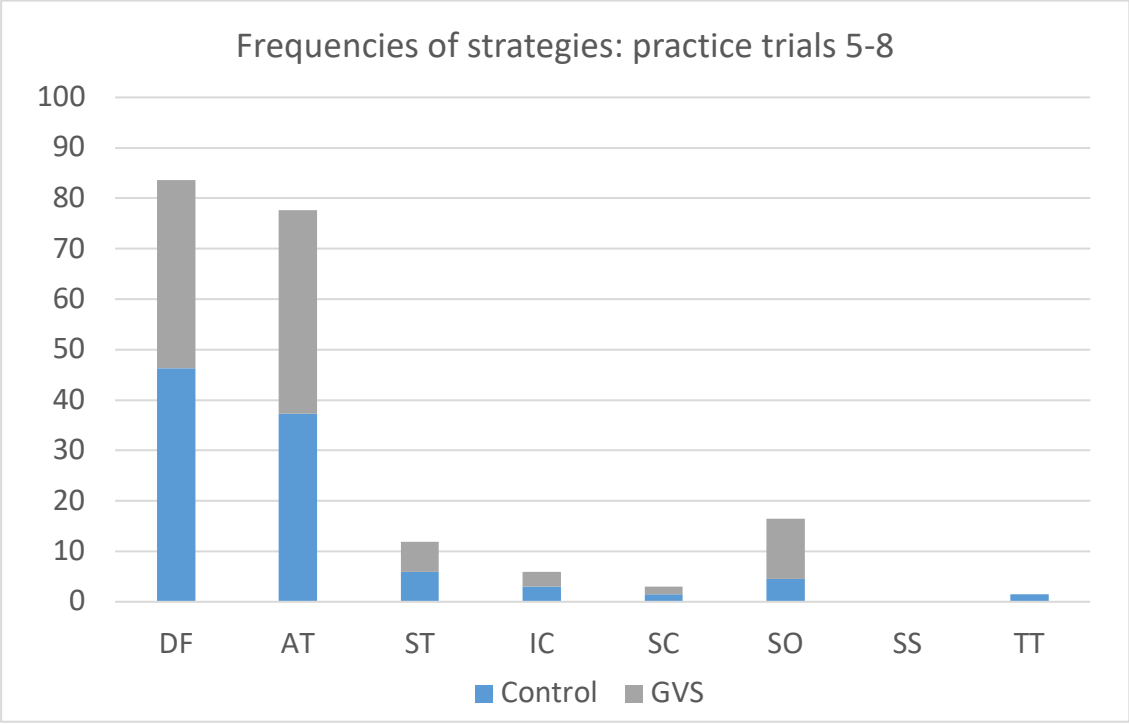

Figure 3.9. Frequencies of strategies used by participants in trials 5-8 during the practice phase. DF and AT were predominantly used in these later trials, totalling to an 84% of overall trials and confirming that spatial learning had occurred. As with previous graph, this dataset represents accurate trials.

Results - Test phase

After completing the initial data checks from the practice data, a repeated-measures ANOVA with Platform (GVS, Control), and Condition (allocentric, egocentric) as within-subject factors compared accuracy, target proximity and escape latency in the test phase trials.

Accuracy. A RM ANOVA revealed no main effect of Platform $F(1, 14)= .27$, $p=.61$, $\eta^2=.02$ or Condition $F(1, 14)= 1.57$, $p=.23$, $\eta^2=.10$, (see Figure 3.10). The two-way interaction between Platform and Landmark did not reach statistical significance, $F(1, 14)= 3.50$, $p=0.08$, $\eta^2=.20$. Given the small sample size and the exploratory nature of this study, as well as studies suggesting that interaction tests are low powered in small samples (see Greenland et al., 2016) this interaction was explored further. Bonferroni-corrected ($\alpha=0.05$) pairwise comparisons indicated that responses were more accurate towards the GVS platform ($M= 0.79$, SD= 0.22) compared to the Control platform ($M= 0.63$, SD= 0.32) in the allocentric condition only, $t(15)= -2.56$, $p=.006$. Additionally, responses towards the GVS platform showed an effect of Condition [$t(14)= -3.54$, $p=.023$] whereby responses were more accurate in the allocentric ($M= 0.79$, SD= 0.22) rather the egocentric condition ($M= 0.55$, SD= 0.37). Further statistics are reported on part A, Appendix C.

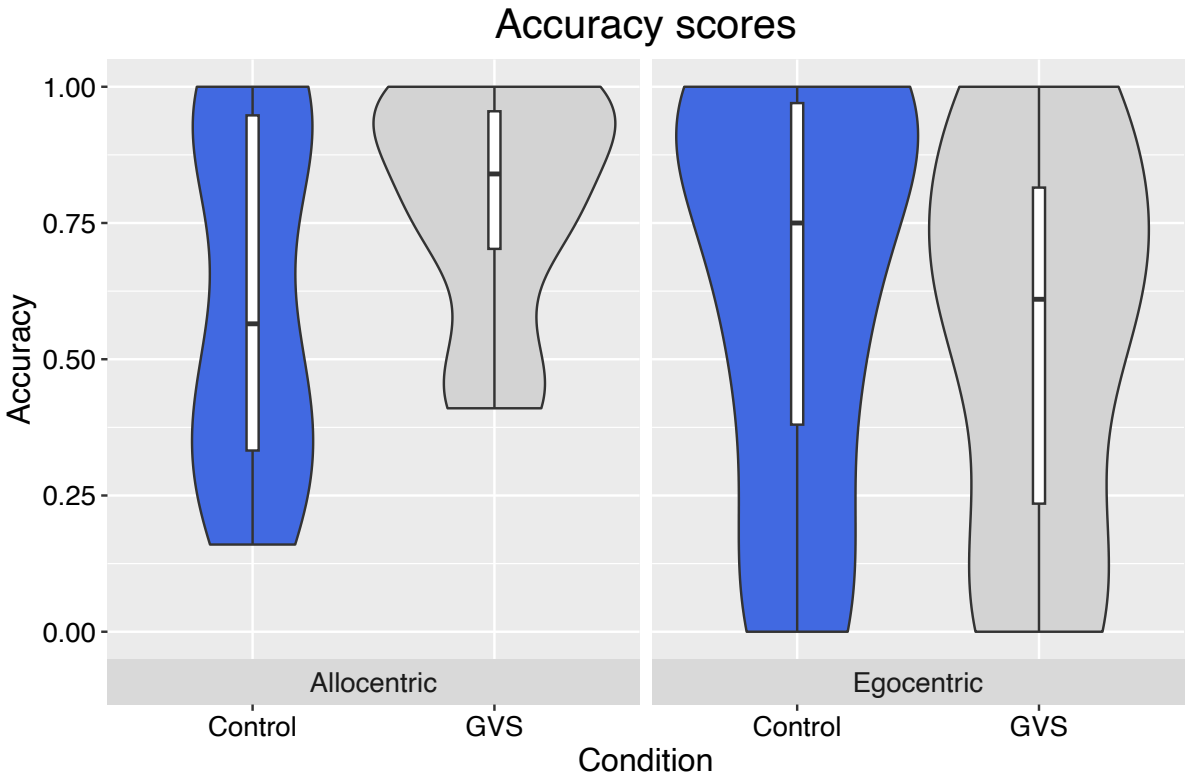

Figure 3.10. Violinplots illustrating % accuracy for the experimental conditions. Scores reflect correctly navigating to platform area from memory. Boxplots represent the median and inter-quartile ranges, width of the violinplots reflects kernel density estimations.

Target proximity. Due to statistical power limitations, analysis for this measure included all participants tested and not only those who estimated the platform's location inaccurately. Descriptive statistics showed similar performances for the GVS (*M*= 7.59cm, *SD*= 4.19) and Control (*M*= 7.88cm, *SD*= 4.14) platforms. A RM ANOVA revealed no main effect of Platform $F(1, 14)= .107$, $p=.75$, $\eta^2=.008$ or Condition $F(1, 14)= .312$, $p=.59$, $\eta^2=.22$, (see Figure 3.11). The two-way interaction between Platform and Landmark also failed to reach statistical significance $F(1, 14)= 2.45$, $p=.14$, $\eta^2=.148$.

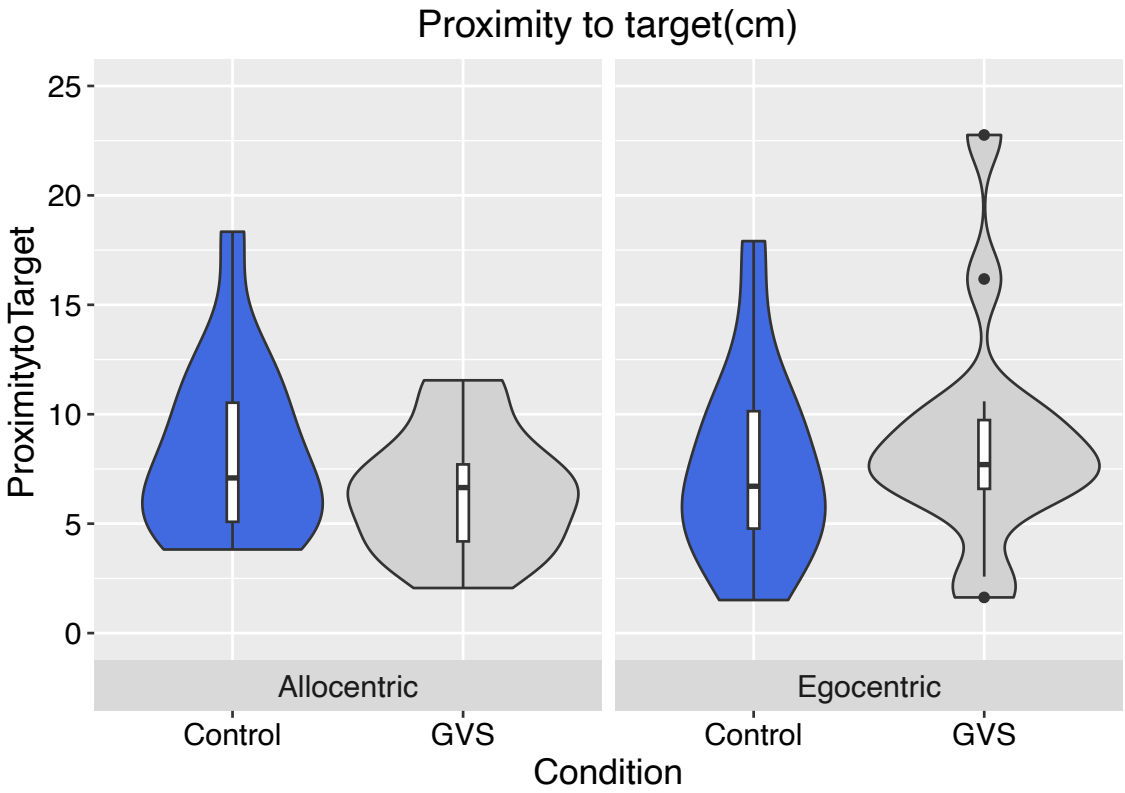

Figure 3.11. Violin plots illustrating performance on the proximity to the target platform measure. Scores represent the distance (in cm) of how far from the actual target participants estimated the hidden platform to be. Scores closer to 0 reflect participants estimating the target platform to be closer to the actual location. Boxplots represent the median and inter-quartile ranges, width of the violinplots reflects kernel density estimations.

Escape latency. Descriptive statistics showed that reaction times were shorter in the egocentric (*M*= 10.17sec, *SD*= 3.08) compared to allocentric condition (*M*= 12.20sec, *SD*= 4.49), however a main effect of Condition failed to reach statistical significance, $F(1, 14)= 3.91$, $p=.07$, $\eta^2=.218$. The main effect of Platform $F(1, 14)= 1.15$, $p=.30$, $\eta^2=.076$ and the two-way interaction between Platform and Landmark also failed to reach statistical significance, $F(1, 14)= .026$, $p=.86$, $\eta^2=.002$, see Figure 3.12.

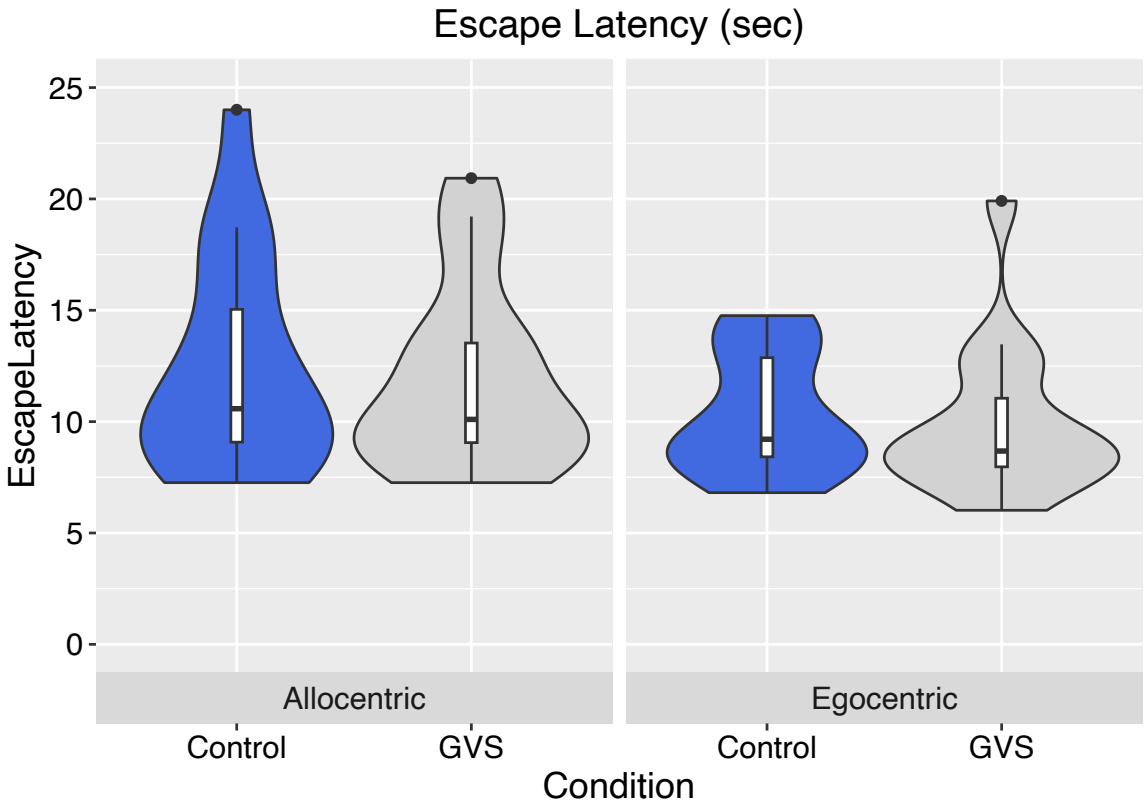

Figure 3.12. Performance for the escape latency measure, which represents the time participants took to move from the starting point to the estimated target platform. Boxplots represent the median and inter-quartile ranges, width of the violinplots reflects kernel density estimations.

Classes of behaviour. The analysis of trajectories used by participants during the completion of this spatial task showed that they mainly navigated directly to the target platform (DF) or they calibrated their direction towards it (AT), a finding that was expected given that the test phase followed the practice phase and at this point, participants were expected to have a good understanding of where the platform was positioned (see Figure 3.13). DF was the predominant strategy seen in the GVS trials, comprising more than 55.7% of total GVS trials, with AT being the second most used strategy at approximately 29%, compared to 35.7% seen in each of the DF and AT the Control trials (see Table 3.1).

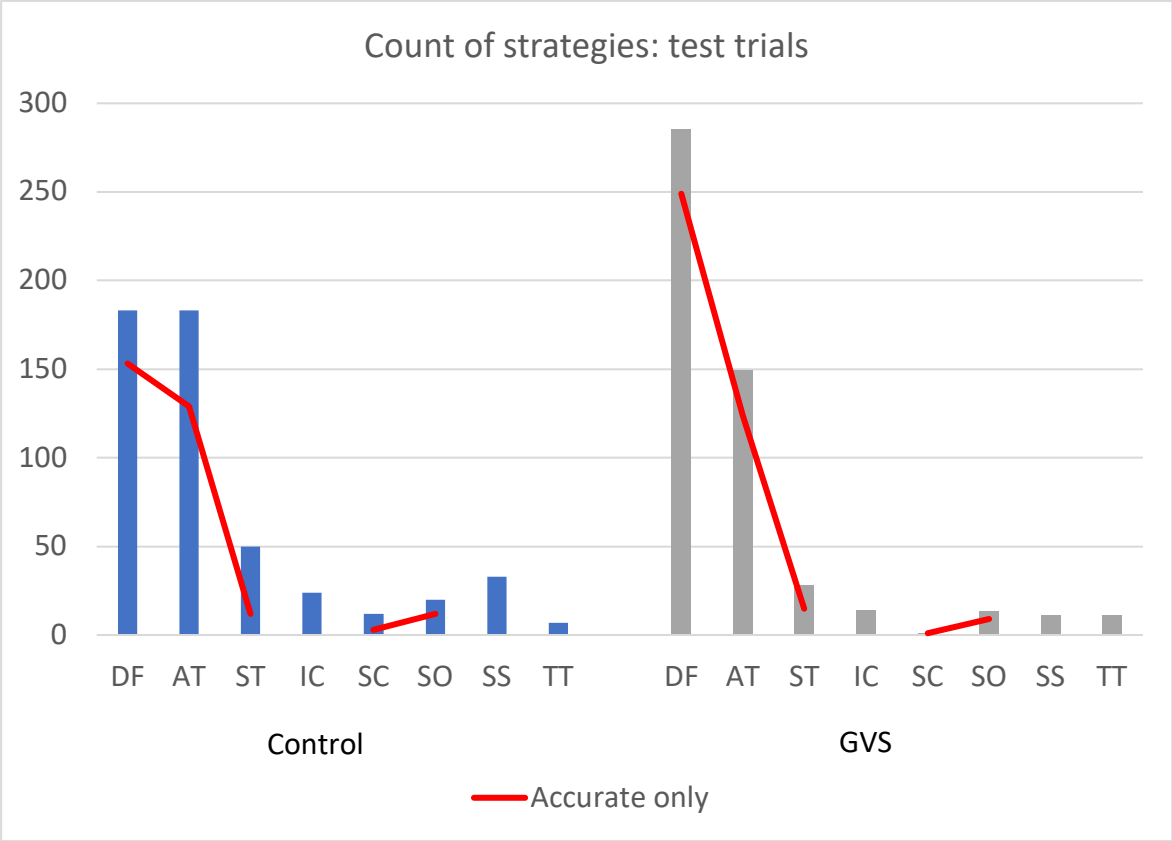

Figure 3.13. Count of strategies used by participants to find the platform in all trials tested. Red line shows accurate trials for each strategy. The predominant behaviours observed were DF and AT for both conditions, whereas the ST and SS were also observed when looking for the Control platform. Five hundred and twelve paths were analysed per condition (see Table 3.1 for percentages).

Differences between percentages of strategies used in all test trials were analysed using chi-square analysis, which showed DF was significantly more frequently used in the GVS trials than the Control trials, $\chi 2$ (1, N = 468) = 22.23, $p < .001$, whereas ST: $\chi 2$ (1, N = 78) = 6.21, p =.013, , SC: $\chi 2$ (1, N = 13) = 9.30, p = .002, and SS: $\chi 2$ (1, N = 44) = 11.01, p = .001, were statistically more frequently used in the Control condition (see Figure 3.14). Differences between percentages were also analysed in accurate trials only and chi-square analysis showed that DF was significantly more frequently used in the GVS trials than the Control trials, $\chi 2$ (1, N = 402) = 22.93, $p < .001$ (see Figure 3.15). Taken together, these results demonstrate that the statistically significant difference previously found in the accuracy scores is a result of participants being

more confident about the positioning of the target and navigating directly towards it.

Condition	Strategy	No of trials	% of total	Accurate only	% accurate
Control	DF	183	35.7	153	83.6
	AT	183	35.7	129	70.5
	ST	50	9.8	12	24.0
	IC	24	4.7		0
	SC	12	2.3	3	25
	SO	20	3.9	12	60
	SS	33	6.4		0
	TT	7	1.4		0
Total		512	100		
GVS	DF	285	55.7	249	87.4
	AT	149	29.1	124	83.2
	ST	28	5.5	15	53.6
	IC	14	2.7		0
	SC	1	0.2	1	100
	SO	13	2.5	9	69.2
	SS	11	2.1		0
	TT	11	2.1		0
Total		512	100		

Table 3.1. Percentages of strategies and accuracy percentages observed in test trials. Approximately 55% of all trials were DF in the GVS condition, and over 87% of them were accurate, demonstrating that the statistically significant difference we previously found in the accuracy measure is a result of participants being more confident about the positioning of the target and navigating directly towards it. See next graphs for statistical analysis between percentages.

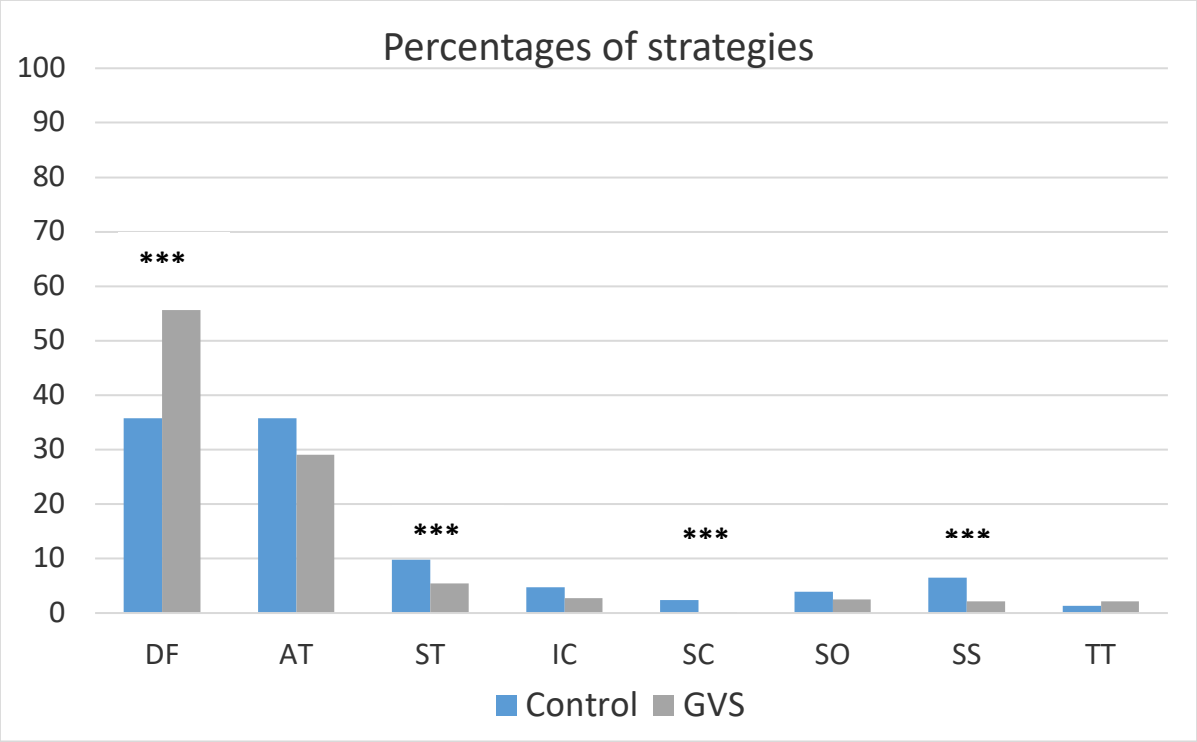

Figure 3.14. Differences between percentages of strategies used in all test trials were analysed using chi-square analysis, which showed DF was significantly more frequently used in the GVS trials than the Control trials, $\chi 2$ (1, N = 468) = 22.23, p < .001, whereas ST: $\chi 2$ (1, N = 78) = 6.21, p =.013, , SC: $\chi 2$ (1, N = 13) = 9.30, p = .002, and SS: $\chi 2$ (1, N = 44) = 11.01, p = .001, were statistically more frequently used in the Control condition.

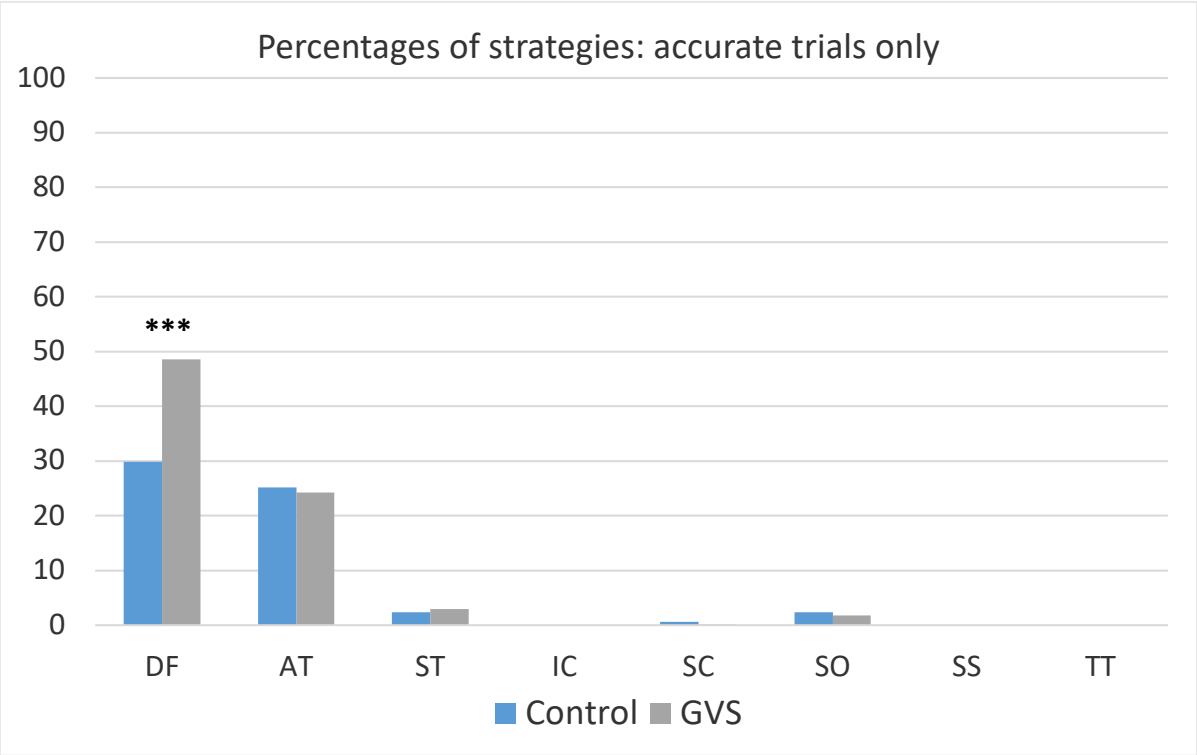

Figure 3.15. Differences between percentages of strategies used in accurate trials only. Chi-square analysis showed that DF was significantly more frequently used in the GVS trials than the Control trials, $\chi 2$ (1, N = 402) = 22.93, p < .001. No other significant differences were found.

Discussion

This chapter sought to explore whether vestibular stimulation facilitates spatial memory within a navigational environment that aimed to address the experimental constraints of Chapter 2. A navigational study within a virtual reality set-up was used, whereby participants' spatial memory was tested on pre-determined locations paired with a vestibular pulse during the learning phase, in a similar fashion with previous experiments. In two separate tasks, participants were asked to navigate to the learnt location in the presence (allocentric condition) or absence (egocentric condition) of visual cues. This helped to investigate whether allocentric, egocentric or both types of spatial representation encoding could be manipulated using vestibular stimulation during spatial learning. If coincident vestibular signals influence spatial learning in both conditions, then search for the target platform would be facilitated regardless of whether visual cues are present, compared to trials that were learnt in the absence of vestibular stimulation.

Contrary to the hypothesis, a RM ANOVA analysis failed to reveal the predicted effects. No main effects of Platform or condition were found in primary (accuracy) or secondary measures (proximity to the target, escape latency). However, results from the allocentric condition showed that, compared to the Control group, participants who received GVS were significantly more accurate at finding the exact location of the hidden platform (see Figure 3.10). Moreover, performance in *accuracy* was overall higher in each of the four different groups tested in the allocentric condition (see part B, Appendix C). This confirms that it is unlikely that the results were due to practice effects, as the results hold regardless of whether the GVS block was presented first or last. It is also unlikely that the results are due to a bias towards a specific visual cue whereby its proximity to the target platform may have made it more memorable to participants, as each group used a different pairing combination of GVS and visual cues. Furthermore, path analysis showed that the GVS group chose significantly more frequently a direct path to the hidden platform, with more than 87% of accurate trials being direct routes to its

location, confirming their confidence in the exact placement of the hidden target (see Figures 3.14 & 3.15).

Contrary to the hypothesis, performance in *accuracy* and *proximity to the target* measures in the egocentric condition was comparable across both groups, and no statistically significant differences were found when means between the GVS and Control groups were tested (see Figure 3.10 - 3.12). Figures 3.10 and 3.11 show a small tendency toward the Control group for more accurate trials and for closer estimations when placing the target. However, this difference derives from one participant who created a spatial relationship between the edge of the room and the ripples in the swimming pool to pinpoint the platform location (based on feedback upon completion, all other participant's feedback was they performed us instructed). Even if utmost care was taken to create a 'spotless' virtual environment that does not provide cues to aid participants to pinpoint their position or the platform's position in space, memorizing locations relatively to points of reference in the surroundings is a preferred strategy for the human brain, when these references, objects or boundaries, are readily available (Save & Poucet, 2009; Taylor & Tversky, 1996). Indeed, once this participant was excluded from the analysis, results were comparable (Accuracy: Control group = 0.61, GVS group =0.58; Target proximity: Control = 7.85, GVS = 8.31), suggesting that vestibular cues did not enhance or impair participant's egocentric representations of space.

The results appear to indicate that vestibular inputs are more likely to affect navigation performance when visual cues are present. It seems that participants' performance is more sensitive to the vestibular input when prominent visual landmarks are in the proximity or within the visual field during the encoding of that target location. The results suggest that vestibular signals were integrated into the formation of the cognitive map of a small-scale environment as participants learnt to navigate within this environment with the target spatial locations likely encoded relatively to proximal visual landmarks. This information was later retrieved to re-calculate straight-forward trajectories to the hidden platform irrespective of the starting position

and was used to aid successful and accurate navigation choosing various direct routes to the exact fixed target location. These results align with reports of vestibular signals influencing the activity of hippocampal head direction and place cells which encode spatial locations relative to prominent landmarks (Hitier et al., 2014), as well as findings that suggest GVS influences hippocampal-dependent spatial information in similar virtual spatial navigation tasks (Hilliard et al., 2019; Iaria et al., 2003). However, in the latter report by Hilliard et al., (2019), the study design deployed an unnatural GVS waveform that was constantly administered as participants were exposed to multiple visual stimuli and boundary information. This makes it difficult to pinpoint which part of the spatial representation was altered by the artificial vestibular input. In our experimental design however, participants received a single GVS pulse simulating a brief head movement only when they reached the target platform. The experimental design also ensured that the fore and background of the environment had no discerning features, with the field of view restricting exposure to only one landmark at each trial (although participants were free to move around to get a better idea where they were in space, see Methods for more details). The current outcomes therefore not only fit the above results but also extend them, supporting our hypothesis that artificial vestibular inputs can influence spatial memory representations and in particular individuate one visuospatial representation from another.

There are several considerations that may have led to the absence of a GVS effect in the egocentric condition. Recall that during active real-life navigation, external information from environmental stimuli such as prominent landmarks or boundaries that is either represented relatively to the body axis (egocentric encoding) or through spatial relationships to the surroundings (allocentric encoding) is integrated with self-motion information (also known as idiothetic) which includes vestibular cues, proprioceptive, motor efference and optic flow, to aid determining and maintaining a course or trajectory for accurate spatial navigation (Hilliard et al., 2019; Save & Poucet, 2009). These cues combined help one track their own position in space and adjust their self-based perception relatively to objects in the surrounding environment so that

they can account for the physical distance between an object and their body in space, as well as orientation changes that occur as they navigate in the environment (Diersch & Wolbers 2019). In the egocentric condition however, given the absence of prominent visual landmarks, participants were encouraged to rely only on 'illusory' self-motion cues as they began always from the same fixed starting point and were expected to find the platform which was also in a fixed location throughout the experiment (Gazova et al., 2013; Maguire et al., 1997). The vestibular and proprioceptive signals are lacking in a virtual environment whereby the body remains static (Diersch & Wolbers, 2019; M. Harris et al., 2012). In the current experiment therefore, the sensory input was provided mainly by the visual system and the vestibular input (one brief pulse of GVS) which was administered only when participants reached the platform. It is possible however that a constant supply of vestibular inputs, coupled with coincident proprioceptive, auditory and somatosensory input, is needed in path integration as the participants move from the starting point to the target platform (Save & Poucet, 2009). Therefore, the conditions created in the virtual environment may not have been ideal to reveal a GVS priming advantage in a task whereby navigation is based solely on idiothetic cues. Future investigations making use of a human analog of MWM in real-space navigational settings instead of an immersed environment could provide further insight into this consideration (see Gazova et al., 2013; Stangl et al., 2018).

It should be noted however that studies that compare performance in real-life settings and immersed environments report that the absence of vestibular input does not necessarily result in significant differences in error performance (Diersch & Wolbers 2019). Furthermore, immersive navigational tasks have been shown to engage the same neural substrates as real-life navigation, including the hippocampal complex (Hilliard et al., 2019; Iaria et al., 2003, 2009; Maguire et al., 1997) and can provide the necessary visual feedback that encourage subjects to use the same navigational strategies and retinocentric frame of reference as in real-world environments (Kozhevnikov & Hegarty, 2001). In addition, optic flow alone has seen shown to be enough to induce the perception of moving while immersed in the environment (Diersch & Wolbers, 2019).

However, in most of the aforementioned studies, participants were presented with some visual assistance when egocentric encoding was tested. For example, some studies would include a flag or another proximal cue next to the starting point, to aid navigation (see Gazova et al., 2013). This brings up another question, that is whether the task was too difficult for participants to perform. My pilot study showed that participants found such an experimental set-up dull and unengaging, whereas by omitting visual proximal landmarks and placing the platforms straight ahead and to the participant's left or right, based on the starting point (see Figure 3.3), a level of engagement was retained while maintaining a reasonable difficulty level for the task. In addition, although average overall accuracy for the egocentric task was relatively lower compared to the allocentric one (Egocentric: 59% versus Allocentric: 68%), this difference derived from a discrepancy between accuracy levels across the two days participants were tested. Indeed, the group of participants who performed the egocentric task on day 1 were as accurate as the group from the allocentric task (70%), whereas performance of participants who performed the allocentric task on day 2 was poorer (overall accuracy 50%). It is unlikely that fatigue effects are the reason for this discrepancy as participants were tested the following day. A more reasonable explanation could be that participants who performed the egocentric task the day following the allocentric task, found the egocentric task more difficult overall, because they were expecting a similar paradigm in which visual landmarks would aid navigation. This is indeed the preferred spatial strategy for navigation for the human brain (Save & Poucet, 2009; Taylor & Tversky, 1996) and was also confirmed by participants' feedback at the end of the session. Taken together, the above considerations suggest a genuine absence of an effect in the egocentric condition rather than the results being specific to the difficulty level of the task.

Future studies could also address cybersickness (exhibited as headaches, sweating, nausea, vomiting, symptoms that were quite prominent in this and similar studies, see Weech, Kenny & Barnett-Cowan, 2019), by implementing a shorter experimental protocol. Indeed, this current paradigm lasted around 60min, with 3 breaks included, which meant participants were

immersed in the environment for a considerable duration of time. Around 90% of participants experienced some symptom of sickness, (assessed verbally after the VR experience) with around 50% experiencing these symptoms to a degree that they were compelled to terminate the session early. Optimizing this step would be beneficial for ultimate results and for implementing these paradigms in clinical populations.

Despite the above limitations, the above results are promising when one considers the overwhelming reports mentioning an egocentric reference frame bias in elderly adults with spatial memory deficits who choose to ignore allocentric spatial representations (Diersch & Wolbers, 2019; Gazova et al., 2013; G. R. Harris et al., 2000; J. M. Wiener et al., 2013). The present results could potentially inform therapeutic protocols to enhance allocentric encoding during navigation using vestibular stimulation. As mentioned during the introduction, VR has been suggested as a rehabilitation tool for vestibular abnormalities such as vestibulo-oculomotor and vestibulo-spinal functions, balance control, unilateral spatial neglect and chronic bilateral vestibular failure (Alpini et al., 1998; Mao et al., 2014; Schautzer et al., 2003; Tsirlin et al., 2009) so could be a promising tool for patients who suffer from spatial representation or spatial memory deficits linked to reduced vestibular input (Driver & Halligan, 1991; Previc, 2013). In addition, the above results could contribute to the creation and enhancement of individualised cognitive maps which could include neighbourhoods, living spaces and other surroundings of patients who present with spatial memory decline.

Summary

This chapter has provided evidence that vestibular information is integrated into the creation of cognitive maps of small-scale environments as one learns to navigate in a new environment. This information is later used during retrieval to re-calculate straight-forward trajectories to key locations, irrespective of the starting position. This integration is more likely to be incorporated in the spatial relationships that are used to create allocentric reference frames based on prominent landmarks that are readily available in the surroundings. Although current

evidence shows that vestibular signals are not used when visual landmarks are absent and one navigates in space based solely on egocentric cues, the results obtained here are inconclusive and need further investigation. Nevertheless, the contribution of GVS to allocentric representations of space looks promising and future studies could investigate its advantage in clinical populations that suffer from spatial memory deficits.

Chapter 4

Introduction

The previous chapters provided evidence of an interaction between vestibular input and short-term visuospatial memory in normative populations. The evidence demonstrated that visual search and spatial learning are enhanced for these spatial locations that were paired with a GVS signal during spatial encoding in 2-D and 3-D virtual environments. Having now identified two paradigms in which the GVS advantage could be extracted, the question now arises of whether the GVS prime could be used to ameliorate spatial memory symptoms in neurological disease. I therefore proceeded to examine whether a similar advantage would be seen in clinical populations who suffer from spatial memory deficits, when tested on same paradigms from Chapters 2 and 3. The current chapter explored this location specific GVS effect in individuals with Alzheimer's disease (AD), a clinical population whose spatial memory deficits are amongst the first symptoms observed (Agrawal et al., 2020; Driver & Halligan, 1991; Previc, 2013). The following sections will first focus on the clinical presentation of memory loss in AD and its underlying mechanisms. The need for an effective AD treatment with limited side-effects will be next discussed, as well as the suggestion to use GVS to improve spatial memory symptoms in this particular clinical population, before the experimental approach is presented.

Early symptoms in AD and underlying mechanisms

Alzheimer's disease is an irreversible, progressive brain disorder which results in a constellation of cognitive deficits, such as diminished memory, language and executive function skills (Snowden et al., 2007). This neurodegenerative disease is the leading cause of dementia showing an increasing prevalence as the elderly population of occidental nations continues to rise (Previc, 2013; Puente-González et al., 2020). Recent projection studies predict that, if current data are maintained, an approximate 300% increase in dementia cases is expected to occur by 2050, resulting in more than 130 million patients worldwide (Prince et al., 2015; Puente-González et al., 2020).

As mentioned in the General Introduction section, several cortical regions such as the parietal-temporal and parietal-insular cortexes, as well as the medial-temporal cortex - which includes the hippocampus and the parahippocampus gyrus - have been shown to be major components of a network of brain areas that support navigation in humans (Hitier et al., 2014; Hüfner et al., 2007; Maguire et al., 1997; Previc, 2013; Shinder & Taube, 2010). This topographical cortical system receives signals from multiple sensory systems, including vestibular inputs about head movement and body position in space, which are then used to detect one's location and direction in space and subsequently inform spatial perception and spatial memory processes (Agrawal et al., 2020; Hitier et al., 2014; Maguire et al., 1997; Previc, 2013, refer to General Introduction section for a thorough literature review of the vestibular system-spatial memory link). Interestingly, this "navigation network" of brain areas has been shown to decline in normal aging. It is the first one to functionally and anatomically degenerate in Alzheimer's patients, providing with more than 90% diagnostic specificity of AD over other types of dementia (Mosconi, 2005; Previc, 2013) and is believed to be linked to the topographical short term memory impairment, one of the earliest symptoms in AD (Agrawal et al., 2020; Previc, 2013). Some clinical studies have shown that the hippocampus is the first brain region to exhibit neurodegeneration (Cherrier, Mendez & Perryman, 2001; delpolyi, Rankin, Mucke, Miller & Gorno-Tempini, 2007). This has also been defined in a cellular level, with degradation of place cells in the hippocampus of a mouse model with AD being highly correlated with the deterioration of the animal's spatial memory (Cacucci, Yi, Wills, Chapman & O'Keefe, 2008). Recall from the General Introduction chapter that place cell activity is believed to create an internal representation of space by integrating spatial information from multiple modalities and provide the brain with spatial reference maps (Moser, Kropff & Moser, 2008). Indeed, several studies have shown that, among other symptoms such as spatial disorientation, wandering and misplacing of objects (Hamilton, Fay & Rockwood, 2009), patients with AD are significantly more likely to present with spatial deficits when tested on paper and pencil tests

used to assess navigation abilities such as the Money Road Map test (Agrawal et al., 2020; Wei, Oh, Harun, Ehrenburg & Agrawal 2018) or on activities closely linked to spatial ability, such as driving (Agrawal et al., 2020; Wei et al., 2017). More specific to spatial memory deficits, impairments in landmark recognition are consistent (Puthusseryppady, Emrich-Mills, Lowry, Patel & Hornberger, 2020; Zakzanis, Quintin, Graham & Mraz, 2009) however reports of impairment in egocentric and allocentric representations of space during navigation are inconclusive (Howett et al., 2019; Puthusseryppady et al., 2020). Several studies have shown that egocentric navigation is preserved in elderly populations and that memory deficits are restricted to allocentric spatial representations (see Gazova et al., 2013 for example). These studies suggest an egocentric reference frame bias in elderly adults with spatial memory deficits, who choose to ignore allocentric spatial representations (Diersch & Wolbers, 2019; Gazova et al., 2013; M. Harris et al., 2012; J. M. Wiener et al., 2013). This is believed to be due to age-related alterations in the neural system that support allocentric computations which may drive the elderly to use more frequently egocentric rather than allocentric strategies (see review from Colombo et al., 2017). Furthermore, studies that have investigated the interaction between both navigation strategies have showed impairment in the process of switching between strategies in AD patients suggesting specific deficits in the spatial organization processes (Puthusseryppady et al., 2020; Serino et al., 2015).

In addition to the spatial memory deficits noted above, several other signs have been shown in people with Alzheimer's, including the inability to maintain upright posture and balance control (Previc, 2013). Consequently, individuals with AD are at increased risk of falls (Agrawal et al., 2020; Fernando et al., 2017), with some studies revealing up to a six-fold increased risk of falls, compared with aged-matched no demented elderly (Puente-González et al., 2020). Indeed, the prevalence of balance impairments in these studies ranged from approximately 10% to 50% depending upon the assessment approach used (Puente-González et al., 2020). This impairment in the vestibular control of balance has been suggested to begin

during the subjective cognitive decline stage of AD, being one of the earliest noticeable symptoms of AD along the disease spectrum (Biju et al., 2022) with some studies proposing it could be a predictive biomarker of cognitive decline in AD (Puente-González et al., 2020).

Several underlying mechanisms have been linked to the aforementioned early symptoms of spatial and balance deficits associated with spatial disorientation, wandering, and increased risk of falls. For several decades, AD neuropathology has been associated with the appearance of senile plaques due to the build-up of beta-amyloid protein (Sadigh-Eteghad et al., 2015), as well as several other health risk factors such as age, cerebrovascular deficiency, lack of exercise, traumatic brain injury, low education levels and diabetes (Cumming et al., 2019; Previc, 2013). Within the last decade however, mounting reports have now been suggesting that the lack of vestibular sensory input is an additional potential contributor to AD pathology (Agrawal et al., 2020; Bigelow & Agrawal, 2015; Previc, 2013; Previc, Krueger, Ross, Roman & Siegel, 2014), with several studies proposing a strong link between reduced vestibular input and cognitive deficits – most notably spatial memory deficits - in individuals with AD (Agrawal et al., 2020; Bigelow & Agrawal, 2015; Previc, 2013). A theory that potentially explains this link is that reduced vestibular input may contribute to the degeneration of cholinergic neurons in the brain structures that comprise the "navigation network", such as the medial temporal region (which includes the hippocampus, as noted above), which could consequently lead to degeneration of central pathways of individuals with AD (Agrawal et al., 2020; Previc, 2013). More specifically, Previc (2013) hypothesised that the underlying pathology that leads to the degeneration of neurons in these brain structures is anterograde degeneration, in which destruction following axonal disintegration spreads forward along the axon towards the higher projection zones (Baloyannis, Vassiliki & Michmizos, 2004; Previc, 2013). This pattern of neuron degeneration is seen following damage to other sensory organs, such as the olfactory bulb (which also projects to the medial temporal region), in which neurons from several synapses receiving inputs from this sensory organ have been shown to undergo apoptosis (Kovács, Raabe & Greenlee, 2008; Previc,

2013) in both rodents and humans (Capurso et al., 1997; Kovács et al., 2008). In support of this theory of the assumed contribution of reduced vestibular input to the neurodegeneration of the "navigation network", hippocampal atrophy in healthy adults has been associated with vestibular sensory dysfunction as shown by a recent study including over 100 healthy adults who were noted to have significantly reduced hippocampal volume (Kamil, Jacob, Ratnanather, Resnick & Agrwal, 2018). Indeed, hippocampal neuron degradation may provide the neuroanatomic link between spatial impairment and reduced vestibular input in AD as suggested by recent reviews (Agrawal et al., 2020; Previc, 2013). This link is further supported by evidence that shows poorer function in vestibular end-organs involved in detecting the orientation of the head (the saccule) in individuals with AD compared to age-matched healthy adults (Harun, Oh, Bigelow, Studenski & Agrawal, 2016). Indeed, the saccule is believed to contribute information about the orientation and encoding of topographical space and it has now been suggested to be particularly relevant for spatial cognition, with reduced function strongly associated with impaired spatial ability (Agrawal et al., 2020).

Current treatments in AD

Despite significant research by pharmaceutical industries, there are only limited pharmaceutical treatments currently approved for AD (Puente-González et al., 2020; Salawu, Umar & Olokoba, 2011). These treatments are only symptomatic, aiming mostly to improve patients' quality of life and they do not alter the rate of decline or the course of illness (Mossello & Ballini, 2012; Weller & Budson, 2018). In addition, these approaches are of limited efficacy, as they only provide moderate improvements to individuals' livelihood while presenting with several side effects (Mossello & Ballini, 2012; Puente-González et al., 2020; Salawu et al., 2011).

Certain transcranial techniques (which stimulate the brain with transcranial magnetic or direct current stimulation) have also been suggested as non-invasive neurostimulation tools to improve symptoms of AD. For example, transcranial direct current stimulation (tDCS) is a cost-

effective rehabilitation strategy that applies a weak direct electrical current (usually 1/2mA at a constant frequency) to the scalp through one or two stimulation electrodes in targeted brain regions (Cammisuli, Cignoni, Ceravolo, Bonucceli & Castelnuovo, 2022). This current application modulates neuronal activity by inducing changes in the extracellular *milieu*, which in turn lead to changes in resting membrane potential of the neuronal populations in the proximity of where the electrodes are placed (Mahdavi & Towhidkhah, 2018). It has been shown that tDCS has positive implications in cognitive abilities, quality of life measures and functional autonomy in neurodegenerative patients (see review by Cammisuli et al., 2022). More specifically, recent clinical trials using tDCS have suggested it has the potential to improve motor and cognitive aspects (e.g., verbal fluency and divided attention) of Parkinson's Disease (PD) (Firouzi et al., 2021; Fregni, Simon, Wu & Pascal-Leone, 2021) as well as word recognition (verbal and visual), visuo-constructive ability and language skills in AD (Boggio et al., 2006; Ferrucci et al., 2008; Fregni et al., 2021). This and similar neurostimulation methods such as TMS (Transcranial Magnetic Stimulation, a safe non-invasive form of brain stimulation that modulates neuronal activity through electromagnetic induction, Groppa et al., 2012) however present with many limitations under the light of ameliorating spatial memory symptoms in AD. Stimulation is usually applied over limited superficial brain areas with the distribution of the current reaching the cortex depending on the intensity and duration of the stimulation (Cammisuli et al., 2022; Wilkinson, 2021). This raises the need for specialist knowledge to help identify not only the correct part of the scalp that is to be stimulated but also the optimum stimulation frequency and electrode montage/application (Cammisuli et al., 2022; Wilkinson, 2021). It also favours therapeutic pathways that target easily accessible areas such as the motor, sensory and visual cortices (Cammisuli et al., 2022; Thair, Holloway, Newport & Smith, 2017). Although recent studies have shown that these neurostimulation applications could be possible for administration within a home environment with the help and supervision of a remote specialist (Cammisuli et al., 2022; Pilloni et al., 2020), the constraint arising from the difficulty of modulating activity in

deep lying areas (such as the hippocampus for example) still remains. This is particularly important when aiming at developing therapeutic techniques for spatial memory impairment. In addition, stimulation protocols vary according to intensity and modulation duration, as well as the size and montage of the electrodes or even the orientation of the electric field in relation to the anatomic parts of the cortex targeted, which often leads to inconsistent results (Cammisuli et al., 2022). The need therefore arises for an effective neurostimulation method that could modulate activity in brain areas linked to spatial memory ability and is both easy to use and cost-effective, but most of all, does not require extended specialist knowledge for its application.

The current study

In this chapter, I investigate through a preliminary study whether GVS could be an alternative neuromodulation method for the treatment of early signs of AD, in particular spatial memory impairment. Similar to tDCS, the use of GVS does not result in discomfort (Rorsman et al., 1999) and few side effects have been reported from its use (see Khoshnam, Häner, Kuatsjah Zhang & Menon, 2018; Wilkinson et al., 2019 for recent studies in PD). As mentioned in previous chapters, some studies report that GVS influences brain areas clustered under the "navigation network" of brain areas responsible for spatial memory, such as the hippocampus (Hilliard et al., 2019; Hitier et al., 2014; Hüfner et al., 2007; Mosconi, 2005; Previc, 2013; Shinder & Taube, 2010). This suggests that this vestibular stimulation technique could provide access to deep lying brain areas that are difficult to modulate through other brain stimulation methods. GVS has already been shown to modulate visuospatial memory function in animals (for a review see P. F. Smith et al., 2010) and healthy individuals (Wilkinson et al., 2008), as well as individuals suffering from other neurodegenerative diseases to AD, such as Parkinson's (Wilkinson, 2021) or even similar cognitive modalities, such as visuospatial attention in brain-injured patients presenting with visuo-spatial neglect (Rorsman et al., 1999). Vestibular stimulation via GVS has also been shown to influence hippocampal-dependent spatial learning in healthy young adults (Hilliard et al., 2019). Devices are becoming increasingly suitable for home

application and self-administration due to simple user interfaces with the potential to set stimulation protocols by researchers/clinicians a priori (Wilkinson, 2021). With accumulating reports of a strong link between vestibular stimulation and spatial memory improvement, it is surprising how researchers have not conceptualised GVS as a therapeutic pathway in early AD pathology so far. Indeed, with the prevalence of the disease being projected to more than double within the next three decades, the need for development of preventative strategies in early diagnosis is eminent (Cumming et al., 2019; Mosconi, 2005).

An exploratory pilot study was conducted with community-based AD participants to assess whether the GVS advantage in spatial memory retrieval seen in the earlier normative participants of Chapters 2 and 3 could be replicated in a clinical population who show topographical memory impairment (Previc, 2013). The clinical participants were therefore invited to perform in the 2-D MWM task described earlier that engages allocentric encoding which seems to be the most compromised in AD (Diersch & Wolbers, 2019; Gazova et al., 2013; M. Harris et al., 2012; J. M. Wiener et al., 2013). The data obtained in the current study could shed light on whether vestibular signals could enhance allocentric representations of space in participants whose memory and visuo-perceptual systems are already compromised. It was anticipated that the results could inform future non-invasive therapies for persons with spatial memory deficits.

Recruitment

Participants were recruited via community-based memory clinics (Alzheimer's Society and Age UK) and via physician referral from the East Kent Hospitals University NHS Foundation Trust. All participants had a recent diagnosis of cognitive impairment and memory deficits (within the last five years, see inclusion criteria on Table 4.1) from Cognitive Neurology clinics and were in receipt of treatment under the supervision of a consultant neurologist. Diagnosis was documented in the patient's medical records and was confirmed by clinicians on the basis of a combination of MRI or SPEC brain scans and neuro-psychometric assessments

such as Mini-Mental State Examination (MMSE) and Wechsler Memory Scale (WMS).

Participants who met the inclusion criteria described on Table 4.1 were invited to participate. Given the exploratory nature of this study and to facilitate study recruitment, inclusion criteria prioritised participants diagnosed with AD however a case of vascular dementia was also accepted in the absence of other AD participants not being available at the time (subject to satisfying all other inclusion and exclusion criteria and subject to memory impairment being documented in their records).

Table 4.1.

Recruitment criteria

Inclusion Criteria
Participants must have received a diagnosis of dementia by a professional clinician
Participants must demonstrate cognitive impairment within a five-year window (capable of treatment gain) as indicated by the MoCA assessment (see text)
Capacity to consent to the study
No significant speech and communication difficulties
Normal/corrected to normal vision
Exclusion Criteria
No history of stroke or transient ischaemic event
No history of recent (i.e., within 6 months) significant psychiatric illness
No history of seizures
Absence of clinical signs indicating cognitive impairment
No recent head injury or other significant neurological history
No diagnosed inner ear pathology
No lesions or abrasions on the mastoids
No metal implants in the head
No electronic implants

Fifteen participants expressed interest in the study and underwent a phone interview, during which the process was explained in detail, the inclusion/exclusion criteria were verified and study requirements were elaborated upon. During this phase, participants were encouraged

to express any concern and ask questions. One participant was discontinued during this initial phone screening due to safety issues (presence of pacemaker). An in-person screening process followed, in which participants were invited to the University of Kent, diagnosis was confirmed and the MOCA and the rest of the assessment battery was administered (see Figure 4.1). From the fourteen remaining participants, five were discontinued due to a combination of the following exclusionary factors during this screening process: failure to achieve the desired MOCA threshold scores (N=5) and stroke history (N=1)/ comorbid Parkinson's disease (N=1)/ significant speech and communication difficulties (N=1)/ mastoid lesions (N=2). One additional participant was discontinued due to an Alzheimer's diagnosis 9 years prior to study enrolment, which is more than the 5-year window that is clinically considered capable of treatment gains by the consultant clinician. The remaining eight participants were then invited 2 weeks after their initial follow-up (to provide them with a rest period and not to overburden them with frequent visits), to conduct the 2-D MWM task (see Figure 4.1). Two additional participants decided to withdraw due to stressful life events or hospitalisation during this phase, which reduced the total number of participants to six (final N=6).

Ethical considerations

Prior to taking part in the study, all participants were asked to give their written informed consent after being given a verbal and written detailed description of the study. The study was approved by the University of Kent's Psychology research ethics committee and all participants were treated in line with the guidelines provided by the British Psychological Society (BPS).

Assessment battery

Cognitive function was first assessed via Montreal Cognitive Assessment (MoCA ®), a rapid screening instrument that assesses mild cognitive dysfunction (Original Version 7.1, www.mocatest.org). Administration and instructions were followed according to the authors, and

several cognitive domains were tested, among others visuo-constructional skills (including clock drawing), memory, attention and executive function. Given that the main interest of this preliminary study was in early symptoms concerning topographical memory impairment and balance deficits, a cut-off score of 18 out of 30 on the total score of MoCA was used, so that participants with moderate (range 10-17) or severe (range below 10) cognitive impairment were excluded from the study (see severity levels for MoCA test at www.mocatest.org).

As noted above, because the main focus of the current study was visuospatial memory, in addition to the MOCA test, the following assessment battery was also administered to help characterise the memory impairment, in the following order: Visuospatial reproduction I from WMS-III (Wechsler, 1987), Rey Osterreith Complex Figure (ROCF, Meyers & Meyers, 2015; Rey, 1941), Road Map Test (Money, Duane & Walker, 1965) and Visuospatial reproduction II from WMS-III (30 minutes after the administration of the Visuospatial reproduction I session). Furthermore, the Mini-BESTest, Balance Evaluation Systems Test (© 2005-2013 Oregon Health & Science University) was administered to assess balance dysfunction at baseline and potentially interrogate a link between balance impairment and visuospatial performance. If a correlation were to be found, then future studies could further examine if the effects of GVS on memory were constrained by the integrity of the balance system. A clinical cut-off for individuals with AD has not been defined in this test, however it has been shown that the mini-BEST has higher sensitivity in detecting balance impairments in individuals suffering from similar neurodegenerative diseases, such as those suffering from Parkinson's disease (King, Priest, Salarian, Pierce & Horak, 2012) compared to other frequently used balance tests (such as the Berg Balance Scale for example, see King et al., 2012). These studies have shown that scores below 21 out of 28 are indicative of balance deficits (King et al., 2012). All sections (anticipatory, sensory orientation, reactive postural control and dynamic gait) were tested on each participant, when possible. Furthermore, the Modified Vertigo Symptom Scale (MVSS), a self-assessment tool to determine severity of balance disorders (Yardley, Masson, Verschuur,

Haacke & Luxon, 1992) was scheduled upon completion of the study. In the sections that follow, each of these assessment tests is briefly introduced, followed by a detailed analysis of participant characteristics and their performance on these assessment tests.

Rey-Osterreith Complex figure: This test was included to assess visuo-constructional ability and visual memory performance. Copy and Immediate Recall were used in the current study as a measure of incidental learning and participants were not told ahead of time that they would be asked to reproduce the figure at a later time. Each of the reproductions of the figure were timed to the second. During the copy condition, an 81/5 by 11-inch stimulus card was presented horizontally in front of the participant and participants were asked to copy the figure as accurately as they could. Immediately after completion of the copy condition, participants were asked to draw again the figure from memory. No time limit was imposed and participants were told to take as much time as they need to draw the figure. Scoring was performed according to the Boston Qualitative Scoring System using the comprehensive scoring method. The maximum score that could be achieved was 36 for each session.

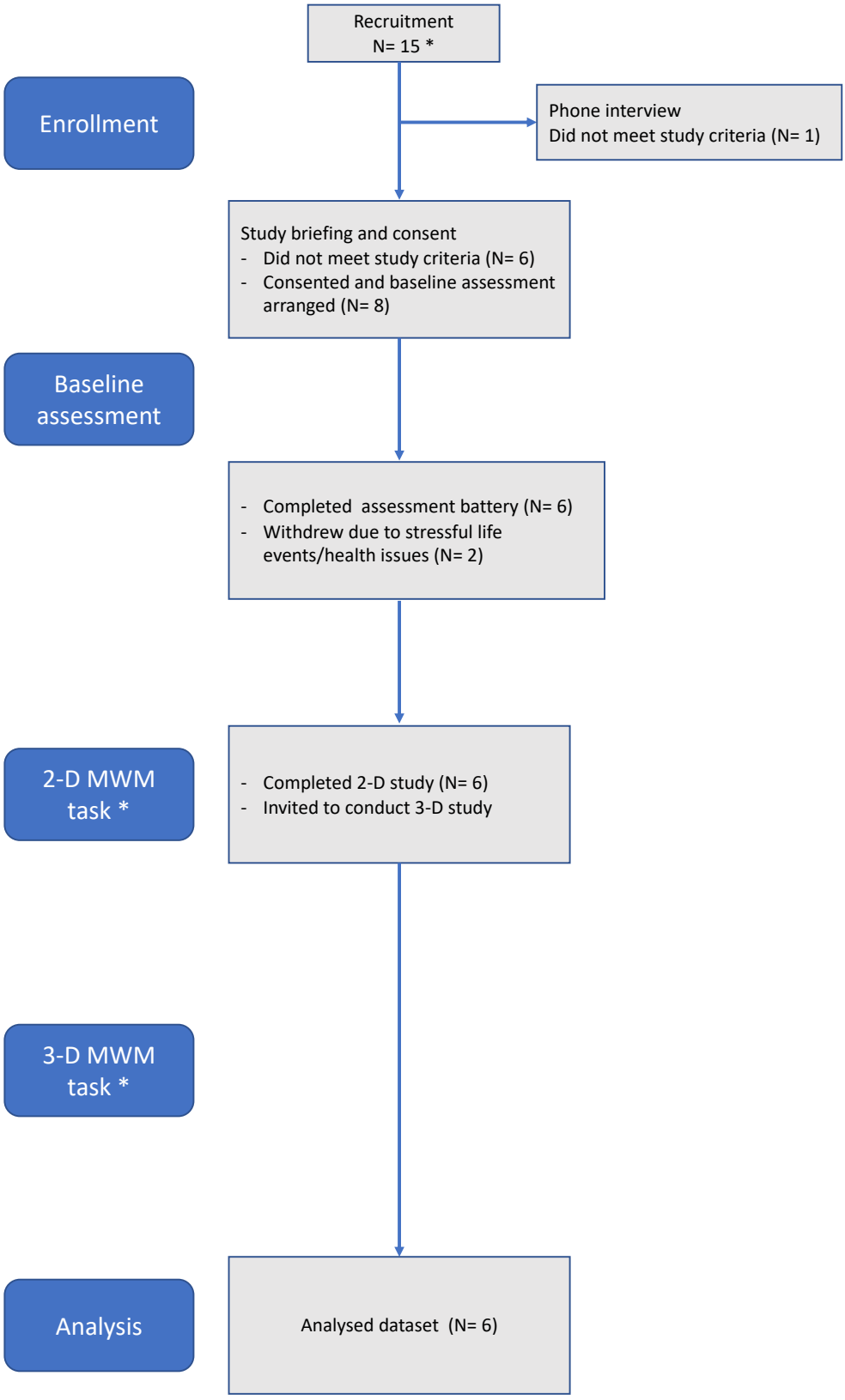

Figure 4.1. Flow chart of the current study. Asterisk indicates parts of the study that were interrupted by the Covid-19 pandemic.

Visuospatial Reproduction I & II from the WMS III were used to assess visual memory. In brief, during Visuospatial reproduction I**,** participants were first shown a series of designs, each for 10 seconds, and were then instructed to draw each one from memory. Thirty minutes after the first administration, Visuospatial reproduction II followed, in which, participants were asked to recall and draw the designs from memory (order was not important). A recognition, copy and discrimination task were included, with old and new designs. Administration and scoring were performed according to the authors instructions. The maximum score that could be achieved was 104 for each session.

Money Road Map test (MRMT). This paper and pencil test was administered to assess navigation abilities, as it has been shown by previous studies that is sensitive to detect spatial memory deficits in individuals with AD (Agrawal et al., 2020; Wei et al., 2017). The test consists of a 2-dimensional representation of a city map with a fixed orientation, on which a pathway with a 32 right or left step dotted route was drawn (Money et al., 1965). Participants were instructed to imagine themselves taking that route and deciding whether a right or a left turn was required at each intersection. The main outcome was the number of errors or missed responses (Wei et al., 2017). Participants performed a practice run of a different map, containing 8 intersections, to ensure they understood instructions prior to the real test. No time limit was reinforced and the maximum score that could be reached was 32 points, with a cut-off of under 10 errors.

Participant characteristics

The sample consisted of 3 males and 3 females, age range 59 - 78 (M = 71.34, SD = 6.74). Participants' mean years of education was 12 (range 9 - 14, SD = 2.28) and the duration of symptoms ranged from 1 to 5 years (M = 3.5 years), further demographics are presented on Table 4.2. At interview, memory impairment was prevalent for all participants, as indicated by the need to repeat instructions several times during assessment. Overall cognitive dysfunction was

confirmed by the MOCA assessment (see Table 4.2). In addition, visuospatial impairment was present in all participants' performances in the visuospatial section of MOCA and/or verified by consultants' comments in participants' records (wandering off and getting lost, not remembering how to drive to familiar places etc.).

On a general note, participants performed better at visuospatial assessments of immediate recall, assessed by the Visual Reproduction I and Rey-Osterreith Complex figure tests, than at delayed recall, assessed 30min after administration of the first part of Visual Reproduction section of the WMS- III, as indicated by the overall retention percentage for each participant (see Table 4.2). The results obtained reflect scores observed in similar studies on AD participants (see Griffith et al., 2006 for VR I& II or Melrose, Harwood, Khoo, Mandelkern & Sultzer, 2013 for ROCF test) with slight deviations in the Visual Reproduction II and ROCF Copy scores, which were lower in the current study, probably due to a higher mean of participants' age and lower mean of years of education. Performance on the ROCF Copy condition was significantly correlated with age ($r = .90$, $p = .014$, $d = .81$) and marginally correlated with MOCA scores ($r = .818$, $p = .046$, $d = .67$) and gender ($r = .78$, $p = .07$, $d = .60$), with males performing higher. There were no other significant correlations between ROCF and other demographic variables, including education and time from first diagnosis. No significant correlations were found between VR I and II scores as participants' retention scores were extremely low during delayed recall (see Table 4.2, see discussion section for a detailed explanation on the absence of significant correlations between neuro-assessment measures). In the paragraphs that follow, each patient's performance on these visuospatial assessments is briefly outlined, focusing on the MoCA, ROCF and VR I & II scores, before the 2-D MWM task is introduced.

Table 4.2.

Participant clinical and demographic characteristics at study entry

Subject	Diagnosis	Age	Gender	MOCA /30	Mini-Best /28	VR I & II /104	MRMT /32	ROCF /36
01	AD	76	M	20	19	38 - 0 (0)	20	18 – **0 (0)**
02	EAD	59	F	18	17	45 - 0 (0)	20	**15** - **0 (0)**
03	MD	70	F	21	17	52 - 17 (33)	16	17 - 11 (64)
04	AD	74	M	22	26	51 - 0 (0)	26	17 - 8 (47)
05	VaD	78	M	23	15	75 - 8 (11)	19	19 - **7 (37)**
06	EAD	71	F	20	25	42 - 0 (0)	14	16 - 7 (44)
Mean (SD)		71.34 (6.74)		20.7 (1.75)	19.83 (4.58)	50.5 – 4.83 (13.12)(7.06)	19.16 (4.12)	17 - 5.5 (1.42)(4.51)

Note: EAD: early onset AD, VaD: vascular dementia, MD: mixed dementia (Alzheimer's and vascular). VR I & II: shows raw scores for recall total scores in each I and II sections, (% retention from first Recall to 30min Delayed Recall, shown in parenthesis). ROCF: shows raw scores for Copy and Immediate Recall sections (% retention, Copy - Immediate recall, shown in parenthesis). Bold and underlined – below average score.

Participant 01

The Participant's scores on the visuospatial/executive section of MoCA reflected moderate impairment, however the participant scored zero on the delayed recall memory section of MoCA. Similar performance was seen on the more complex visuospatial production of ROCF, scores in the Copy condition were above average and were indicative of good visuospatial functioning and moderate executive function. However, the participant did not retain any information for the Immediate recall condition of the ROCF, nor the delayed recall of the Visual Reproduction sections, despite being prompted several times. Taken together, the above assessment battery revealed severe memory but moderate executive function deficits in this participant.

Participant 02

The participant's scores on the visuospatial/executive section of MoCA reflected moderate

impairment, however the participant also scored zero on the delayed recall memory section of MoCA. Their performance on the more complex visuospatial production of ROCF in the Copy condition was below average to mildly impaired and was indicative of poor visuospatial functioning (extreme difficulties with accuracy and detail), as well as poor executive function (extremely poor planning and neatness). The participant did not retain any information for the Immediate recall condition of the ROCF, nor the delayed recall of the Visual Reproduction sections, despite being prompted several times. Taken together, the above assessment battery revealed severe memory and executive function deficits in this participant.

Participant 03

The participant was notably diligent throughout the assessment and made every effort to comply with the instructions. Their scores on both the visuospatial/executive section and delayed recall memory sections of MoCA were moderate. The participant's performance on the ROCF in the Copy condition was average and indicative of moderate visuospatial functioning and only slight impairment in executive function. Only slight visuospatial memory impairment was detected in regard to detail retention. Similar results were obtained from the Visual Reproduction recall session, indicated by good retention scores (however higher than the rest of the group). Taken together, the above battery revealed only moderate memory and executive function deficits in this participant.

Participant 04

The participant's scores on the visuospatial/executive section of MoCA reflected superior performance, however the participant scored zero on the delayed recall memory section of MoCA. The participant's performance on the ROCF in the Copy condition was average and indicative of good visuospatial functioning and moderate executive function. However, in the Immediate recall section, participant's performance was noteworthy of great executive impairment and poor visuospatial memory impairment as indicated by low detail retention. Participant could not recall designs from the delayed recall of the Visual Reproduction section,

despite being prompted several times. Taken together, the above battery revealed good executive function skills but poor visuospatial memory in this participant.

Participant 05

The participant's scores on the visuospatial/executive section of MoCA reflected superior performance, however the participant scored poorly on the delayed recall memory section of MoCA. Similar performance was seen on the more complex visuospatial production of ROCF, scores in the Copy condition were above average and were indicative of good visuospatial functioning and moderate executive function. In the immediate recall section however, their performance was indicative of some executive impairment and poor visuospatial memory retention, as evidenced by poor planning and low accuracy/detail retention (it should be noted that participant gave up the production after 36seconds, while group range was 1min19sec – 2min15sec). The participant could not recall designs from the delayed recall of the Visual Reproduction section, despite being prompted several times. Taken together, the above battery revealed moderate to good executive function skills but poor visuospatial memory in this participant.

Participant 06

The participant's scores on the visuospatial/executive section of MoCA reflected moderate impairment, however the participant scored zero on the delayed recall memory section of MoCA. Similar performance was seen on the more complex visuospatial production of ROCF, scores in the Copy condition were average and were indicative of good visuospatial functioning and moderate executive function. In the Immediate recall section, participant's performance was noteworthy of great executive impairment and poor visuospatial memory. Participant could not recall designs from the delayed recall of the Visual Reproduction section, despite given ample time. Taken together, the above battery revealed moderate executive function skills but poor visuospatial memory in this participant.

Overall, it seems that the neuro-assessment battery revealed similar results across

participants' memory and executive function across tests. All six participants presented with memory deficits that ranged from severe to moderate. Similar results were found for executive function. In addition, the MRMT also revealed visuospatial deficits in all but one participant (Participant 04, see Table 4.2), however it should be noted that this is the only one participant out of the group who continues to drive to unfamiliar places (even goes on road trips), whereas the rest of the group do not drive (N= 2) or restrict themselves to only familiar places (N= 3). In the section that follows, the 2-D MWM task is introduced, which was conducted two-weeks after the assessment battery was administered.

2-Dimensional Morris Water Maze Task

In the current paradigm participants were encouraged to navigate within a 2-D visual field and learn the location of a target platform in the presence or absence of a GVS prime (see Chapter 2). In subsequent test trials, participants' spatial memory for these target locations was tested. Based on the results seen in the normative population study, we hypothesised that *accuracy* and participants' estimations of the target location (*distance from target* measure) would favour the GVS-paired platform location. Given the exploratory nature of the study, the other outcome measures tested in Chapter 2 were also investigated (*RTs* and *moves to target*), even if a GVS advantage was not found in the normative population study. This decision was made because the normative group may have a neurological resilience to GVS that gives them narrower sensitivities than their clinical counterparts. Path analysis was also considered here, in which, by visually inspecting the paths participants took to move to the target platform from the starting position (obtained by screenshots at the end of each trial), it was assessed whether participants moved directly or slightly calibrated their moves to reach the target or chose a more deviated route (see Chapter 3). The methods and procedure followed are detailed below.

Method

Materials. Please see Chapter 2 for details on this section. The same invisible grid (with 31 rows at the y coordinate and 31 columns at x coordinate that divided the background area) used in the normative experiment was presented here to measure the number of moves made to reach the target while participants were instructed to navigate the circular area. The starting position was indicated by a boxed arrow (in the current study it was presented in bolder borders so that it would be easier for patients to find as a pilot study showed it was difficult to locate). The starting position varied across 8 different positions (four cardinal points plus four starting points placed in the middle of the space in between) and was illustrated as an arrow image. Recall that in the same paradigm in Chapter 2, participants were instructed to move the cursor to the starting position and click once with the left mouse button to engage the arrow image to their mouse movements, before they begin navigating the circular area. In order to simplify this step for the clinical population, this part was skipped and the arrow image was engaged automatically to the mouse movement from the beginning of the trial. Therefore, in the current study, participants were asked to click only once, with the left of the mouse, inside the target square, during the learning phase, or where they estimated the target square to be (given that this was hidden), in the test phase. The hidden platform was always a black square, which depending on the experimental condition, was either paired with GVS or was the Control platform. The x, y coordinates for the GVS and Control platforms were counterbalanced between two spatial locations with the following coordinates: 9,7 and 9, 23. The three external cues were anchored in the following positions in x, y coordinates: sun 29,10 ; ball 2, 28; cloud 5,4.

Procedure. Recall from Chapter 2 that each experimental session consisted of one practice block and two test blocks. Each practice and test block contained a learning phase, in which participants learned the location of the hidden platform starting from eight different positions

followed by a test phase that consisted of 48 test trials (12 repetitions of 8 starting points x 4 conditions, 1x upright and 3x rotated: 90º, 180º and 270º, see Figure 4.2). As before, to ensure that participants learnt the locations of the platforms, no rotated conditions were included in the learning phase. Participants were given explicit verbal and written instructions to move directly to the target and this was already practiced during the learning phase. The procedures described above were illustrated to the participant during a practice block, which was conducted at the beginning of the experiment and served to provide elaborate verbal feedback on participant's performance to ensure the task was understood. By the end of the practice block, participants appeared to be clear on how to conduct the experiment (this was also confirmed by screenshots of learning trials, see Data analysis section). Participants were given verbal and written instructions to find the target as fast as possible and as accurately as possible by choosing the quickest route possible, but no explicit clarifications were given about the rotated conditions. As opposed to previous 2-D experiments, these instructions were included at the beginning of each trial, as during a pilot study (with volunteers who did not meet the study criteria but were intrigued to carry on with the study), participants manifested lack of retention for instructions. In total, participants completed 24 (8 starting points x 3 platforms – practice, GVS, Control) trials for the learning phase and 144 (48 test trials x 3 platforms) trials for the test phase. The experiment lasted 20 minutes. Participants were counterbalanced across four different groups (performed GVS/Control block first and GVS/Control platforms were counterbalanced across the two spatial locations). In addition, contrary to previous 2-D MWM experiments, the achievement score at the end of each block was removed, as it seemed to discourage participants during the pilot study, given the low accuracy.

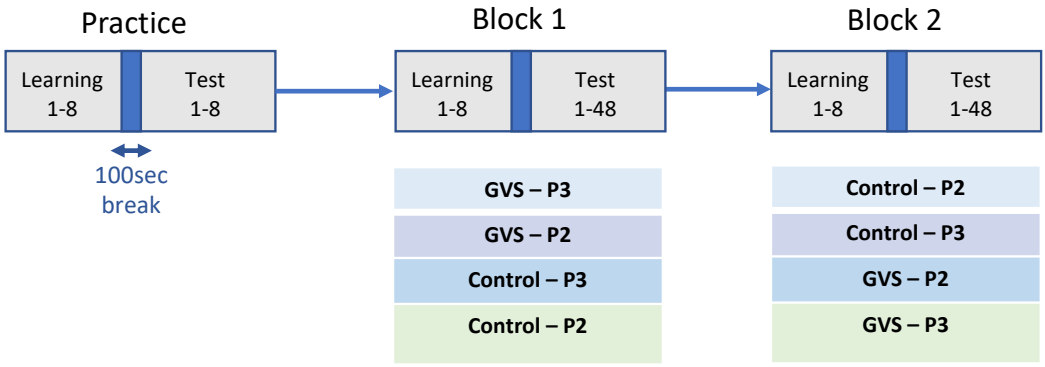

Figure 4.2. Schematic representation of the paradigm used in this experimental set-up. Each participant completed a practice block (consisting of 8 learning and 8 test trials), followed by two test blocks (consisting of 8 learning trials and 48 test trials). The colored tables show the allocation of participants in four different groups. If P1 is considered the practice platform, P2 and P3 test platforms were associated with GVS or Control blocks in a way that half of the participants completed the paradigm having associated the P3 platform with GVS and half of them the P2 platform with GVS, in order to eliminate to eliminate bias. In addition, half of the participants completed the Control block first and half of them second to limit practice effects.

GVS Stimulation Protocol. All stimulation was performed using the bilateral bipolar configuration of anode left and cathode right, as previously described in previous chapters. Thresholding was also included in this experiment to ensure that the stimulation was not perceived by participants and was conducted prior to the experiment using a blinding technique, following the same process as in previous chapters. Stimulation occurred between 0.25 - 0.3 mA; GVS stimulation was first assessed for each participant at 0.3mA and if perceived, was adjusted to 0.25mA. As with previous experiments, participants who still noticed the stimulation during this step were due to be excluded from the study, however none of the participants declared they perceived the stimulation. All participants reported they didn't perceive the stimulation on the perception questionnaire nor were aware of any patterns of stimulation while they conducted the 2-D MWM task.

Data analysis for 2-D MWM task. Prior to statistical analysis, place learning was verified by visually examining screenshots of learning trials for each of the GVS and Control block for each participant. All participants moved directly towards the platform from the second (N = 1) or from

the third (N = 5) learning trial and maintained these predominantly direct paths through the remainder of the learning trials. As previously mentioned, main outcome variables were *distance from target, RTs and moves made.* In the sections that follow, I expand upon the various analysis performed in order to analyse the data from each of these measures.

Distance from the target. This was one of the main DVs as it represents a continuous variable, as opposed to the binary measure of *accuracy*. Based on the study on the normative population, *accuracy* was predicted to be very low in the current paradigm, since participants were not given any confirmation of the target location in the test trials. It was therefore important to include a measure that would provide an indication of how far from the target participants estimated the target platform to be. Recall that for the data derived from the normative population, due to the presence of outliers and the expected skewed distribution of this measure (zero represents participants estimating correctly the target platform's location, therefore zero distance from the target), a modified z-score correction was applied because the median was considered a more robust indicator of central tendency and was less sensitive to these extreme scores. In the current study however, an analysis of all obtained raw data from this measure was chosen for two reasons. Firstly, one could not be sure of the exact nature of the underlying skewed distribution and extreme scores could potentially consist of meaningful data. Indeed, by visually inspecting the distribution of scores obtained in the current study, it was found that this dataset potentially followed a binomial distribution, hence encouraging further analysis of these scores. Secondly, a statistical analysis based on the median (such as Wilcoxon signed-ranks test for paired data, which would be typically used in this instance), would result in loss of statistical power, as quickly assessed by bootstrapping the median and the mean difference in our dataset (see Table B.1 in Appendix D) and interpreting the confidence intervals, in which, median differences result in wider CIs (Michiels, Heyvaert, Meulders & Onghena, 2017). Due to these limitations, simulation-based methods were implemented to provide significance levels. Simulation-based methods such as randomization tests do not work under parametric assumptions (e.g., random

sampling, normal distribution assumptions, independence of data), and are an increasingly common nonparametric alternative statistical tool to hypothesis testing, especially in clinical studies (Bulté & Onghena, 2008; Heyvaert & Onghena, 2014; Levin, Feron & Kratochwill, 2012). They are used to construct confidence intervals for measures of interest with the advantage of providing a range of plausible values for the computed effect size (Michiels et al., 2017). In the paragraph that follows, we briefly explain the basis of these tests (refer to the pre-mentioned papers for more details), before introducing the results section.

Similar to bootstrapping, a randomization test builds a sampling distribution of the statistic of interest by resampling the observed data. The basis of its validity rests on the random assignment of measurement occasions to experimental conditions to test hypotheses for causal effects (Bulté & Onghena, 2008; Michiels et al., 2017). More specifically, other potential datasets are simulated that could have been derived by "shuffling'' and randomly assigning different observed scores from the set of observed outcomes to the two treatment conditions, until all the permissible alternative treatment assignments are simulated (Bulté & Onghena, 2008; Michiels et al., 2017). By randomizing the scores in this manner, one can observe where the value of the mean difference obtained in the observed dataset falls relative to all mean differences that could have been obtained, and subsequently, test how extreme the observed statistic is relative to the randomized distribution, as if the null hypothesis were true, i.e., the two treatment conditions do not differ on the outcome as if the outcome was independent of treatment assignment (Bulté & Onghena, 2008).

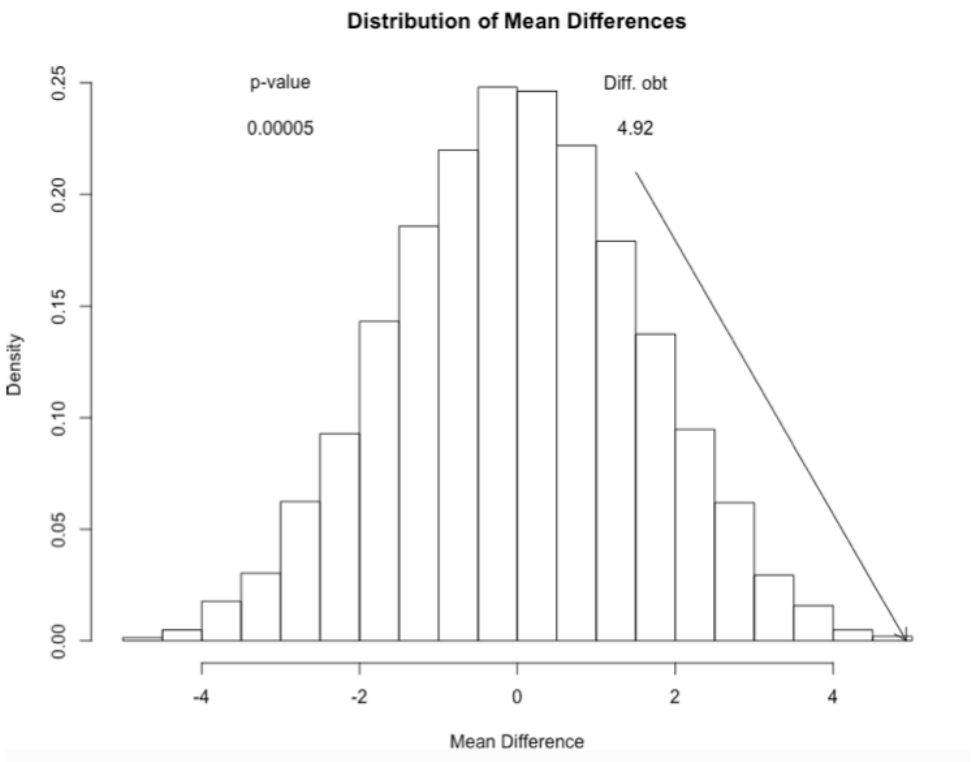

Figure 4.3. Example of randomization tests histogram of the distributions of mean differences. The graph represents data from all trials (upright and rotated) from the *distance from target* measure (see Page 158). Randomization tests create a sampling distribution of a statistic of interest (here mean difference) by simulating potential datasets that could have derived by randomly "shuffling" observed scores and assigning them to different treatment conditions, as if the null hypothesis were true. This randomization process then calculates how extreme the observed statistic is relative to the randomized distribution, and therefore tests statistical significance.

In the current study, scores were assigned to either the GVS or the Control trial group, as if the null hypothesis were true (i.e., there is no differential effect of GVS on recall as measured by the *distance from target* variable). Two different analyses were carried out for this measure, one on a group level and one on an individual level. Performance on a group level was observed first and then the generalizability of an average group effect to individual subjects was tested. Both analyses are explained in detail below. The randomization scheme in both group and individual-level analyses that follow is the same and it yields the same collection of permissible combinations of scores, with the only difference between the two being that in the individual level analysis the experimental units are repeated measurements from the same participant, taken from each trial of the experimental paradigm (Michiels et al., 2017), whereas in the group

analysis, the experimental units are repeated measurements from different participants (Michiels et al., 2017). In addition, the possible rearrangements of the data between GVS and Control trial scores are computed by randomly shuffling GVS and Control data while maintaining pairs of scores together. In both analyses, the mean difference was tested, as only immediate effects were explored (Michiels et al., 2017) and the need to standardize was redundant.

R was used to execute the code provided by Michiels et al., (2017) and carry out the randomizations tests on the individual level analysis (instructions downloaded from https://ppw.kuleuven.be/mesrg/software-and-apps/softwareandapplets, see Appendix E for the code used for the group analysis of paired data. Statkey, a set of online statistical tools that help construct bootstrapping intervals and determine statistical significance in randomization tests (http://www.lock5stat.com/StatKey/index.html), was used to visualise data distributions and to verify various steps of the analysis for these simulation-based methods. See Figure 4.3 for an output example using the current dataset.

Reaction times, accuracy **and** ***moves to the target.*** *Reaction times* were measured from the time point of picking up the arrow image until dropping it in the target platform location. Given that only 3 trials were accurate in the dataset, trials in which participants clicked on the adjacent box were also considered accurate so that RT data could be used. Outliers were removed as previously described using a z-score correction whereby a grand mean RT was calculated across all correct trials completed by the participants and then subtracted from every individual trial RT, before being divided by a grand standard deviation $Z = (X - \mu) / \sigma$. Any resulting z-scores that were greater than 2.5 (and therefore an outlier of less than $p<0.001$) were removed from the analysis (4 outliers in total). The same trials were also considered for the *moves to the target* measure, which represents the number of square grids travelled from the starting position to the target location.

Results

Distance from target – Group analysis

All trials. Participants' estimations of the target spatial location were overall closer to the actual target position in the GVS trials (M =3.42, Mdn = 2, SD = 4.50), 95% CI [2.98, 4.04], compared to the Control trials (M =8.34, Mdn = 3.34, SD = 7.40), 95% CI [7.46, 9.20]. when all four conditions (upright and three different orientations) were considered. The effect size of this mean difference was large (d = .79). Randomization tests found this mean difference statistically significant (p <.001), CI of mean difference distribution [-2.95, 3.04], therefore the mean difference of 4.92 between the two groups not included in the 95% confidence interval limits of the mean distribution, see Figure 4.4.

Upright trials. When participants were tested for only the upright condition, their estimations of the target spatial location were overall closer to the actual target position in the GVS trials (M = 2.45, Mdn = 1.32, SD = 2.92), compared to the Control trials (M = 8.90, Mdn = 8.40, SD = 7.72), see Figure 4.4. The effect size of this mean difference was large (d = 1.07). Randomization tests verified this result is statistically significant (p = .029), 95% CI of mean difference distribution [-6.02, 6.21], therefore the mean difference of 6.45 between the two groups not included in the 95% confidence interval limits of the mean distribution.

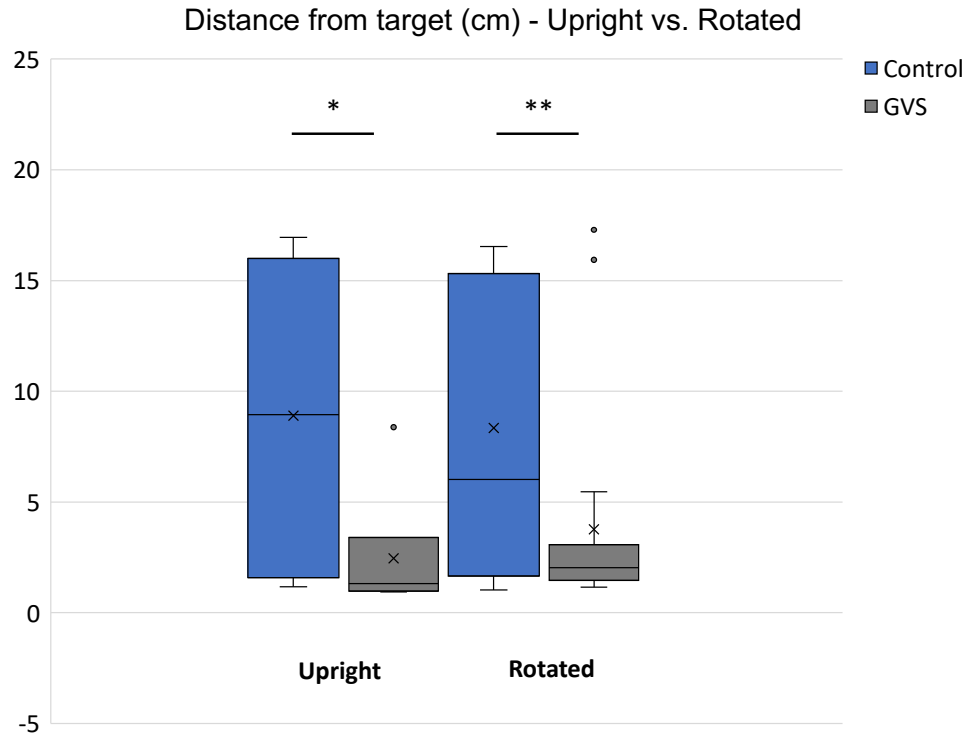

Figure 4.4. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm). Participants' estimations of the target location were significantly closer in the GVS trials than the Control in both the upright (p = .029) and rotated conditions (p = .006); recall scores closer to zero indicate closer to the target, with zero scores meaning target has been reached. Please note that due to the limited number of permissible assignments in the upright condition, randomization tests were not very powerful, even if the mean difference was larger than that of the rotated conditions.

Rotated trials. Across all three rotated conditions, participants' estimations of the target spatial location were overall closer to the actual target position in the GVS trials (M = 3.77, Mdn = 2.03, SD = 4.78), compared to the Control trials (M = 8.18, Mdn = 6.02, SD = 6.73), see Figure 4.4. The effect size of this mean difference was large (d = .76). Randomization tests verified that this mean difference is statistically significant (p =.006), CI of mean difference distribution [-3.25, 3.29], therefore the mean difference of 4.41 not included in the 95% interval limits. Descriptive statistics indicated an advantage for the GVS-paired platform in each of the three rotated conditions; 90 degrees: M= 2.56, SD = 1.83; 180 degrees: M = 4.10, SD =5.70; 270 degrees: M = 4.67, SD = 5.73, compared to the Control platform; 90 degrees: M= 7.47, SD = 6.80, 180 degrees: M = 8.44, SD =7.92, 270 degrees: M = 8.60, SD =7.22, (90-degree d = .99,

180 degree d = .63, 270 degree d = .60). Randomization tests failed to reveal a statistically significant difference in the 90-degree mean difference (p =.061), CI of mean difference distribution [-5.14, 5.13]. All p > 0.05 in all tests for the 180- or 270-degree orientations, possibly due to the presence of outliers in these trials (see Figure 4.5).

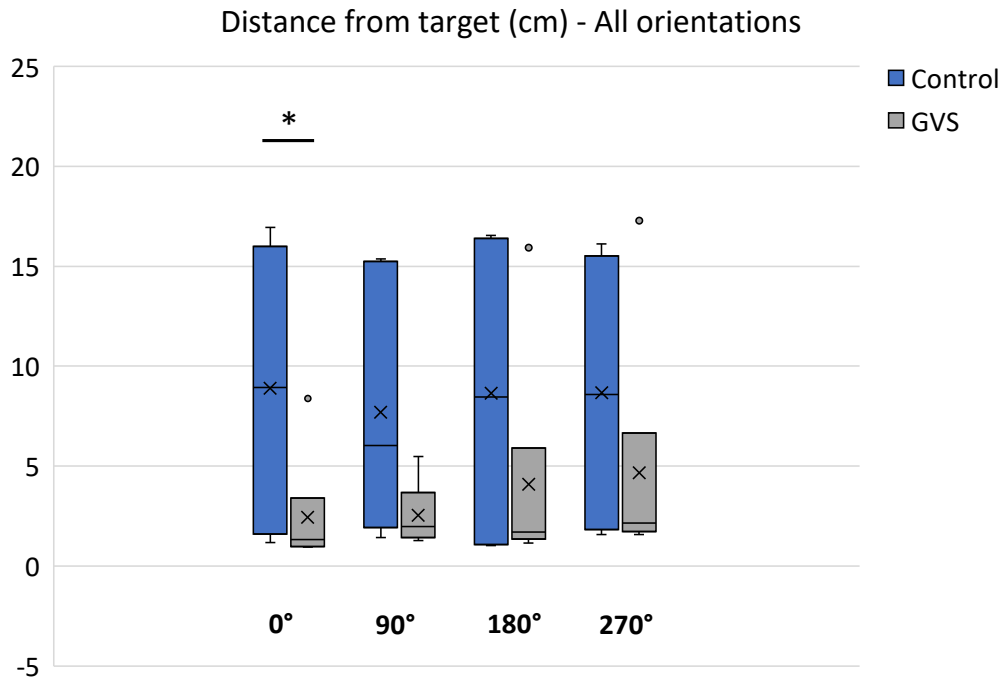

Figure 4.5. Performance in all conditions tested on the *distance from target* measure (in cm, upright trials included for comparison). Participants' estimations of the target location were marginally closer in the GVS trials than the Control trials in the 90-degree orientation (p = .061), all p > .05 in all other orientations, possible due to the extreme outliers present.

***Distance from target* – Individual level analysis**

Participant 01

Descriptive statistics indicated that participant's responses were closer to the target in the GVS trials (M = 1.79, SD = .63) compared to the Control (M = 13.97, SD = 6.56), when all four conditions were considered (upright and trials from the three different orientations). The effect size of this mean difference of 12.17 was large (d >1) and randomization tests showed that it was statistically significant (p<0.001), 95% CI around the mean difference value [9.07, 15.27].

Similar mean differences were obtained when only upright (GVS: *M* = 1.75, *SD* = .56; Control: *M* = 16.96, *SD* = 2.14)), difference 15.21, p<0.001, 95% CI [8.81, 21.61], or rotated trials (GVS: *M* = 1.81, *SD* = .67; Control: *M* = 12.97, *SD* = 7.21, difference 11.16, p<0.001, 95% CI [7.83, 14.49]), were considered, in both cases *d* > 1, see Figure 4.6.

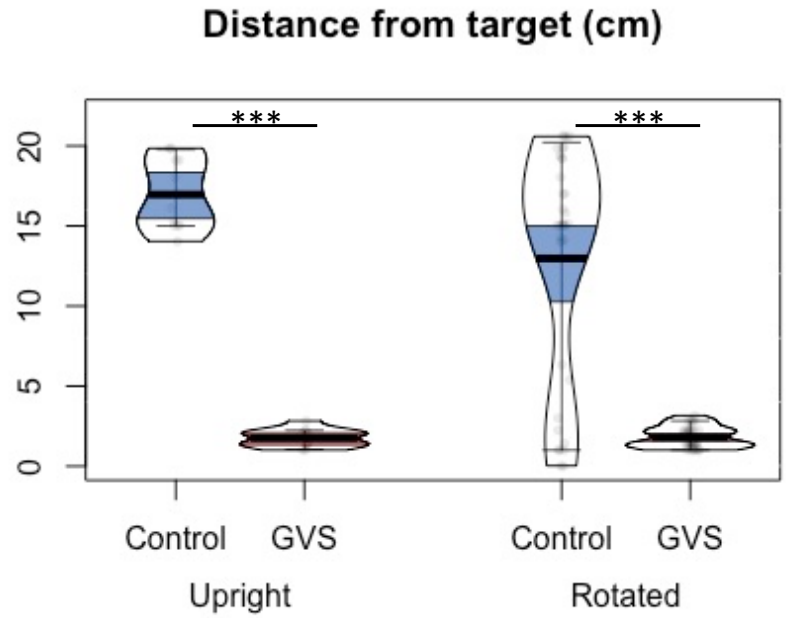

Figure 4.6. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 1. Participant's estimations of the target location were significantly closer to the actual target in the GVS than the Control trials in both the upright (*p* <.001) and rotated conditions (*p* <.001).

Participant 02

Descriptive statistics indicated that participant's responses were closer to the target in the GVS trials (*M* = 11.77, *SD* = 5.32) compared to the Control (*M* = 15.92, *SD* = 2.54), when all four conditions were considered (upright and trials from the three different orientations). The effect size of this 4.16 mean difference was large (*d* = .99). Randomization tests showed that this mean difference of 4.16 was significant (p<.001) when all trials were considered, 95% CI [2.22, 6.10]. Similar effect sizes were obtained when only upright (GVS: *M* = 8.38, *SD* = 1.55; Control: *M* = 15.67, *SD* = 4.71, *d* > 1), difference of 7.29, p=.003, 95% CI [2.63, 11.96], or rotated trials (GVS: *M* = 12.89, *SD* = 5.65; Control: *M* = 16, *SD* =1.26, *d* = .76), difference of 3.11, p=.002,

95% CI [1.11, 5.11], were considered, see Figure 4.7.

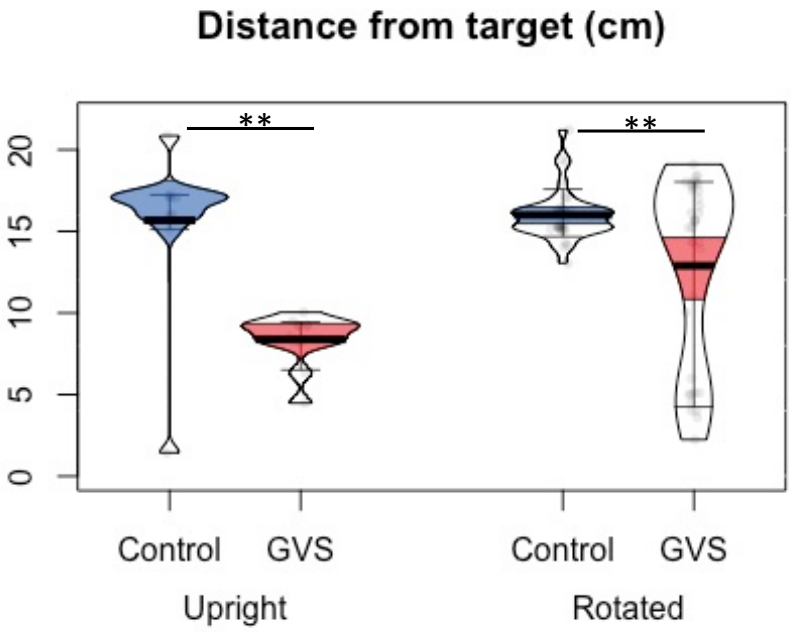

Figure 4.7. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 2. Participant's estimations of the target location were significantly closer to the actual target in the GVS than the Control trials in both the upright (p = .003) and rotated conditions (p = .002).

Participant 03

Descriptive statistics indicated that participant's responses were slightly closer to the target in the GVS trials (M = 1.43, SD = .52) compared to the Control (M = 1.72, SD = .53), when all four conditions were considered (upright and trials from the three different orientations). The effect size of this difference was medium (d = .55). Randomization tests showed that this mean difference of .29 was significant (p = .002), 95% CI [.10, .47], when all trials were considered. Performance in the upright trials reached ceiling (GVS; M = 1, SD = .00; Control: M = 1.17, SD = .39, d = .58), therefore no significant effect was found for the .17 mean difference, p = .51, 95% CI [-.03, .37]. However, in the rotated trials (GVS: M = 1.57, SD = .53; Control: M = 1.89, SD = .43, d = .66), a difference of .32 was found significant p = .009, 95% CI [.10, .56], see Figure 4.8.

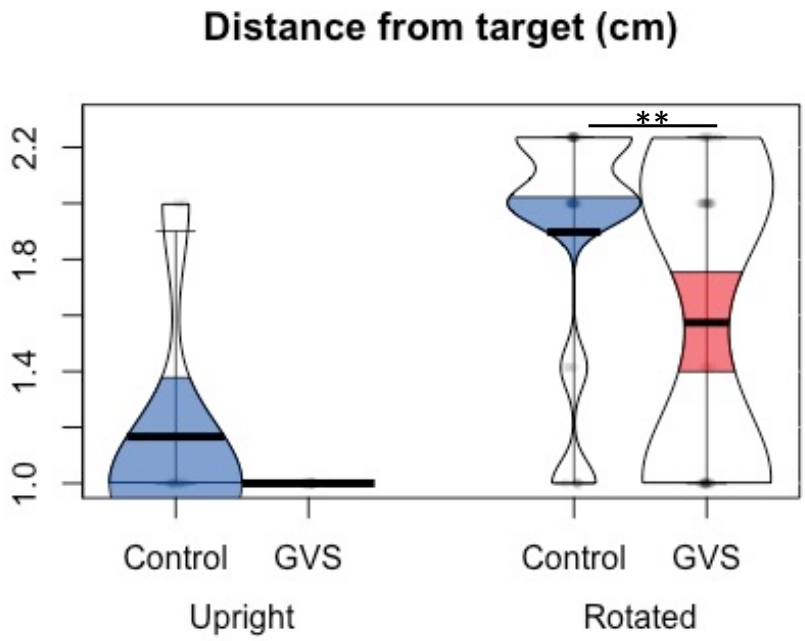

Figure 4.8. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 3. Participant's estimations of the target location were significantly closer to the actual target only in the rotated condition (p = .009).

Participant 04

Descriptive statistics indicated that participant's responses were slightly closer to the target in the GVS trials (M = 2.14, SD = 1.07) compared to the Control (M = 2.53, SD = 1.14), when all four conditions were considered (upright and trials from the three different orientations). Randomization tests showed that this mean difference of .39 was significant p = .011, 95%CI [.11,.68], when all trials were considered. The effect size of this difference was small (d = .35). The mean difference of the upright trials were also statistically significant (GVS: M = .94, SD = .47; Control: M = 2.25, SD = .62, mean difference = 1.31, d > 1, p =.001, 95% CI[.49, 2.14]), however the mean difference of .08 between the rotated trials (GVS: M = 2.54, SD = .89; Control: M = 2.64, SD = 1.26, d = .09), were not found significant, as expected, p = .54, CI [-.17, .34], see Figure 4.9.

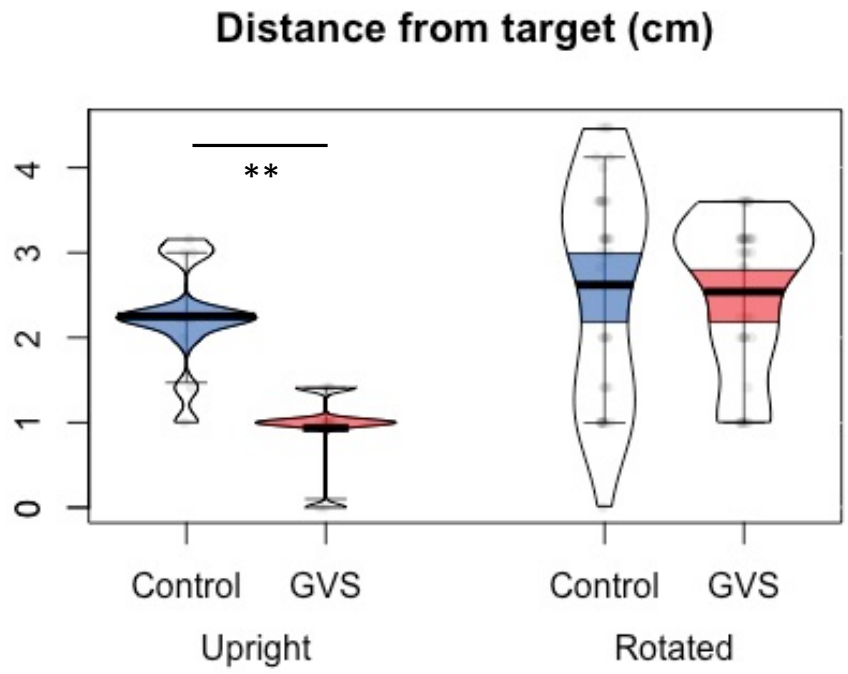

Figure 4.9. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 4. Participant's estimations of the target location were significantly closer to the actual target only in the upright condition (p = .001).

Participant 05

Descriptive statistics indicated that participant's responses were closer to the target in the GVS trials (M = 1.89, SD = 2.24) compared to the Control (M = 14.33, SD = .94), when all four conditions were considered (upright and trials from the three different orientations). The effect size of this mean difference was large (d > 1). Similar effect sizes were obtained when only upright (GVS: M = 1.48, SD = .43; Control: M = 14.56, SD = .80, d > 1) or rotated trials (GVS: M = 2.02, SD = 2.56; Control: M = 14.24, SD = .99, d > 1) were considered. Randomization tests showed that this mean difference of 12.44 was significant, p < .001, CI [9.02,16.02] when all trials were considered. In the upright trials, the mean difference of 13.08 was also found significant p < .001, CI [4.96, 21.37] as well as the rotated trials the mean difference of 12.22, p < .001, CI [7.82,16.22], see Figure 4.10.

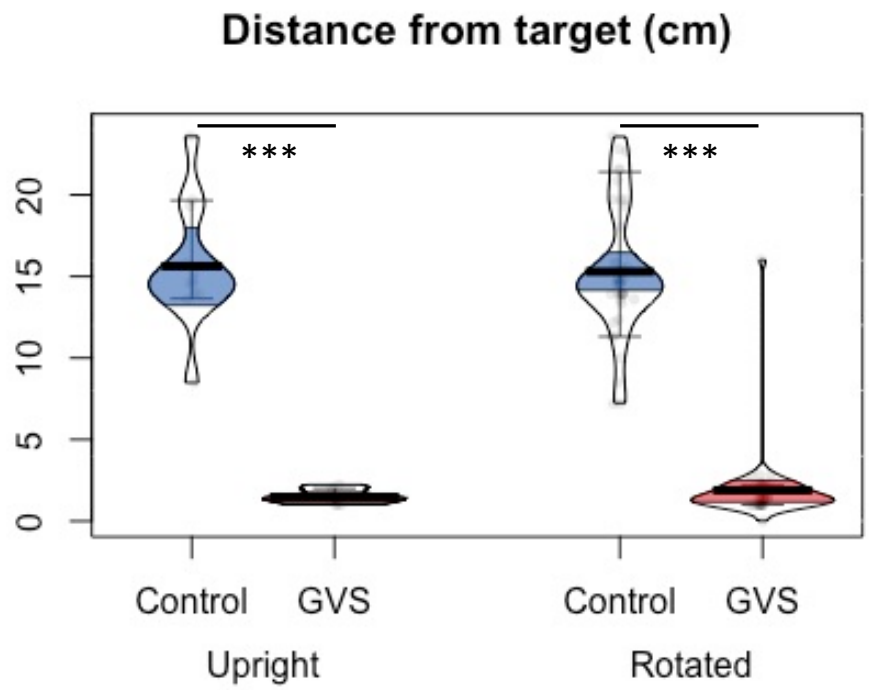

Figure 4.10. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 5. Participant's estimations of the target location were significantly closer to the actual target in both the upright ($p < .001$) and rotated ($p < .001$) conditions.

Participant 06

Descriptive statistics indicated no GVS advantage when all four conditions were considered (upright and trials from the three different orientations), as participant's responses were slightly closer to the target in the Control trials ($M = 1.44$, $SD = .53$) compared to the GVS trials ($M = 1.61$, $SD = .53$). As expected, randomization tests were not significant when all trials were tested (p=.19, CI[-0.07,.41]). It seems that this failed to reach significance because the upright trials were significant closer for the GVS condition (GVS: $M = 1.15$, $SD = .31$; Control: $M = 1.73$, $SD = .52$, $d > 1$), difference .58, p = .017, 95% CI [.12,1.14], however a GVS advantage was not present in the rotated trials (GVS; $M = 1.75$, $SD = .49$, Control; $M = 1.34$, $SD = .51$), see Figure 4.11.

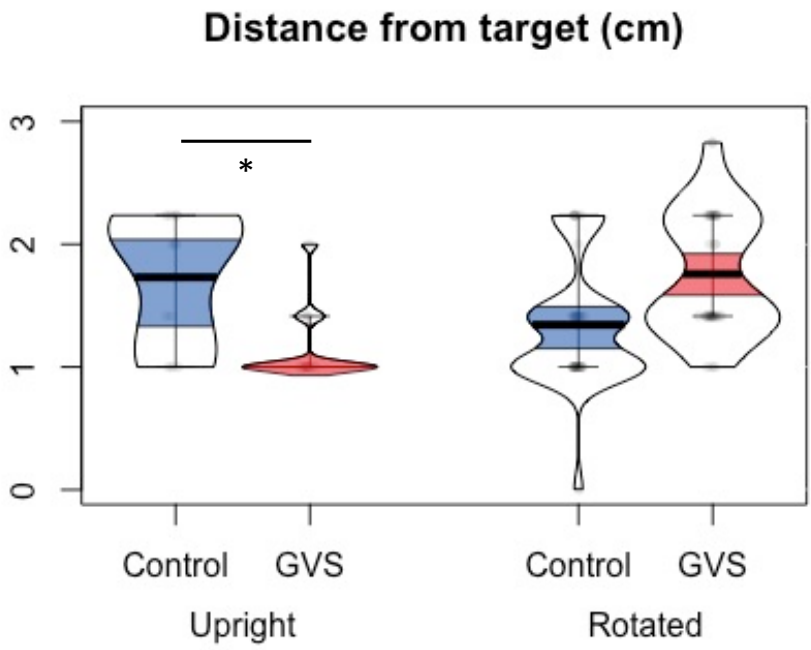

Figure 4.11. Performance in each of the upright and rotated conditions on the *distance from target* measure (in cm) for Participant 6. Participant's estimations of the target location were significantly closer to the actual target only in the upright condition (p =.017).

Accuracy and Reaction time. Accuracy was very low in this dataset, however including the adjacent box to the target location in the accuracy measure (see Methods) resulted in higher accuracy in the GVS trials (0.49) compared to the Control trials (0.29) in the upright condition (data not shown). This difference was found significant: $t(5) = -2.95$, p =.03, CI [-.55, -.04]; no significant differences were found in the rotated conditions. Furthermore, descriptive statistics indicated that participants' reactions times were slightly shorter in the GVS trials (M = 4109.83, SD = 1245.57) compared to the Control trials (M = 4682.83, SD = 1827.19), when all four conditions were considered (upright and trials from the three different orientations). This tendency was present when upright and rotated conditions were compared; upright trials: GVS (M = 4033.78, SD = 1059.53), Control (M = 4645.27, SD = 1955.31), rotated trials: GVS(M = 4109.83, SD = 1245.56), Control (M = 4692.88, SD = 1827.19), or across each of the conditions, when tested individually (see Figure 4.12), however no statistically significant differences were found (all $p > .05$).

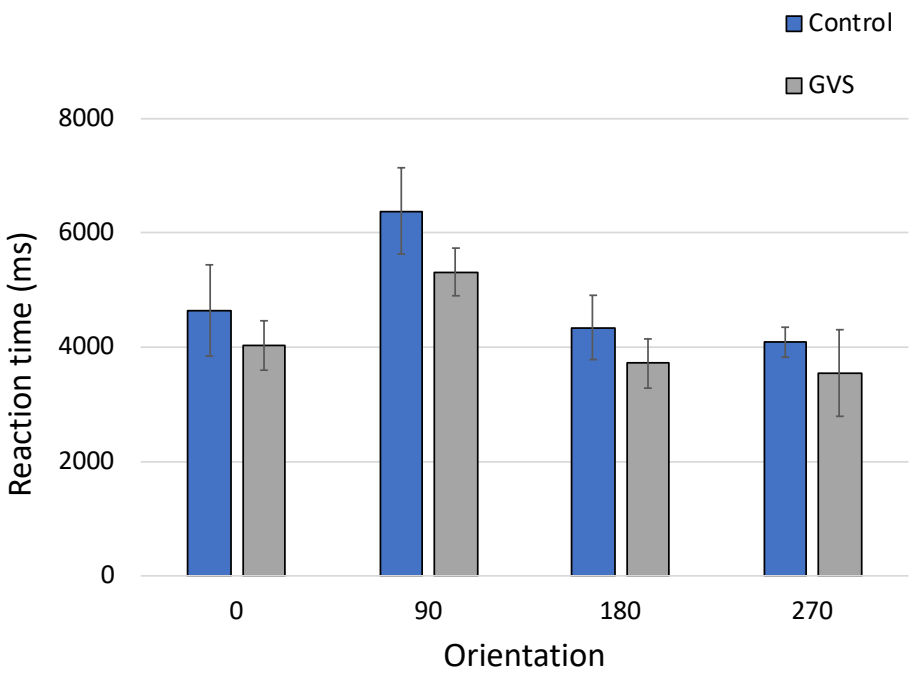

Figure 4.12. Participants' reactions times in each of the four orientations tested. A slight tendency was found for the GVS trials, but this failed to reach statistical significance.

Moves to the target. Overall, *moves* made to the GVS-paired platform were fewer (M = 29.86, SD = 4.71) than the moves made to move to the Control platform (M = 44.03, SD = 37.85), $t(23)$ = 1.98, p =.060, CI [-.67, 29.00] verified by randomization tests; mean difference 14.17, p = .066, CI [-.93, 29.27]. Descriptive statistics showed that a mean difference was maintained across all conditions (similar graph to RTs, data not shown), however, given that these results were not statistically significant, they were not pursued further.

Path analysis. DF and AT were the predominant strategies seen in the GVS trials, comprising 87 % of total GVS trials, compared to 49% seen in DF and AT in the Control condition, with a prevalence ratio of 1.77 (data not shown). A chi-square analysis revealed that the difference between frequencies in the two groups was statistically significant, $\chi 2$ (1, N = 552) = 91.62, p < .001.

Discussion

This chapter described a preliminary pilot study that was conducted to provide the first investigation into the effects of GVS on the visuospatial ability and spatial memory of individuals with AD. To the best of my knowledge, no previous reports have investigated spatial memory benefits in an AD population using galvanic vestibular stimulation. Through a 2-D paradigm of the MWM task, which is used extensively to test spatial memory in rodents and humans, it was examined whether participants would be more accurate at remembering the exact location of a pre-determined target that was associated with a unique vestibular signal as provided by a brief, sub-sensory pulse of GVS during encoding. This hypothesis has been proven successful on a normative population (see Chapter 2) and it was predicted that estimations of the target's location would be closer to the exact location in the upright condition for that spatial location paired with GVS. As mentioned previously, participants were also tested in the rotated conditions given the exploratory nature of the study, however performance on this part of the study was harder to predict.

On a group level, descriptive statistics showed a GVS advantage in the proximity to the target measure when all trials from upright and rotated conditions were combined, as well as when each condition (upright or rotated) was tested separately. Randomization tests verified that these differences on a group level were statistically significant. On an individual level, descriptive statistics and randomization tests indicated a GVS advantage in the same measure in 5 out of 6 participants in the upright condition, with the only exception being a participant who reached ceiling performance in the upright trials (Participant 03). A statistically significant GVS advantage was also seen in all but two participants in the rotated conditions (Participants 04 and 06). When trials failed to reach significance in the rotated trials, it was due to participants' estimations of the target's location being further from the actual target location only on the 180 degrees trials (Participant 04) or the 180- and 270-degree display orientations (Participant 06), as indicated by descriptive statistics. This suggests that perhaps participants found these particular

orientations more cognitively demanding, indicating a task-specific limitation rather than an actual lack of a GVS effect.

First and foremost, the above results provide further evidence that a GVS prime can facilitate navigation to a formerly encountered location, as investigated in a MWM task specific to spatial memory. The current study replicates results presented in Chapter 2 and 3 as well as confirms that formerly obtained outcomes (L. Smith et al., 2020) extend beyond vestibular-guided visual search to visuospatial memory processes involved in navigation. Furthermore, these results suggest that the GVS prime is effective in participants whose memory and visuo-perceptual systems are compromised, as confirmed by the results obtained from the neuro-assessment battery, which showed deficits in spatial memory and visuospatial ability, as well as impairment in executive function (see Table 4.2). This suggests that aspects of visual memory do not need to be fully functional for the GVS prime to influence visuo-spatial performance. These results are promising, especially when the focus is to develop therapeutic strategies to ameliorate spatial memory in clinical populations whose cognitive apparatus has already begun to decline (Rudrauf, 2014). The fact that the advantage holds across a group of participants with mixed demographic and clinical characteristics speaks for a wider scope of patient benefit, which could potentially extend to applications beyond individuals with AD, possibly to different types of dementia (for example vascular or mixed dementia).

As mentioned in the introduction, previous research suggests a link between reduced vestibular input and spatial memory processing networks in AD (Agrawal et al., 2020; Wei et al., 2017, 2018), proposing that reduced vestibular input (specifically saccular, Agrawal et al, 2020) may contribute to the degeneration of cholinergic neurons in the medial temporal region and subsequent loss of synaptic connectivity in the hippocampus in individuals with AD (Agrawal et al., 2020; Previc, 2013). Given that the present study demonstrated direct immediate improvement in spatial memory performance in these participants with dementia, and based on the above studies, one could speculate that the GVS improvement seen may be due to neuro-

plastic changes in synaptic connectivity centred in the hippocampus. These could subsequently improve neural communication associated with the control and storage of information in short-term memory processes. These mechanisms have been suggested in other electrical stimulation methods when older healthy adults were tested on working memory performance (see Reinhart & Nguyen, 2019) or in GVS studies testing visual search on young normative populations (L. Smith et al., 2020).

In addition, it appears that this effect holds in an allocentric paradigm that encourages the encoding of spatial locations based on object-to-object spatial relationships and more closely resembles navigational tasks due to its dynamic rotational component (Galati et al., 2000). As noted elsewhere in this thesis, these results suggest that the GVS priming advantage holds for objects that do not fall at the precise co-ordinates of the GVS primed location but are displayed at another location on the spatial display which was not previously associated with a vestibular signal. Therefore, this data strongly suggests that the GVS priming effect is based on relative rather than absolute representations of space and replicates previously published results in visuospatial search tasks (L. Smith et al., 2020). Although reports of GVS enhancing egocentric representations are no longer sparse, to date very few reports have investigated an allocentric advantage of GVS in healthy adults or neurodegenerative populations, and of those who have shown beneficial effects, these are limited to visuospatial perception (see Oppenländer et al., 2014 for a study conducted on individuals with neglect) and do not extend to memory tasks. The current study is the first one to provide preliminary evidence for an allocentric advantage of GVS spatial priming in a clinical population of AD. These results are promising as several studies have shown that allocentric representations of space are the ones that are affected the most in individuals with AD (Colombo et al., 2017; Diersch & Wolbers, 2019; Gazova et al., 2013; M. Harris et al., 2012; J. M. Wiener et al., 2013). Given the early termination of the study, participants were not examined in the 3-D virtual MWM task, which would have provided an opportunity to assess and potentially replicate and confirm these allocentric results in a task that

resembles more closely real-life navigational settings. Nevertheless, the present results could potentially inform therapeutic protocols to enhance locations of interest in individualised cognitive maps which could include neighbourhoods, living spaces and other surroundings of patients who present with spatial memory decline. As noted above, given the promising results seen in the current study with the advantage seen across a group of participants with mixed demographic and clinical characteristics, the scope of patient benefit could potentially be quite broad.

Furthermore, the GVS prime appears to be effective despite originating from a vestibular system that is compromised by AD, as measured by the mini-BEST balance test. Recall that the mini-Best was administered to assess balance dysfunction at baseline and was included to potentially interrogate a link between balance impairment and visuospatial performance. All sections (anticipatory, sensory orientation, reactive postural control and dynamic gait) were tested on each participant. If a correlation were to be found, then future studies could further investigate if the effects of GVS on memory were constrained by the integrity of the balance system. Recall from Introduction that scores below 21 out of 28 are indicative of balance deficits (King et al., 2012). The current findings echo results from studies that have shown that individuals with AD present with balance impairment (Liu, Chen & Yue, 2020; Puente-González et al., 2020) with 4 out of 6 participants scoring below the above cut-off for balance deficits on the mini-BEST balance test (21 out of 28). Interestingly, the two participants who did not show improvements in the rotated conditions in the *distance from target* measure scored higher than the cut-off (both scored above 21/28, King et al., 2012). This may suggest that participants who benefit the most from this GVS advantage are the ones who show the most impairment in balance control. This would reflect results from similar studies that have used electrical stimulation to improve short-term memory in elderly adults and have shown larger benefits in those participants who were most compromised (see Reinhart & Nguyen, 2019 for example). Given the small sample size and omission of a full vestibular assessment (which incorporates a

number of standard head and eye movement tests), a meaningful interpretation from this observation is however hard to make.

Limitations

Several limitations of this study should be noted. Firstly, given the small sample size and the heterogeneity of the sample, conventional (parametric) the inferential power of the statistical analysis was limited. Although some studies have shown that randomisation tests are more efficient when tested on a heterogeneous patient population (Berger, 2000) and that they can be run on a sample as small as four (see Stripling, Brouke & Baesens, 2016), the sample size recruited here is still some way below the much larger number typically enrolled in a properly powered trial. This small sample size also makes it difficult to determine clinical and demographic mediators and may have contributed to the lack of significance among correlations between assessment measures (MoCA and miniBEST when compared to both sessions of VR and ROCF). Moreover, recall that on its own, AD is considered a heterogeneous condition with multiple phenotypes, which often makes comparison between studies difficult (Mapstone, Steffenella & Duffy, 2003; Snowden et al., 2007). The fact that our small sample consisted of a group of participants with mixed demographic and clinical characteristics suffering from AD as well as other types of dementia further complicates such comparisons and further interpretation. Future directions increasing sample size and recruiting individuals with similar deficits thus reducing heterogeneity would be necessary to conduct a powerful analysis.

Another limitation is that the task difficulty was high in the 2-D MWM task, particularly for the rotated conditions. This was seen already from the pilot study, however given that the participants who volunteered for that study were those who did not meet the inclusion criteria because they presented with severe cognitive impairment according to the MoCA assessment, it was assumed that participants who would score higher on the MoCA would perform better. It is therefore possible that the true pattern of underlying influence was constrained by a floor effect. In hindsight, fewer rotations would have sufficed to test allocentric encoding while reducing task

difficulty.

Moreover, a further shortcoming in the present study is that, beyond the mini-Best, vestibular function was not assessed. Theoretically speaking, the memory advantage relies on the GVS signal being effectively encoded and conveyed by the peripheral vestibular organs and then relayed through the indirect circuit from brainstem nuclei to the hippocampus via vestibular multi-modal neurons. If any part of this system is compromised, the effect derived from the GVS prime may be diminished. Recall that 4 out of 6 AD participants scored below the cut-off in the mini-Best test, indicating that the vestibular system was compromised to a degree. However, as mentioned above, by incorporating measures specific to vestibular function, future research could further clarify the association between the specific type of vestibular deficit and spatial memory, while linking it to the benefits obtained by the administration of GVS (Agrawal et al., 2020).

An additional limitation is that, given the preliminary nature of this study, the GVS advantage was tested only on short-term visual spatial memory using only one type of experimental paradigm. Other types of memory, such as working memory or long-term declarative memory could be also tested, as they have been shown to be affected in the early stages of AD (Jahn, 2013). Furthermore, the application of GVS has been associated with allied improvements in well-being and functional independence in other neurodegenerative diseases such as Parkinson's disease and brain injury (Lajoie et al., 2021; Wilkinson et al., 2019). Future studies could therefore incorporate additional measures that measure quality of life for the patient, caregiver and family such as the Alzheimer's Disease Related Quality of Life (ADRQL, Rabins, Kasper, Kleinman, Black & Patrick, 1999) or the Cornell-Brown Scale for Quality of Life in Dementia which incorporates patient and caregiver perspectives into the rating (Ready & Ott, 2003).

Conclusion

Limitations aside, the current study could contribute the groundwork for future non-

invasive approaches that target spatial memory deficits in clinical populations and it is the first report to date that provides evidence that GVS has the potential to enhance allocentric representations of space in individuals with dementia.

Chapter 5
General Discussion

Overview

Over the last few decades, the known role of the small structures in the inner ear has evolved from being just a mechanical system that senses rotational movements and linear accelerations of the head in three dimensions to influencing several cognitive, affective, motor and perceptual functions (Fitzpatrick & Day, 2004; Khan & Chang, 2013). A strong body of evidence from animal studies report that damage to one or both vestibular labyrinths result in deficits in spatial memory processes and navigation which may be long-lasting, if not permanent (P. F. Smith et al., 2010). Lesion studies in animals and humans further support this link (P. F. Smith & Zheng, 2013). Recent advances in neuroimaging have provided insights into cortical pathways behind this interaction and have established that the vestibular system plays an essential role in various functions linked to spatial cognition and memory (Hitier et al., 2014). The theoretical underpinnings behind the vestibular-spatial memory interaction however remain undefined.

The overall goal of the thesis was to provide evidence to support an interaction between vestibular input and spatial memory processes and to understand how vestibular inputs might be used by spatial memory processes. Chapter 2 mainly explored whether salient vestibular signals that are presented incidentally with visual stimuli can be used by visual memory to individuate one visual memory event from another. Three experiments were conducted using an experimental design that explored whether a spatial location encoded with a salient GVS signal (multi-sensory encoding) was processed faster in a subsequent recall test than other locations which were encoded without stimulation (uni-sensory encoding). The first two were based on a visual search task that tested object-location associations and the third on a MWM task that tested spatial memory following learning of key locations within a 2-D environment. Chapter 3 aimed to overcome the methodological limitations identified in the last paradigm of Chapter 2

(see next section), which were believed to have limited the GVS advantage from being revealed and therefore tested participants in a VR experimental design that also focused on spatial memory following multisensory encoding however had a stronger navigational component. Two different conditions were created to further define the GVS prime. The first one tested the influence of the artificial vestibular input under conditions in which decisions could draw on allocentric representations of space in which participants were encouraged to rely on environmental cues to navigate to the hidden platform. The second condition, on the other hand, drew on egocentric representations of space in which participants had to rely on the starting point to locate the hidden platform. Having identified two paradigms in which a GVS advantage could be captured, Chapter 4 tested whether the GVS prime might hold therapeutic value in a group of people with Alzheimer's disease spatial memory impairment.

Summary of results

In Chapter 2, a visual search paradigm was used to test whether visual stimuli that were co-incidentally associated with a brief, sub-sensory vestibular input would be recalled faster than control stimuli that were presented to participants in the absence of stimulation during encoding. This was tested in healthy participants immediately after stimulation as well as 30 minutes post completion of the initial task (Experiment 1, with additional timepoints in Experiment 2). The findings confirmed and extended upon a previous study by demonstrating that visual search is facilitated for only those visual stimuli that are accompanied by the salient vestibular pulse during encoding (see L. Smith et al., 2020), with delayed responses stronger than immediate effects. The results also confirmed that the GVS pulse only influenced specific aspects of the object representation, in particular only spatial information about the location of the paired stimulus was enhanced, whereas an effect of Image (or an association between Image and its location during priming) was absent. This test paradigm was more cognitively demanding than paradigms used in previous work (see L. Smith et al., 2020) because of the presence of distractor objects that shared common elements with the target-object on the visual display. More

specifically, in this paradigm the search for Location (implicit) was associated with the search for Image (explicit) and if the search for Image made the task of processing visual information overly complex due to the distractors, the search for Location was subsequently delayed. I believe this interfered with the GVS implicit advantage and my subsequent study therefore employed an experimental task that was more spatial in nature and not so difficult to perform. This new, navigation task was performed within a 2-D environment and required participants to learn and later remember the exact location of a hidden target (Experiment 3). The results confirmed that exact spatial locations were remembered more accurately when paired with GVS during encoding. However, this effect was only revealed when participants encountered the learnt scene at the exact orientation (i.e., viewpoint) as during encoding, with spatial representations presented in varied orientations not influenced by the GVS input.

Chapter 2 evidenced an interaction between vestibular inputs and processes involved in visual search and spatial navigation, however the last experiment also revealed that the 2-D MWM task possibly encouraged self-based encoding of key locations within the spatial representation of the environment learnt which may have limited the GVS effect from generalising across fixed to variable viewpoints in the rotated conditions. Chapter 3 therefore tested healthy participants in an immersive environment which generated a first-person perspective at all times and therefore eliminated the need for such mental transformations. An environment in which participants could constantly update their point of view as they move in space was considered more appropriate to test the integration of vestibular inputs in spatial learning. It was tested whether egocentric (self-to-object), allocentric (object-to-object) representations of space, or both, could be influenced by vestibular input. Results from the allocentric condition showed that, compared to the Control group, participants who received GVS during encoding were significantly more accurate at later finding the exact location of the hidden platform or placed the platform location significantly closer to its actual position. Contrary to the hypothesis, performance in the egocentric condition was comparable across both

groups. The results appear to indicate that vestibular inputs affect navigation performance when landmarks are present during spatial learning (further on this below). It seems that participants' performance is more sensitive to the vestibular input when prominent visual landmarks are in the proximity or within the visual field during the encoding of the fixed target location. The results suggest that vestibular signals may be integrated into the formation of the cognitive map of a small-scale environment as participants learn to navigate within a new environment, with the target spatial locations likely encoded relatively to proximal visual landmarks. This information is then later retrieved to re-calculate straight-forward trajectories to the hidden platform irrespective of the starting position and was used to aid successful and accurate navigation choosing various direct routes to reach the exact fixed target location.

The fact however that an effect was absent in the egocentric condition could also reflect the absence of vestibular and proprioceptive signals, which are lacking in a virtual environment. As mentioned in the respective chapter, a constant supply of vestibular inputs may be required during path integration, which, coupled with coincident proprioceptive, auditory and somatosensory information, provide estimates of self-motion and help one understand where they are in space (Save & Poucet, 2009). Given the absence of prominent landmarks and this additional sensory information, participants were expected to only rely on 'illusory' self-motion cues to navigate between the two fixed locations (starting point-target platform) while they remained static. If participants physically navigated in a real environment, cues generated by the physical movement (vestibular inputs included) could have contributed to the continuous spatial updating and therefore could have potentially elicited an egocentric effect as well. The experimental paradigm therefore may have been more sensitive to allocentric than egocentric effects.

Finally, Chapter 4 sought to investigate whether the GVS advantage in spatial memory retrieval seen in previous chapters could be replicated in clinical populations whose initial symptoms include topographical memory impairment. I therefore planned to administer both the

2D and 3D paradigms developed in the as part of an exploratory pilot study conducted with community-based individuals with Alzheimer's disease (however due to early termination of the study, only the 2-D paradigm was used). At a group level, it was found that, compared to sham stimulation, participants placed the target location significantly closer to the exact location when this had been primed with GVS (when all trials from upright and rotated conditions were combined, as well as when each condition - upright or rotated - was tested separately). On an individual level, the GVS advantage in the *proximity to the target* measure was observed in 5 out of 6 participants in the upright condition, with the only exception being a participant who reached ceiling performance in the upright trials (Participant 03). A statistically significant GVS advantage was also seen in all but two participants in the rotated conditions (Participants 04 and 06). When trials failed to reach significance in the rotated trials, it was due to participants' estimations of the target's location being further from the actual target location only in few conditions (180 degrees trials for Participant 04 and 180- and 270-degree trials for Participant 06), as indicated by descriptive statistics. This perhaps suggests that these particular orientations were more cognitively demanding, indicating a similar task-specific limitation seen earlier in my normative populations (Experiment 3, Chapter 2) rather than an actual lack of a GVS effect. This outcome gives further evidence that the observed GVS spatial advantage holds under conditions in which the viewer is encouraged to encode target location based on its relative position to other objects. The results also confirm that the GVS prime is effective in participants whose memory and visuo-perceptual systems are widely compromised, as confirmed by the results obtained from the neuro-assessment battery, which showed deficits in spatial memory and visuospatial ability, as well as impairment in executive function. Furthermore, the results show that aspects of visuospatial memory do not need to be fully functional for the GVS prime to influence visuo-spatial performance.

Theoretical insights

This thesis has generated new theoretical insights about how vestibular inputs with are

integrated with visual representations of space. Recall that the first experiment in this thesis drew on object-location associations to test whether vestibular inputs influence spatial or object aspects of visual memory encoding). The advantage seen suggests that the effect of the GVS prime is particularly relevant to spatial aspects of the memory representation. This is consistent with the notion developed in the General Introduction that brief vestibular signals are integrated in spatial memory representations to help index discrete visual events. Chapters 3 and 4 confirmed the role of the GVS advantage in spatial representations of space and particularly spatial memory processes. The results from the experiments in these chapters showed that the GVS facilitation is expanded onto navigational tasks that more closely resemble real-life settings and involve object-to-object representations of space.

As mentioned in the Introduction, vestibular inputs are projected to multiple cortical areas and can modulate various cognitive, affective and motor functions. The current data however suggest that vestibular inputs are also likely to contribute towards visuospatial memory processes in a more specific manner, over and above any general cognitive enhancement or compensation mechanisms shown by previous studies (Bächtold et al., 2001; Brandt et al., 2005; Dilda et al., 2012; Ghaheri et al., 2014; Ghahraman et al., 2016; Hanes & McCollum, 2006; Wilkinson et al., 2008, 2012). The finding that a task-irrelevant but temporally coincident sub-sensory vestibular stimulus can guide subsequent visual behaviour to a specific spatial location has not been previously reported. Multisensory encoding however is observed elsewhere in the cross-modal literature and the results reported here indicate for the first time that vestibular signals are indeed used to enrich spatial aspects of visuospatial representations in a similar way to other sensory modalities in the cross-modal literature, such that memory retrieval for a visual event is facilitated if accompanied by a temporally coincident auditory or tactile stimulus during encoding (Driver & Spence, 2000; Lacey et al., 2011; Lehmann & Murray, 2005). Demonstrations of visual-vestibular interactions have also been reported, albeit not with this level of specificity within memory function. For example, when visual and vestibular cues were

put in conflict, both animals and humans constantly switch between visual and vestibular information so that eventually self-motion perception is biased towards the most reliable cue. This optimal (or near optimal) convergence of inputs from the vestibular and visual senses taking place to reduce perceptual uncertainty about self-motion has now been reported by several studies (see Angelaki et al., 2009). In addition, similar facilitation effects have been found within individual somatosensory sub-modality pathways in which temporally coincident vestibular signals have been shown to increase sensitivity to both mechanical and electrical stimuli (Abekawa et al., 2018; Ferrè et al., 2014). The latter studies however have solely focused on effects detected during vestibular stimulation instead of investigating effects that inform subsequent judgements (visual target identification on a visual search task from Chapter 2) or spatial memory processes (memory retrieval for a fine-grain spatial location from Chapters 2, 3 and 4) which is another novelty of the results in this thesis.

As mentioned elsewhere in this thesis, the work conducted here aimed to explore the nature of the interaction between spatial memory processes and vestibular input at the psychological level. Combined, the results provide one potential psychological mechanism that could explain the specific role of the vestibular input in visuospatial memory processing. Head information derived from both otoliths and semicircular canals is constantly changing as one moves in space, with vestibular signals providing updated implicit information about the constant changes in head position relatively to other objects in the environment (Angelaki et al., 2009; Bottini et al., 1994; Bottini & Gandola, 2015; Brandt et al., 2017; Hitier et al., 2014; Wolbers & Hegarty, 2010). This information subsequently helps the brain adjust the ever-changing posture and gaze (Angelaki & Cullen, 2008; Dilda et al., 2012; Fitzpatrick & Day, 2004; P. F. Smith et al., 2010) but also helps encode a cognitive map with locomotion in space associated with a continuous updating of this current cognitive map (Brandt et al., 2017). Given that spatial updating accompanies head turns (Reuschel, Rösler, Henriques & Fiehler, 2012) as one is presented with a new scene/angle/perspective of the environment, it is possible that

vestibular contributions help to create awareness as to one's body in space relative to the new environment as an allocentric reference frame (for example, how close we are to objects of interest and which objects are around that could be used as landmarks to help with navigation, see Brandt et al., 2017). Furthermore, vestibular inputs could carry information about the motion or position of the head and body in space that informs the allocentric visual representations of space in a similar way other cells associated with cognitive mapping do (e.g., place, grid, head direction; Brandt et al., 2017; Jacob et al., 2014). The facilitation that came from immersion in Chapter 3 which allowed for self-based encoding at all times by providing a first-person view of the environment further supports this theoretical mechanism. The fact that participants navigated from different starting points directly towards the target platform during recall (Chapter 3) also supports the contribution of the vestibular inputs into the creation of allocentric spatial configurations and thus cognitive maps. The results reported in this thesis provide a novel possible mechanism the cross-modal interplay behind the visual-vestibular interactions which entails vestibular inputs enriching the spatial aspects of a temporally coincident allocentric visual representations so that they were stored more effectively within short-term memory storage processes and were distinguished from other similar representations presented in the absence of stimulation (L. Smith et al., 2020).

This thesis implemented various experimental paradigms and used both clinical and neuro-typical samples to identify how spatial memory representations are influenced by vestibular input. The fact that the GVS spatial enhancement was replicated in three different stimulation and experimental paradigms that drew differently on visual search and navigational processes suggests an omnibus effect that is relatively independent of experimental paradigm and the length of the stimulation protocol (e.g., Experiment 3, Chapter 2 whereby a shorter protocol also revealed an effect compared to Experiment 1). In addition, the fact that the advantage holds across a group of young participants and elderly individuals whose memory and visuo-perceptual systems are already compromised further speaks to the pervasiveness of the

GVS prime. Overall, the findings from this thesis fit within an emerging body of literature that has shown human memory to be profoundly affected by the vestibular afference (Bächtold et al., 2001; Dilda et al., 2012; Ghaheri et al., 2014; Wilkinson et al., 2008).

Clinical implications

Results from Experiment 1 (Chapter 2) could help constrain therapeutic non-invasive approaches for the symptomatic relief of hemi-spatial neglect, a condition that represents a deficit in attention and awareness to one side of the visual field following unilateral brain damage such as stroke (Halligan & Robertson, 2000). Visual search paradigms such as these in Experiment 1 that show facilitation towards a spatial location following coincident GVS priming could be adjusted to train and drive attention towards the neglected visual field (L. Smith et al., 2020). Similar protocols could be adjusted for individuals diagnosed with hemianopia; a similar but functionally unrelated condition that results in sensory loss restricted to one side of the visual field (Halligan & Robertson, 2000). GVS has already been shown to have beneficial effects on brain-injured individuals with similar disorders (Rorsman et al., 1999; Wilkinson et al., 2014), however these involved relatively long (i.e., 20min) and repeated stimulation protocols compared to the current approach which by using sub-sensory priming may not require such intensive intervention.

As mentioned above, findings from this thesis suggest that vestibular inputs enhance spatial representations in such a way that not only visual search is facilitated in subsequent encounters, but also that navigational accuracy, regardless of the starting point (Chapter 3). This outcome that GVS influences allocentric representations of space seems quite promising and provides the groundwork for other investigations of how best to enrich cognitive maps for practical purpose. Results from chapter 4 revealing allocentric beneficial effects in individuals with AD following brief GVS pulses extend the potential benefit to clinical populations. Potential applications in navigational strategies however are not only relevant for amnestic patients (Colombo et al., 2017) but also for the general elderly population, with accumulating

reports suggesting that egocentric navigation is preserved in elderly populations and that navigational deficits are restricted to allocentric spatial representations (see Gazova et al., 2013 for example). Exploring the modulatory effects on cognitive mental mapping could inform future studies that attempt to refine therapeutic strategies that more efficiently target navigational deficits in amnestic and non-amnestic populations. For example, the paradigms used in the earlier part of this thesis could be amended and individualised to enhance individual's memory of a location of an object (an important object such as phone or keys for example) or position of their house on a mental map.

As mentioned in Chapter 4, the "navigation network" of brain areas involved in spatial memory has been shown to decline in normal aging and this decline is believed to be associated with reduced vestibular sensory function (Agrawal et al., 2020; Bigelow & Agrawal, 2015). Although progressive loss of vestibular function occurs with age, growing evidence now supports that chronic reduced vestibular input in healthy older adults is strongly associated with poorer spatial cognitive ability (Agrawal et al, 2020; Bigelow & Agrawal, 2015). This age-related vestibular impairment is specific to spatial memory and spatial navigation, and not related to other phenotypes of cognitive deficits, such as verbal memory or language skills for example (Bigelow & Agrawal, 2015; Semenov et al., 2016). Based on the data derived in this thesis, one could subsequently explore the specific spatial contribution of GVS in studies of elderly individuals with spatial representation deficits linked with reduced vestibular input (Agrawal et al., 2020). Future studies could investigate whether prolonged GVS protocols could replace the natural vestibular input that is lost during normal aging by extending the exposure to GVS which would incorporate a greater number of primes and in turn increase synaptic learning and retention.

In terms of individuals with dementia, results from Chapter 4 provide the groundwork for future non-invasive approaches that target spatial memory deficits. Based on insights from pilot studies in Chapter 2 where four GVS pulses did not result in significant differences in

performance but eight pulses significantly enhanced accuracy for location, protocols that incorporate a greater number of primes may provide further benefits to space learning and retention. Moreover, long-term follow-up assessments could establish the longevity of the GVS effect seen. This would confirm the advantage is beneficial beyond the short-term window following GVS application and would be of vital importance when designing therapeutic approaches based on GVS. Treatments such as these however could target these conditions at an earlier stage with GVS protocols potentially administered as early as the behavioural and biomarkers of the disease are detected (Agrawal et al., 2020; Previc, 2013). Targeting specific population such as those with amnestic mild cognitive impairment (aMCI, Liu, Chen & Yue, 2020), could be a much-needed attempt to slow the progress of memory impairment (Agrawal et al., 2020). Researchers could also investigate whether the GVS advantage would hold on spatial memory tests that are currently used in clinical diagnosis (such as the 4 Mountains Test, see Chan et al., 2016), which have been shown to have high sensitivity over pre-dementia stages. This would facilitate GVS's integration into clinical applications and bridge the gap between clinical practice and research. Furthermore, the restorative potential of GVS could be explored further than spatial memory. Other memory types could be investigated (such as long-term declarative or working memory for example, which have also been shown to be affected during the early stages of the disease, see Jahn, 2013). Allied improvements in well-being and physical independence could also be explored, as such improvements have been shown following GVS application in similar neurodegenerative diseases that are linked to reduced vestibular input (e.g., Parkinson's disease, Wilkinson et al., 2019).

Limitations – Future directions

The previous sections highlighted the imperative gains the experiments in this thesis offered to further the theoretical understanding between vestibular and spatial memory interactions. The insights gained here however are clouded by several ambiguities. Many of these issues were discussed at the end of each chapter, therefore only overreaching limitations

are discussed here.

This thesis was restricted in addressing two main differences observed in this thesis' dataset. The first difference is in the results derived from the normative population showing that the GVS advantage was found only in the allocentric condition of the 3-D MWM study but not in the allocentric conditions of the 2-D study. As mentioned elsewhere in the thesis, the experimental paradigm in Chapter 2 possibly encouraged self-based encoding of key locations within the spatial representation of the environment learnt which may have limited the GVS effect from generalising across fixed to variable viewpoints in the rotated conditions, which subsequently led to the absence of an effect in the allocentric conditions. This suggests that a first-person viewpoint is needed during encoding (recall that if participants learnt during priming that the platform's location is to their left – therefore they rely on self-based cues- in the rotated conditions the platform was no longer to their left but was rotated accordingly, resulting in them losing this spatial relationship). Indeed, immersion in Chapter 3 allowed to get around this restriction because spatial updating took place as participants virtually moved in space, hence eliminated the need for mental rotations. This confirmed that self-based encoding that provides a first-person view of the environment facilitates the contribution of the vestibular input. The above observation could possibly explain the difference between the allocentric conditions between the 2-D and 3-D study in the normative population. Indeed, Brandt et al., (2017) hypothesized that the vestibular system might make a differential contribution to spatial orientation and navigation paradigms depending on whether locomotion occurs or not. For example, the authors proposed that in a dynamic environment, the otoliths and semicircular canals contribute towards allocentric spatial representations. In a static condition however, when the participant is sitting in front of a screen to perform a navigational task, the otoliths contribute towards an egocentric frame of the visual scene. The results from Chapter 3 however suggest that a dynamic VR environment that creates the illusion and perception of moving could encourage allocentric encoding even in static participants. An allocentric advantage was also seen in static

participants who composed the clinical sample in Chapter 4 (however this effect was absent in the normative sample, which is the second difference in the dataset, discussed below). This is further supported by evidence that GVS causes a change in the afferent firing of semicircular canals (Day & Fitzpatrick, 2005), which suggests that semicircular canals were also active in our experimental paradigm alongside the otoliths. In addition to VR set-ups, future studies could incorporate real-life paradigms (see below) that allow movement in real space during navigation to shed further light into the discrepancy between the results obtained here and the hypothesis by Brandt et al., (2017).

The fact that the clinical population was still able to maintain these spatial relationships in the rotated conditions of the 2-D study however (compared to the normative population) may reflect the fact that elderly with dementia rely more on self-based cues to navigate, as their allocentric representations are compromised (Colombo et al., 2017). It could be that the elderly population relied only on egocentric cues during priming and managed to carry these relationships over to the rotated conditions. Indeed, a literature search revealed that age-related alterations in the neural system supporting allocentric computations may drive the elderly to more frequent use of egocentric rather than allocentric strategies (see review by Colombo et al., 2017), It is highly unlikely however that their performance would be better than the younger population. A more feasible alternative explanation may be that individuals with dementia manifest deficits in switching from egocentric to allocentric strategies (see Serino et al., 2015) and therefore the ability to convert information from upright to rotated conditions may be compromised. This impairment may have facilitated revealing an effect in this population compared to healthy adults. Indeed, Hilliard et al., (2019) has shown that healthy individuals with lower spatial working memory capacity benefit the most from GVS stimulation. It may the case that the same applies for clinical populations and future studies could investigate this further by including experimental paradigms that specifically dissect these two conditions.

It should be noted that although GVS is considered to simulate a natural head movement,

the content provided by the visual and vestibular inputs is incongruent, i.e., GVS induces an illusory head movement however visual and proprioceptive inputs indicate the head is stationary (Palla & Lenggenhager, 2014). This mismatch could enhance the visual event by amplifying the salience of the vestibular input which in turn would make the GVS-paired visual representation more memorable (L. Smith et al., 2020). Furthermore, GVS involves unnatural peripheral stimulation and activates brain regions which are not activated by natural vestibular stimulation (Ferrè et al., 2014). Future studies should address whether the current findings would be replicated by stimulating the vestibular system under conditions in which visual and vestibular interactions naturally occur (L. Smith et al., 2020). In addition, given the performance variability seen in descriptive statistics between participants in the clinical dataset (Chapter 4) and that the percept induced by the vestibular stimulation is likely to vary between participants (Palla & Lenggenhager, 2014), future studies could also consider whether beneficial effects could be found in all participants tested by carefully titrating the amplitude of the GVS signal for each participant or even apply different amplitudes within the same participant to determine whether enhancement would be dependent on specific intensities. Including assessment tests that determine spatial ability and are quick to deliver could further help investigate a correlation between spatial ability and GVS advantage.

Incorporating human analog studies of the Morris Water Maze task which could take place in a physical room instead of a virtual environment may also be beneficial in addressing the methodological issues that arose from both virtual paradigms and remaining static during navigation (Brandt et al., 2017; Gazova et al., 2013). Experimental paradigms such as these could also encourage better integration of vestibular signal content within visual memory representations during path integration as they may offer closer perceptual and semantic correspondence between the incoming vestibular and visuospatial inputs (Palla & Lenggenhager, 2014). Investigating the above could help determine the most effective stimulation protocols and enhance current understanding of the psychological role of the vestibular system but most

importantly, improve the therapeutic benefit of GVS applications in amnestic patients.

Conclusion

The current thesis has evidenced a connection between the vestibular and memory systems whereby artificial vestibular stimulation can enhance visual search and spatial memory recall of previously encountered locations. Taken together, the previous chapters provide evidence that visual spatial memory processes make use of temporally coincident vestibular inputs so that search for that location at subsequent encounters is facilitated and the previously presented scene recalled more accurately. The effect speaks for specific rather than generic effects reported elsewhere in literature. This facilitation to individuate one visual memory from another holds only when visual landmarks are present and within the field of view whilst learning this spatial environment. This spatial memory advantage was also observed in elderly adults with spatial memory deficits, findings which may have potentially profound implications for ameliorating spatial impairment in amnestic patients as well as elderly populations that present with spatial memory deficits.

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Appendix A

Questionnaire for GVS perception

Participant ID:

Please help us to understand your perceptions of the stimulation that you received.

Q1.) How strong was the sensation of the stimulation?

a.) Could not feel anything at all

b.) Slight sensation, but unsure if it was the result of the stimulation

c.) Felt a definite sensation of being stimulated

d.) Strong feeling of being stimulated

e.) Currents were too strong, stimulation was overpowering

Q2.) What did the stimulation feel like?

a.) A brief pulsating sensation behind the ears?

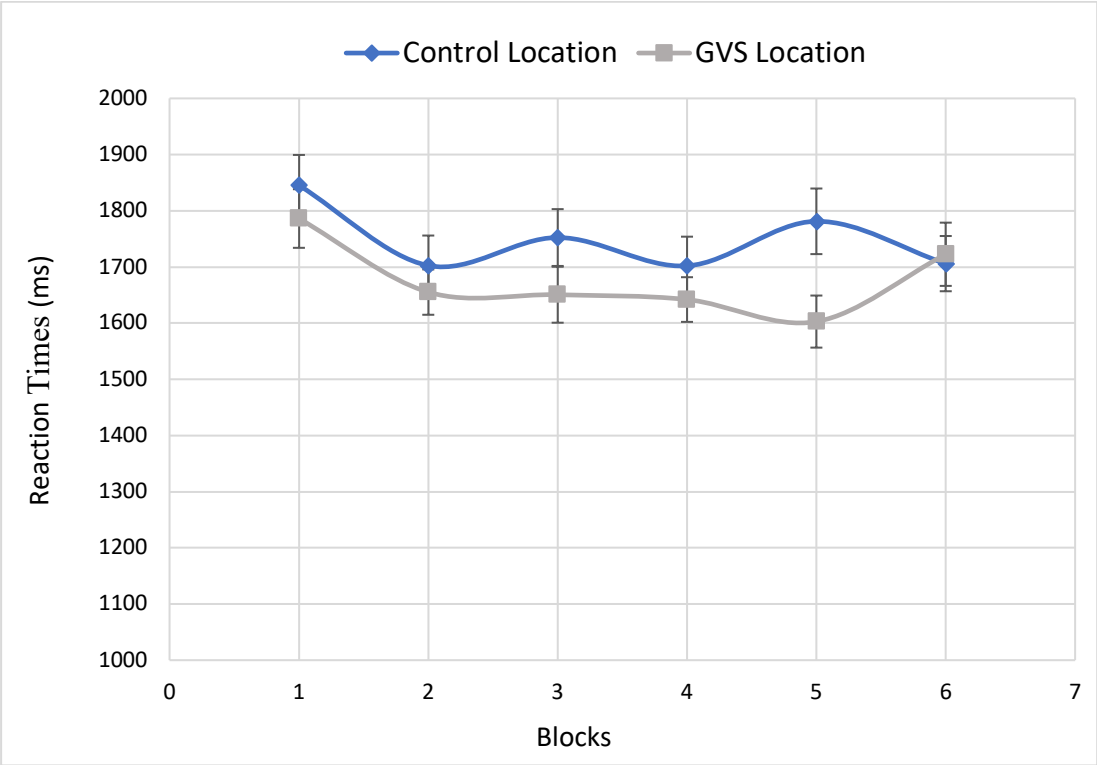
b.) A continuous sensation or wave of activity behind the ears?

Q3.) How often did you notice the stimulation?

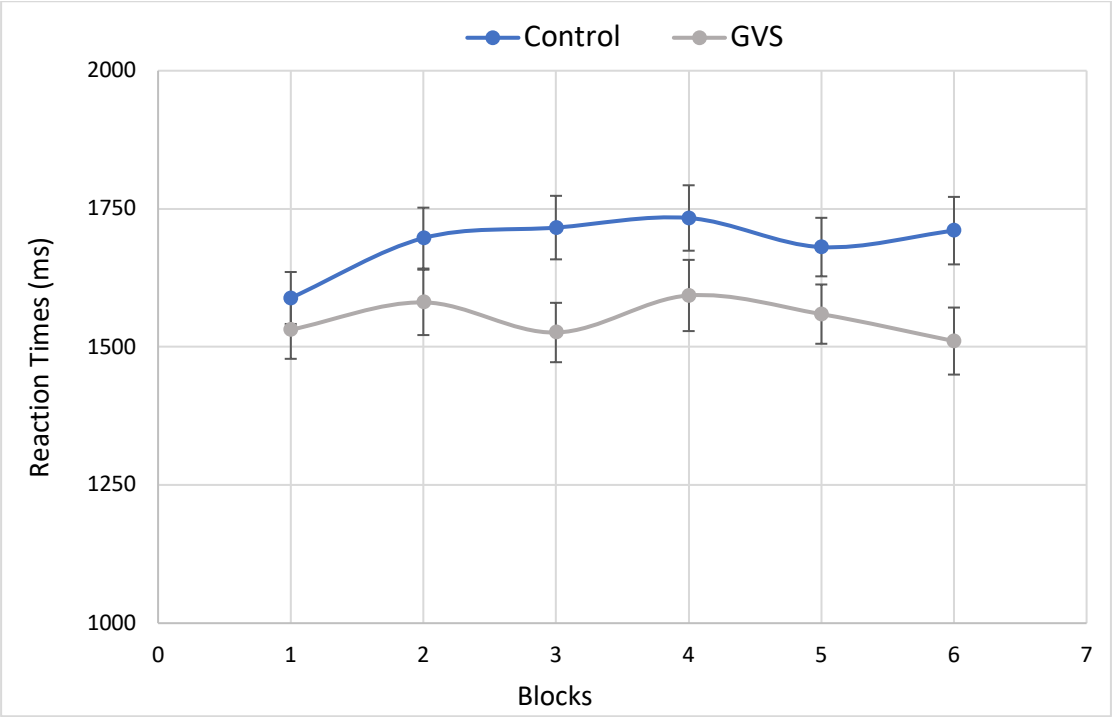
Q4.) Did you notice any patterns in the stimulation?

Thank you for your feedback!

Appendix B



A. Reaction times for the Control and GVS location in all four arrays in each of the six blocks in Part I of Experiment 1 (Chapter 1). Each data-point represents all three images (GVS, Control, GVS) for each of the GVS and Control locations. This data-point analysis was carried out to investigate whether the reduced number of GVS pulses administered played a role in the lack of effect seen in Experiment 1. The effect was only found significant in the fifth block, after participants have received 15 pulses of GVS ($p = 0.02$). Error bars represent standard error of the mean. Further graphs in this Chapter are all structured in this way, for graph simplification GVS location is referred to GVS and the Control Location is referred to as Control.



B. Effect of Location for the 6 key comparisons in all four arrays in each of the six blocks in Part II. Each data-point represents all three images (GVS, Control, New) for each of the GVS and Control locations. Error bars represent standard error of the mean.

Appendix C

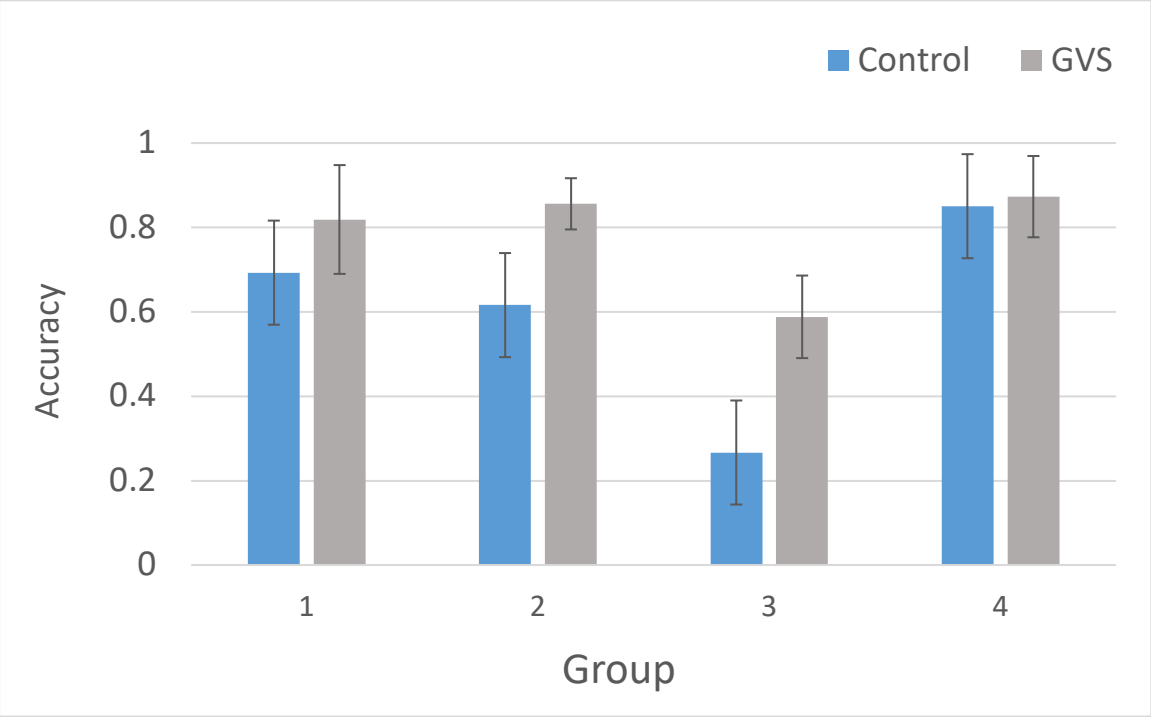
A. Bonferroni-corrected Pairwise comparisons – Accuracy

Platform (GVS, Control)	Condition (Ego, Allo)	Condition (Ego,Allo)	Mean difference	Standard Error	Sig. *	95% CI	
						Lower Bound.	Upper Bound
Control	Ego	Allo	.002	.134	.988	-.286	.290
GVS	Ego	Allo	-.243	.095	.023	-.446	-.039

Condition (Ego, Allo)	Platform (GVS, Control)	Platform (GVS, Control)	Mean difference	Standard Error	Sig. *	95% CI	
						Lower Bound.	Upper Bound
Ego	Control	GVS	.090	.118	.460	-.164	.344
Allo	Control	GVS	.115	.048	.006	-.258	-.052

Based on estimated marginal means
*Adjustment for multiple comparisons: Bonferroni

B. Accuracy measures in all four groups participants were tested in the allocentric condition.



Accuracy measures in all four groups participants were tested in the allocentric condition. Each pair of columns represents 4 participants. Accuracy for the GVS location was overall higher than for the Control location in each group tested. Error bars represent standard error of the mean in each group.

Appendix D

Table B.1.
Bootstrapping analysis of mean and median of distance from target measure (Chapter 4)

	Control trials		GVS trials
Mean (within group)	7.79 (CI: 6.87, 8.59)		3.45 (CI: 2.92, 3.97)
Median (within group)	3.34 (CI: 2.24, 3.87)		2 (CI: 1.41, 2)
Bootstrapping the mean difference		4.93 (CI: 2.63, 7.34)	
Bootstrapping the median difference		1.86 (CI: 0.22, 10.31)	

Wilcoxon singed-ranks test for paired data – *Distance from target* measure - Grouped analysis

All trials. A Wilcoxon singed-ranks test for matched pairs indicated that the difference between the GVS and Control pairs of observations when all four conditions were considered was not statistically significant, $T = 20$, $z = 1.99$, $p = .063$*, CI [.06, 12.30], effect size r = .68$^{\nabla}$.

Upright trials. Wilcoxon signed-ranks test for matched pairs indicated that this difference was statistically significant $T = 21$, $z = 2.20$, $p = .031$, CI [.38, 14.15], with a large effect size r = 0.89.

90-degree rotation trials. A marginally statistical significance was seen in the 90-degree orientation was found by Wilcoxon signed-ranks test for paired samples, $T = 20$, $z = 1.99$, $p = .063$, CI [.24, 11.33], $r = 0.81$.

*Given the small sample size, exact test results are reported.

$^{\nabla}$The effect size for Wilcoxon paired tests was calculated according to Cohen's classification of effect sizes using the following formula:

Z/√N, where Z is the absolute standardized test statistic and N is the number of paired data.

Appendix E

 # R code for Randomization Test on Matched Samples

```
# Dataset
a <- c()
b <- c()
dat <- data.frame(a,b)

diffObt <- mean(dat$a) - mean(dat$b)
difference <- dat$a - dat$b

nreps <- 500
set.seed(1086)
resampMeanDiff <- numeric(nreps)
for (i in 1:nreps) {
  signs <- sample( c(1,-1),length(difference), replace = T)
  resamp <- difference * signs
  resampMeanDiff[i] <- mean(resamp)
}
diffObt <- abs(diffObt)
highprob <- length(resampMeanDiff[resampMeanDiff >= diffObt])/nreps
lowprob <- length(dat$resampMeanDiff[dat$resampMeanDiff <= (-1)*dat$diffObt])/nreps
prob2tailed <- lowprob + highprob
cat("The probability from the sampling statistics is = ",prob2tailed,'\n')

hist(resampMeanDiff, breaks = 30, main = "Distribution of Mean Differences",
```

```
    xlab = "Mean Difference", freq = FALSE)
text(1.5,.25,"Diff. obt")
text(1.5,.23,round(diffObt,2))
arrows(1.5, .21, diffObt, 0, length = .125)
text(-3,.25,"p-value")
text(-3,.23, prob2tailed)

# Compare to Student's t
tvalue <- t.test(dat$a, dat$b, paired = T)$statistic

cat("The t value from a standard matched-pairs t test is= ",tvalue, '\n')

t.test(a, b, paired = TRUE, alternative = "two.sided")

# Confidence limits
CIupper <- quantile(resampMeanDiff,.975)
CIlower <- quantile(resampMeanDiff,.025)
cat("The 95% confidence limits are = ", '\n',CIlower, " and ", CIupper, '\n')
```