Behavioural manipulations of Parietal lobe function

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Thesis submitted for the degree of

Doctor of Philosophy

Academic department of Neuro-Otology, Division of Brain Sciences

Imperial College London

2014

Statement of Publications

The data presented in Chapters 3, 4 and 5 has been published in the Journal of Neuroscience, Brain Stimulation and Cortex respectively:

- **Arshad Q, Nigmatullina Y, Bronstein AM (2013) Handedness-related cortical modulation of the vestibular-ocular reflex. The Journal of Neuroscience 33:3221-3227.**

- **Arshad, Q., Nigmatullina, Y., Roberts, R. E., Bhrugubanda, V., Asavarut, P. & Bronstein, A. M. (2013) Left Cathodal Trans-Cranial Direct Current Stimulation of the Parietal Cortex Leads to an Asymmetrical Modulation of the Vestibular-Ocular Reflex. *Brain Stimulation.*7 (1):85-91.**

- **Arshad, Q., Nigmatullina, Y., Bhrugubanda, V., Asavarut, P., Obrocki, P., Bronstein, A. M. & Edward Roberts, R. (2013) Separate attentional components modulate early visual cortex excitability. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior.* 49 (10), 2938-2940.**

Statement of originality

Work in Chapter 3 was conducted jointly with Yuliya Nigmatullina who was also in the process of obtaining her PhD, however the data obtained has been carefully separated to avoid any replication of data reported in either thesis.

The data analysis of the VOR recordings in Chapter 3 was performed jointly by myself and Yuliya Nigmatullina as to allow for a more objective measure due to the subjective nature of fitting exponential eye curves.

The computational model in chapter 3 was done in collaboration with Dr Ramil Nigmatullin.

The schematic model in chapter 4 was done in collaboration with Yuliya Nigmatullina.

All the other work in this thesis is my own and conforms to the rules and guidelines set by Imperial College London

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Abstract

The aim of this thesis was to develop a novel behavioural technique to disrupt parietal function in order to induce top-down cortical modulation of low-level brain structures, namely the brainstem mediated vestibulo- ocular reflex and the early visual cortex. The premise of the technique was based upon using stimuli that engaged overlapping neuronal networks. To this end, we employed a technique that involved concurrent vestibular activation and viewing of bistable perceptual visual stimuli or performing visualised spatial attention tasks. The thesis presents data that shows the ability of this technique to induce a handedness related cortical modulation of the vestibulo-ocular reflex and modulation of the early visual cortex. Subsequently we applied trans-cranial direct stimulation to directly disrupt parietal inter-hemispheric balance in order to induce an asymmetrical modulation of the VOR and propose a revised computational model for vestibular processing. The results from these experiments present the first behavioural demonstration that vestibular cortical processing is strongly lateralised to the non-dominant hemisphere. We propose that this technique developed and validated in this thesis can be used to further probe and investigate cognitive parietal function such as numerical cognition and human decision making.

Acknowledgments

- Thank you to Professor Michael A Gresty for teaching me the importance of having a clear research question.
- Thank you to Dr Barry Seemungal for teaching me research techniques
- Thank you to Dr Mary Faldon and Mr David Buckwell for all their technical and scientific advice and support
- Thank you to Miss Janet Mills and Lorna Stevenson for all the administrative help
- Thank you to the undergraduate students, to whom I have had the pleasure of supervising: Flo,Vamsee, Mike, Sanjeev, Usman and Shuaib
- Thank you to Dr Ed Roberts for all his advice
- Thanks to Yuliya Nigmatullina for her massive contribution, help and support.
- Thank you to my supervisor Professor Adolfo Bronstein. The work presented in this thesis could not have happened without his support and encouragement.
- Finally, a thank you to the support of my family, especially my Mother and Grandfather's (Late Ilam Din and Qasim Ali).

Chapter 1: Preface

Ponder for a moment the deceptive simplicity of sensory perception. In a seemingly effortless manner the external world around us is transposed into neural representations. These representations are subsequently transformed into sensory perceptions such as sights, sounds, smells, touch and taste which in turn guide our everyday behaviour and action. Fundamentally, this process provides each of us with a unique and rich sensory conscious percept of the world in which we inhabit.

Omitted from the above 5 Aristotle's cardinal senses is what is often referred to as our "sixth sense", our perception of self-motion in space provided by the vestibular system. Functionally speaking the vestibular system serves two mains functions, (i) stabilisation of gaze during head perturbations and (ii) spatial orientation. As we seldom navigate in pure darkness in the real world no overt conscious vestibular sensation presents in everyday life. Rather it is often accompanied and dominated by other sensory cues such as those provided by the visual and proprioceptive systems.

In modern life, perhaps the starkest example of when we overtly become conscious of our vestibular system is an illusionary sensation many of us have experienced. Recall the following scenario: you are on a stationary train at a station sat by the window looking at the train on the opposite platform. As that train leaves in the opposite direction for a split moment you feel as if you are moving, even though your train remains stationary. This illusionary sensation of movement is termed vection and is proposed to result as a conflict between visual and vestibular motion signals, however it is produced by the visual system. The vestibular system is used in part to stop or suppress this illusory perception of motion.

As exemplified in the above scenario the visual system is able to detect environmental motion based upon external cues (as can the auditory system). However, only the vestibular system can detect internal inertial motion signals derived from head accelerations.

The vestibular system unlike the visual and auditory system does not have a distinct cortical area fully dedicated to it, namely the visual and auditory cortex respectively. In the search for the neuronal correlates of vestibular cortical processing, a multi-sensory area in the fronto-parietal region has been implicated (Dieterich et al., 2003a). A serendipitous finding of these neuroimaging studies was that when vestibular activation was engendered using stimuli that result in the perceptual state of vertigo (dizziness), deactivation of visual cortical areas was observed. Conversely, large field visual motion that evokes a sensation of vection (i.e. the illusionary sensation of motion experienced on a stationary train) activates visual cortical areas whilst deactivating vestibular parietal cortical areas, suggesting that reciprocal inhibitory mechanisms exist at the cortical level between the visual and vestibular systems (Brandt et al., 1998).

Thus, the ecological question arises, why do reciprocal inhibitory mechanisms exist between visual and vestibular cortical areas and why has nature permitted the development of cortical sensory systems devoted to vision and audition only to later abandon such an arrangement for vestibular cortical processing?

Firstly, the reciprocal inhibitory mechanism between the visual and vestibular areas serve to resolve potential conflicting motion signals in the brain regarding self- motion (provided by vestibular cues) versus object motion (provided by environmental cues). Secondly, in respect to why there is no distinct vestibular cortical area can be attributed to the fact that

we seldom experience a pure conscious vestibular percept in everyday life as alluded to above (often combined with other sensory cues). Thus, the parietal lobe offers an ideal neural correlate as it is a site of considerable neuronal convergence of vestibular, visual, auditory and proprioceptive cues which can be subsequently integrated in order to provide an abstract higher-order spatial representation, critical for accurate spatial orientation, a key function of the vestibular system (Brandt et al., 2012, Karnath & Dieterich, 2006).

Fundamental to the facilitation of spatial orientation is the direction and allocation of spatial attention mechanisms. Much knowledge of how spatial attention mechanisms operate arises from observations following lesions to the posterior parietal cortex (PPC) (Mesulam, 1998). Such lesions can lead to spatial neglect, an intriguing disorder as despite patients having normal visual fields they fail to perceive objects on the contralateral side of space. Thus, accordingly it is assumed to be a disorder of visuo-spatial attention.

Further, some authors have drawn analogies between visuo-spatial neglect and acute vestibular dysfunction (vestibular neuritis acute loss of one side of the balance system) as in both spatial neglect and vestibular neuritis a spontaneous bias of both head and eye position is present in the horizontal plane (Karnath & Dieterich, 2006). Moreover, both spatial attention and vestibular signals implicate right hemisphere dominance in the fronto-parietal brain areas. Indeed lesions of the parietal cortex have been demonstrated to induce asymmetrical vestibular–ocular reflex (VOR) (Ventre-Dominey, Nighoghossian & Denise, 2003a) the brainstem mediated reflex which allows for gaze stabilisation during head perturbations. Moreover, neuro-modulation evidence in normal subjects demonstrates that disruption of the fronto-parietal attentional network results in top-down modulation of the visual cortex (Silvanto et al., 2009).

Henceforth, there is evidence from lesion studies and neuromodulation that the parietal lobe is able to modulate, via top down cortical control mechanisms, low-level brain mechanisms and structures, such as the VOR and the visual cortex respectively (Silvanto et al., 2009, Ventre-Dominey, Nighoghossian & Denise, 2003a). However, it remains unknown whether it is possible to use purely behavioural/physiological manipulations in order to induce an asymmetrical top-down parietal modulation with demonstrable changes in:

- (i) the brainstem mediated vestibular ocular reflex;

  and;

- (ii) perceptual measures of early visual cortical excitability.

Chapter 2: Theoretical Framework

2.1 The vestibular system

An exquisitely designed vestibular system exists that facilitates man to detect head acceleration (gravito-inertial signals). It is located immediately adjacent to the inner ear with a mirror symmetrical pattern in both ears (as shown in Figure 1). It allows us to keep our bearings in the world (especially in the absence of other sensory cues such as those provided by the visual and auditory systems). Abnormality of this system leads to the pathological sensation of vertigo which can functionally lead to spatial disorientation.

The vestibular system consists of two parts: firstly, three semi-circular canals on each side orientated orthogonally to each other, forming a loop which is filled with a fluid like substance termed endolymph. The walls of these canals contain cristae and hair cells which can detect angular head acceleration. The second part is composed of the otolith organs, namely the utricle and saccule which detect liner acceleration and head position with respect to gravity (Figure 1).

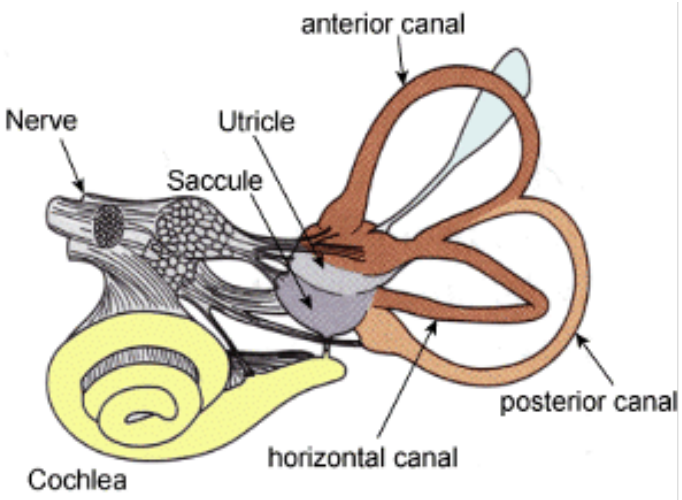


Figure 1: The vestibular system consists of three semi-circular canals (anterior, posterior and horizontal) forming loop like structures filled with endolymph which detects angular acceleration. The otolith organs (i.e. utricle and saccule) detect linear acceleration and gravity. (Figure taken from Vestibular function: evaluation and treatment 2011).

These three semi-circular canals behave as biological accelerometers, as they generate a signal proportional to the change in speed (acceleration) parallel to the heading direction of the accelerometer. During angular head movements, the fluid in the canals moves albeit with a small temporal lag, deflecting the hair cells (Figure 2). Herein one can draw the analogy to a cup of coffee. Place a cup of coffee on a flat table surface and turn the cup in a circular fashion. Note the coffee in the mug starts to turn as well although not instantaneously. The necessity for 3 accelerometers as opposed to just 1 is explicable by the fact that the vestibular system needs to faithfully represent and respond to head accelerations in the 3 dimensions of physical space to facilitate spatial orientation.

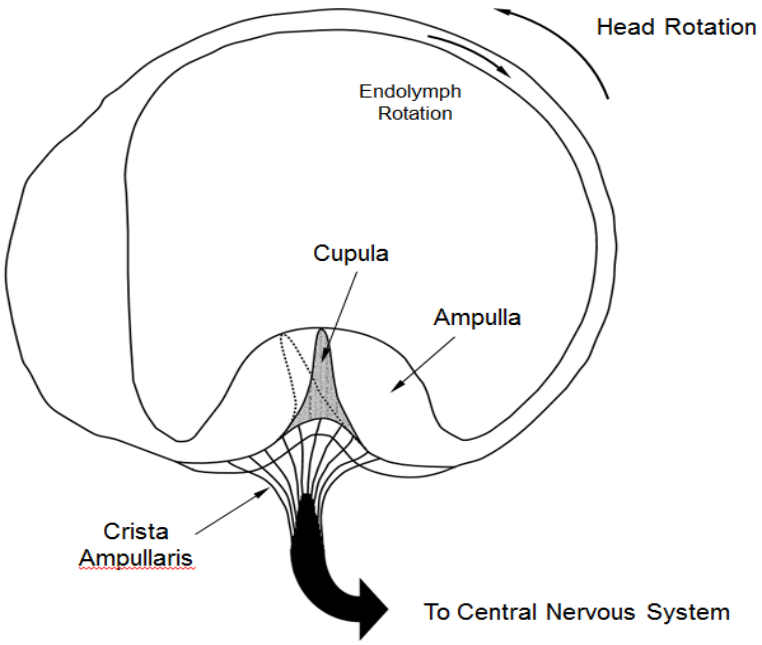


Figure 2: Representation of endolymph fluid motion inside a semi-circular canal in response to head rotation. Note the fluid moves in the opposite direction to that of the head rotation causing the deflection of the cupula, which upon deflection transmits the signal along the vestibular nerve to the CNS. (Figure taken from the Academic Department of Neuro-Otology archives)

However, in addition to spatial orientation what purpose does the fluid moving in our ear in response to head movements sub serve? Well, try the following little experiment, as you continue to read this thesis. Take a moment to rock your head side to side or up and down

and continue reading. You are only able to continue reading (i.e. preservation of visual acuity) as the semi-circular canals generate signals in response to the head movement and thus generate compensatory reflexive eye movement in order to stabilise gaze, via the vestibular-ocular reflex (VOR).

2.2 The vestibular-ocular reflex

Primarily the function of the VOR is to stabilise gaze during head perturbations and moreover to maintain spatial orientation of the retina during either translational or rotational head displacements. Indeed, there are different versions of the VOR to account for head accelerations in different directions, for example, the angular VOR responds to angular translations, whilst the linear VOR responds to linear translations (Angelaki, 2004). In this thesis the focus remains solely upon the angular VOR and any further reference made to the VOR implies by default the angular VOR.

The VOR is an open loop system with a very short latency, in the region of 20 ms. As such, it is faster than any visually mediated mechanisms. As stated above, the main purpose of the VOR is to stabilise gaze during head movements. During, angular head movements of small amplitude the direction of gaze remains fixed. In contrast, hark back to the memorable times of you childhood where many of us turned in circles in order to make ourselves dizzy. In this case the VOR is required to compensate for gaze direction. Such compensation is required, for example, if we spin to the right, the eye drifts to the left (slow phase). As the spin continues the eye cannot continue to compensate by turning to the left infinitely as it is restricted due to the orbital limits of the eye, thus a quick re-setting of the eye is made with a quick resetting movement (fast phase). In doing so the eye becomes successfully re-fixated in the direction of rotation (Figure 3).

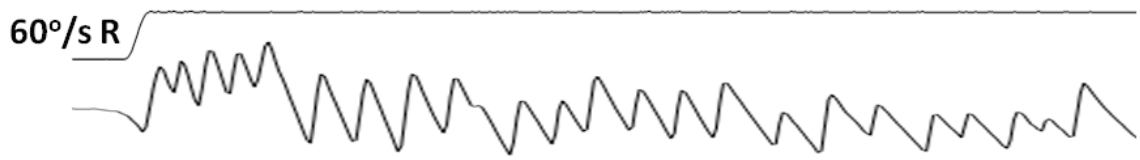


Figure 3: Example trace of vestibular nystagmus in response to rightward rotation following a leftward acceleration at 60 degrees/second. Note in response to rightward rotation (equivalent to a left stop response) a leftward slow phase (eye movement/downward deflection) occurs, followed by a rightwards (upward) quick resitting of the eye position before the next slow phase.

Hence, the VOR produces eye movements (slow phase) that are equal in velocity but in the opposite direction to the head movement velocity signals, ensuring that the images on the retina remain stable. Thus, one can make a functional assessment of the state of the vestibular system by referencing the gain of the VOR, which is determined by the ratio between the head velocity and eye velocity. In the ideal scenario the gain would be 1 (i.e. perfect compensation). That is, for a head acceleration of 90 degrees/second the compensatory eye movement velocity would also be 90 degrees/second.

What is the underlying anatomy and mechanisms that allows for this almost near perfect compensation? Primary vestibular afferents are bipolar cells (with the cell bodies lying in the scarpas ganglion) within the internal auditory meatus and their distal axons synapse with hair cells in the canal cristae (recall that detect head acceleration via deflection). Central axons from the ganglions pass to the brainstem at the level of the trigeminal nucleus and which point they divide into (i) ascending branches which pass to the superior vestibular nucleus and the cerebellum and (ii) descending branches which pass to the medial, lateral and descending vestibular nuclei. These primary vestibular afferents innovate mono-synaptically secondary vestibular afferents which respond not only to vestibular stimuli but also visual input. Hence, these 2nd order neurones innervate the specific ocular-motor

neurones that generate slow phase eye movements. Directionality of the eye movements is governed by the stimulated semi-circular canal which in turn is governed by the direction of the head rotation (Goldberg, 2000, Fernandez, Goldberg & Baird, 1990, Goldberg et al., 1990a, Goldberg et al., 1990b).

In summary this is the classical organisation of the VOR and is considered as a three neurone arc, wherein the semi- circular canals project via the vestibular nuclei to make connections to the extra-ocular muscles (Figure 4).

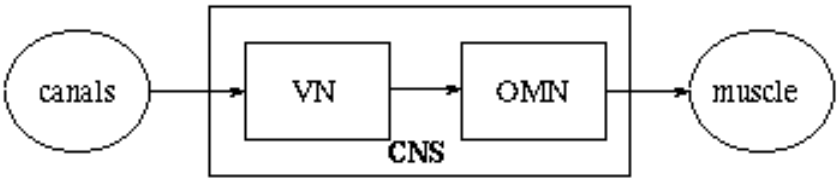


Figure 4: Diagrammatic representation of the classical three neuron arc for the VOR. The semi-circular canals pass a signal along to the vestibular nuclei (VN) at the brainstem level which then project to ocular-motor nuclei (OMN) which innovate the extra ocular muscles to move the eyes.

Thus, consider the case of head turn to the right hand side of space. Such rotations stimulate the right horizontal semi-circular canal leading to activation (via excitatory projections) of the motor and inter neurones of the left abducens nucleus leading to a contraction of the left lateral rectus muscle. The left abducens nucleus sends a signal to the right abducens nucleus with the net result being a conjugate movement of the eyes to the left in response to the right head turn (Figure 5).

Indeed understanding how the oculomotor system generates these reflexive eye movements (via the VOR) is of fundamental importance in order to understand the work to be presented in this thesis. However, in order to fully understand the VOR, one firstly needs to understand the function of the velocity storage mechanism, a neural integrator.

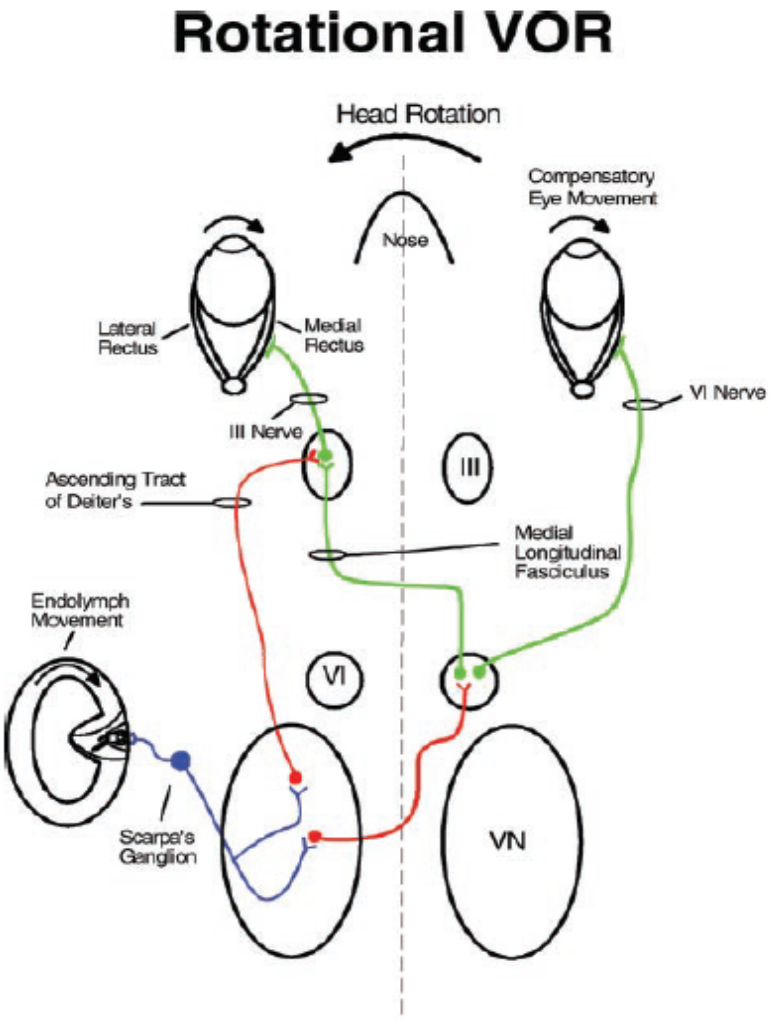


Figure 5: Schematic illustration of the VOR showing the connectivity patterns from the canal to the eyes, i.e. canal ocular connectivity pattern. Blue lines represent afferent projections; red lines second order connections and green lines for abducens neuron projections. (Taken from Dora Angelaki, Journal of Neurophysiology 2004).

2.3 Neural Integration

Principles of summing algorithms are analogous to neural integration. Consider travelling from Leeds to London along the M1 motorway in a car travelling with the cruise control set at 70 m.p.h (so that you are traveling at a constant velocity). If the journey takes 2.5 hours to complete, the distance can be derived by multiplying the velocity with the time (i.e. 70 x 2.5 =175 miles). However, seldom is life so uncomplicated that you are lucky enough to drive along the motorway at constant velocity. There may be an accident causing tailbacks

or average speed cameras due to road works. Herein, in such possible scenarios there are velocity changes that present over time in a non-linear fashion. Hence, in this particular scenario the integration must be done in steps. Suppose we travelled the above journey for a distance X at 50 m.p.h, then distance Y at 72 m.p.h and distance Z at 95 m.p.h. The total time can be derived by calculating the time for the individual 3 components of the journey and obtaining a total by summing the three together in order to obtain the total distance travelled.

A similar predicament is faced by the eye as it travels in the orbit. Assume that we are looking straight ahead and then we are instructed to make a 30 degree saccadic movement to a target in the right hand side of space. The input into the integrator would be the eye velocity as the eyes moves to the target (approximately 350 degrees/second). The eye position is derived by integrating the velocity signal into a position signal so that it can be held at the eccentric target.

As the eye is held at this target the natural elastic forces of the eye have the tendency to return the eye back to the straight ahead position. Hence, in order to maintain the eye looking at the target it requires this process of neural integration in order to maintain position. The neural machinery for such integration is likely to be performed by a distributed network of neurones in the brainstem and cerebellum. A perfect integrator would be able to hold the eye at 30 degrees infinitely over time. However, experiments have demonstrated that brainstem integrators are not perfect, such that the eye may deviate slowly to 29 or 28 degrees over time. This results in changes of position over time that can be quantified by the exponential time constant. This is attributable to biological integrators not being perfect rather they are termed leaky integrators. Thus an integrator that has a longer exponential

time constant is a more perfect integrator than the one with a short exponential time constant. Now we have introduced the concept of neural integration we can move forward to discuss an integrator in action, namely the velocity storage mechanism (Raphan, Matsuo & Cohen, 1979a).

2.4 The velocity storage mechanism

When we move our head in space and stimulate the semi-circular canals there is an initial integration of the head acceleration into a velocity signal. Direct recordings have demonstrated that this canal integration has a time constant of between 5-7 seconds, termed the direct pathway (Buttner & Waespe, 1981). However, the canals can drive the eyes by activating both direct and indirect pathways. This is known since in the laboratory setting, rotation at constant velocity in darkness results in a longer time course for the exponential decay of the oculomotor response: a time constant of between 16-20 seconds. This is significantly longer than the time course derived from the direct pathway (i.e. cupular dynamics alone). Prolongation of this response occurs due to the indirect pathways of the neural integrator (i.e. the velocity storage mechanism VSM) (Buttner & Waespe, 1981, Raphan, Matsuo & Cohen, 1979b).

Such a system allows for the neural integrator to store head velocity signals derived from the activation of the semi-circular canals in order to prolong the oculomotor response, but for what purpose? It is argued that the velocity storage mechanism maintains the velocity signal in the central nervous system during sustained constant velocity rotations or low frequency head movements in order to ensure adequate compensatory eye movements when the frequency of the head motion falls below 0.1 Hz (recall the vestibular system can only detect acceleration and not constant velocity) (Raphan, Matsuo & Cohen, 1979b). Such

a drop in frequency would cause the signal from the canals to fall to zero and hence not allow for adequate compensatory eye movements (Figure 6).

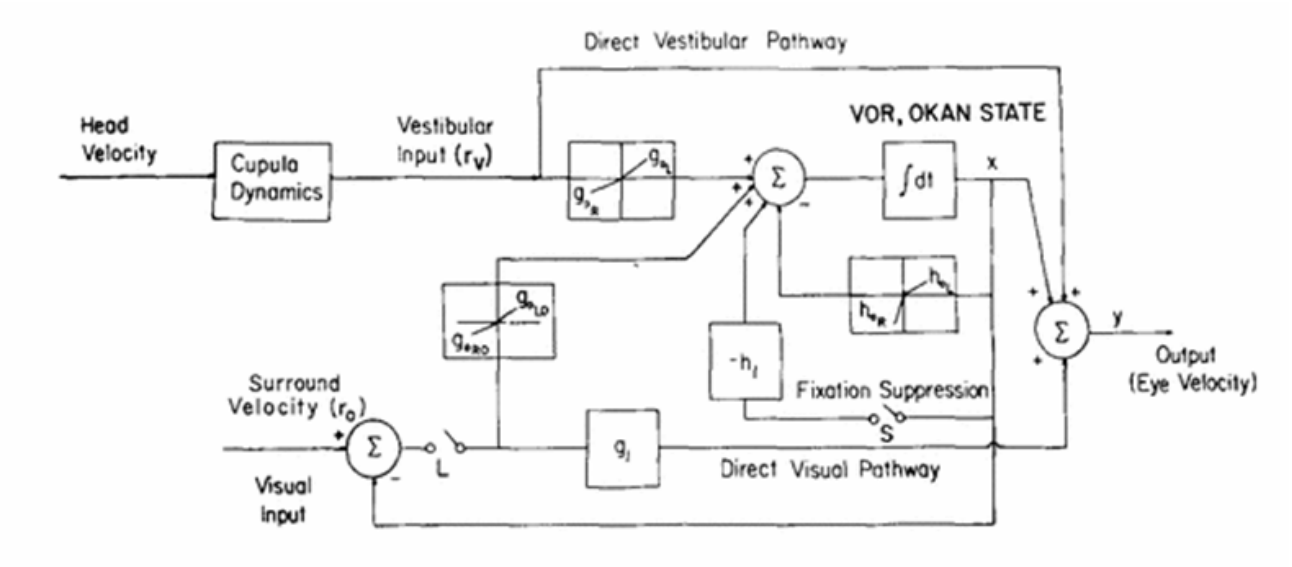


Figure 6: The original proposed model of the velocity storage mechanism (Taken from Raphan, Matsuo & Cohen, 1979).

It is proposed that the velocity storage mechanism is located in the brainstem, however in terms of its neural structure relatively little is known. Sectioning of midline fibres that connect the superior and medial vestibular nuclei have been shown to negate the function of the velocity storage mechanism, as well as lesions that involve the prepositus hyperglossi and cerebellar nodulus (Cohen et al., 1981).

Moreover, one can modulate the function of the velocity storage function in normal healthy subjects. For example, following a velocity step rotation the velocity storage mechanism function is “dumped” if a subject is to visually fixate a light source, hence attenuating the resultant oculomotor response (Waespe, Cohen & Raphan, 1985, Cohen et al., 1981).

However, despite the lack of knowledge regarding the neuronal organisation it is evidently clear that this neural integrator in the brainstem prolongs the vestibular response from 4 to 16 seconds on average (Raphan, Matsuo & Cohen, 1979b). Moreover, it still remains

relatively unknown what influence higher-order vestibular cortical areas have upon the velocity storage function apart from the one case report whereby parietal lesions were reported to result in asymmetrical VOR responses following velocity step rotations (Ventre-Dominey, Nighoghossian & Denise, 2003a).

2.5 Higher-order vestibular processing

Despite significant interest and the subsequent knowledge acquired regarding the structural organisation and function of cortical areas devoted to the visual and auditory systems, such knowledge about the cortical representations of the vestibular system is scant. This is demonstrated by the fact that to date no consensus has been reached regarding its precise location, organisation and function. So it is important to bear this in mind before we proceed further that the exact whereabouts of a well-defined vestibular cortex is a contentious and widely debated topic. Indeed, this fact is nicely exemplified by the postulation over time that 4 out of the 5 parietal lobes (the exception being the occipital lobe) have been implicated in processing vestibular signals, which could potentially be reflective of its widespread network and connections (Dieterich et al., 1998, Grusser, Pause & Schreiter, 1990a, Grusser, Pause & Schreiter, 1990b).

Animal studies have identified several distinct areas in the parietal and temporal areas that receive vestibular afferent signals, such as area 2v at the tip of the intra-parietal sulcus (IPS), area 3 av, the parieto-insular vestibular cortex (PIVC) and the inferior parietal lobe. The aforementioned areas have been implicated by microelectrode recordings to be multi-sensory, such that they receive not only vestibular input but additionally visual and somatosensory input as illustrated in figure 7 (Grusser, Pause & Schreiter, 1990a, Grusser, Pause & Schreiter, 1990b).

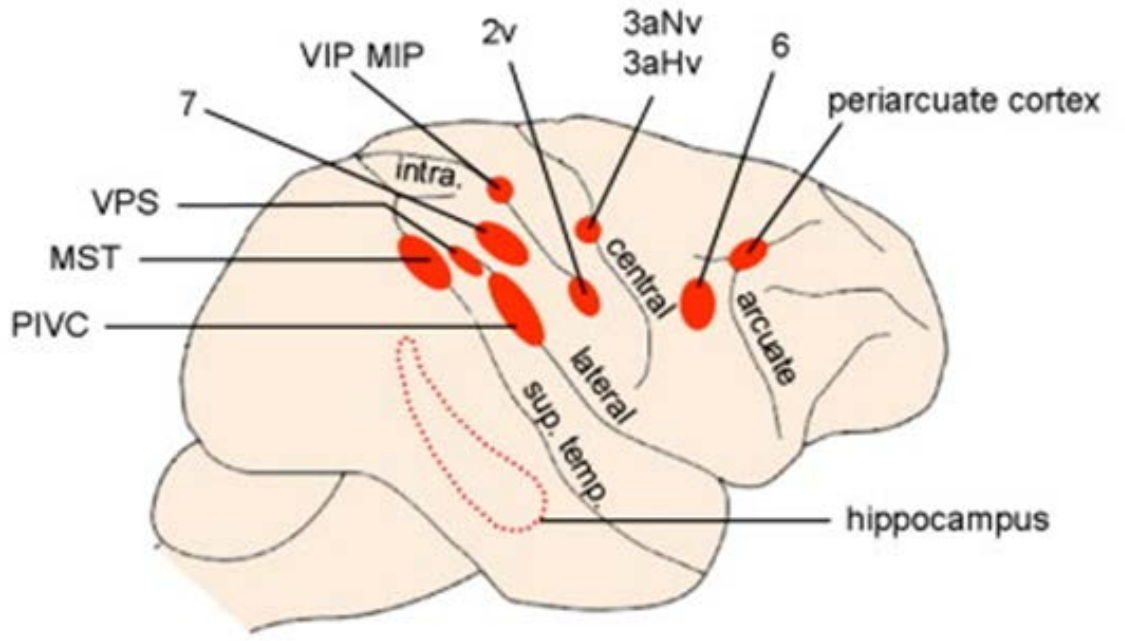


Figure 7: Anatomical loci of areas implicated for vestibular cortical processing in the primate brain (**PIVC, MST, VPS, 7, VIP, 2V, 3av).** (Figure adapted from Grusser, Pause & Schreiter, 1990a)

Thus, why is so little known about vestibular cortical processing in comparison to its sensory counterparts? Perhaps an alternative equally pertinent question would be: why would Darwinian mechanisms permit the development of primary sensory cortices for vision and audition, only to later abandon such organisation for the vestibular system? Ecologically speaking the most parsimonious explanation for this was hinted at in the preface. Consider determining the shape and colour of the things in the room you are sat in now as you read this thesis. This analysis performed requires only visual input. Moreover, when listening to music for example the differentiation between certain tones and melodies requires only analysis by the auditory cortex. However, contrast those examples with that of the vestibular system such as locomotion that are truly multi-sensory, requiring visual, vestibular and somatosensory input. Thus as a consequence of its truly multi-sensory nature it is possible that evolutionary mechanisms co-opted multisensory cortical areas for

vestibular processing rather than devoting a specific sensory cortex in order to reduce computational cost and ensure neural compactness.

In man the earliest reports of cortical areas implicated in vestibular processing arose from eliciting conscious vestibular sensations arising from direct electrical stimulation to the anterior inter-parietal sulcus (PENFIELD, 1957). Much of the recent work in search of the neuronal correlates of vestibular processing (i.e. “the vestibular cortex”) has focussed on finding the analogous area to the primate parieto-insular vestibular cortical area (Grusser, Pause & Schreiter, 1990a, Grusser, Pause & Schreiter, 1990b).

Neuro-imaging studies using vection inducing stimuli (Kleinschmidt et al., 2002, Brandt et al., 1998), or vertigo inducing stimuli (caloric)(Dieterich et al., 2003b, Fasold et al., 2002, Suzuki et al., 2001, Bottini et al., 1994) have isolated areas implicated in vestibular processing. The area that is most strongly associated with vestibular processing is located within the fronto-parietal network. A recent meta-analysis of 28 studies investigating the neuronal correlates of vestibular cortical processing implicates right hemisphere dominance and suggests that the core region to be involved is the parietal opercular (OP2) (Lopez, Blanke & Mast, 2012).

Indeed, there is no primate data to date that is suggestive of a hemispheric dominance that presents for vestibular cortical processing. Dietrich and Brandt were the first to propagate predominance for cortical processing of vestibular processing in the non-dominant hemisphere in humans (Dieterich et al., 2003a). In their studies the strongest determinate co-variant was the subject’s handedness (Dieterich et al., 2003a). This raises the question; why should such a primitive function be lateralised? Arguably dexter hemispheric

preference presents strongly and is well documented for visuo-spatial working memory task performance and indeed this can be reconciled with the functionality of the vestibular system, namely, to maintain spatial orientation (Karnath & Dieterich, 2006, Dieterich et al., 2003a).

2.6 Spatial orientation

Spatial orientation is a key function of the vestibular system. Indeed, it would then follow that the neuronal correlates of vestibular processing implicate the fronto-parietal areas (i.e. overlapping with spatial attention), as this would adequately serve functionality as herein considerable sensory neuronal convergence presents in order to generate internal representations of space (facilitating body perception in 3D space) either in egocentric (body centred) or exocentric (world centred) co-ordinates (Karnath & Dieterich, 2006, Snyder et al., 1998).

The visual system can code for space either in eye (retinal) or head centred co-ordinates. However for the vestibular system such an arrangement is unfeasible because such a system is dependent upon gaze, head position and fixed head-labyrinth co-ordinates (Snyder et al., 1998). This presents a neigh on impossible task for the vestibular system to use this coding system for ocular motor exploration and motor control of space. Thus, it seems that developmental mechanisms have resolved this predicament by coding for space in common egocentric or exocentric co-ordinates rather than eye or head centred coordinates (Karnath & Dieterich, 2006, Snyder et al., 1998).

2.7 Spatial attention

Karnarth and colleagues argue that the intriguing disorder of visuo-spatial neglect arises due to a central disturbance of the processing network that converts peripheral sensory stimuli

into egocentric spatial co-ordinates (Karnath & Dieterich, 2006). Spatial neglect commonly presents after posterior parietal cortical lesions, with such lesions resulting in visual-attentional disorders as evidenced by an inability to detect visual stimuli on the contralateral side of space as demonstrated by the drawing in figure 8, despite having normal visual fields (Mesulam, 1998).

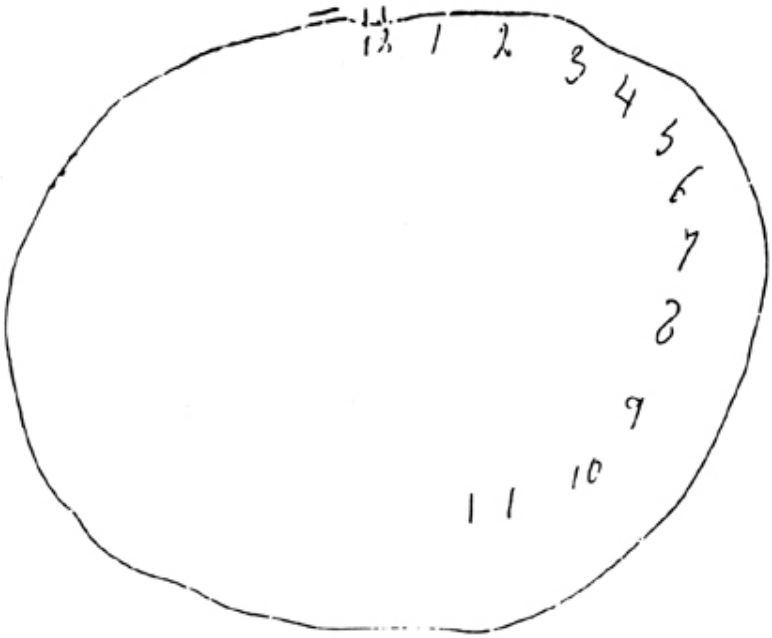


Figure 8: Stark example of spatial neglect. This is a drawing of a clock face by a patient who has had a right posterior parietal stroke. Note that the left-hand side of the clock is neglected, as all the numbers have shifted to the right hand side of the drawing. (Taken from Bradleys' Neurology in clinical practice 6th edition 2012).

Most frequently spatial neglect is associated with lesions in the right hemisphere involving the posterior parietal cortex, tempo-parietal junction and additionally focal lesions of the inferior parietal lobe (Mesulam, 1998). Karnath and colleagues have suggested an additional area to be implicated in spatial neglect, namely the superior-temporal gyrus (Karnath, Ferber & Himmelbach, 2001), however the conclusion that this area is implicated has been challenged experimentally using high resolution lesion mapping techniques demonstrating

that despite this area showing damage, such insults are not associated with spatial neglect (Hillis et al., 2005).

The mechanism(s) that leads to spatial neglect remain unclear, and in part this is due to following question: why does spatial neglect present more commonly following right parietal lesions in comparison to left lesions? Two prominent theories have arisen in order to explain this.

In the first theory the, “hemi-spatial theory”, it is postulated that the right hemisphere directs visual attention to both the right and left visual field, whereas, the left hemisphere directs attention only to the right visual field. Thus, if a left lesion presents, the right hemisphere is adequately able to compensate for the lesion, however such compensation is not possible by the left hemisphere following a right lesion (Mesulam, 1998).

Alternatively the other proposed mechanism is the “inter-hemispheric competition theory”. This stipulates that each hemisphere directs attention to the contralateral visual field balanced by reciprocal inhibitory mechanisms. Thus, accordingly neglect arises as a result of an imbalanced system as the healthy hemisphere is suggested to be released from inhibition (Kinsbourne, 1977). Thus, following a right parietal lesion the left hemisphere is released from inhibition and hence we observe a bias towards the right visual field resulting in neglect of the left hand side of space. The fact that neglect occurs more commonly following right lesions is reconciled in this theory due to the right hemisphere dominance that presents for visuo-spatial abilities (Szczepanski & Kastner, 2013).

Following parietal lesions especially those that involve a visuo-spatial neglect component result in an asymmetrical modulation of the VOR (Ventre-Dominey, Nighoghossian & Denise,

2003a). Moreover, specifically disrupting these fronto-parietal areas using trans-cranial direct current stimulation (tDCS) has been shown to induce top-down modulation of the early visual cortex (Silvanto et al., 2009).

2.8 The visual cortex

It is beyond the remit of this thesis to discuss the whole of the visual cortex. Thus, the focus will remain upon aspects pertinent to the experiments that shall be presented in this thesis, namely the early visual cortex.

The visual cortical areas are located at the back of the cerebral hemispheres, with the bulk occupying the occipital lobes. Take a moment to feel the back of your head roughly in the middle; you will notice a small bump, the inion which corresponds to the area overlapping the early visual cortex (V1). The primary (early) visual cortex receives input from the lateral geniculate nucleus (at the anatomical end of the visual pathways), commonly referred to as V1. The early visual cortex is between 1.5-2 millimetres thick and the total combined number of cells in the right and left V1 is suggested to be in the region of 1 billion cells, although there is considerable variation in volumetric measurements within the normal population (Figure 9).

Conscious visual perception of the world requires normal visual cortical function. Normal healthy individuals can see without the eyes and anatomical pathways by bypassing them and stimulating (either magnetically or electrically) the cortex directly, which can induce a brief percept of light, termed “phosphenes” (Schmidt et al., 1996).

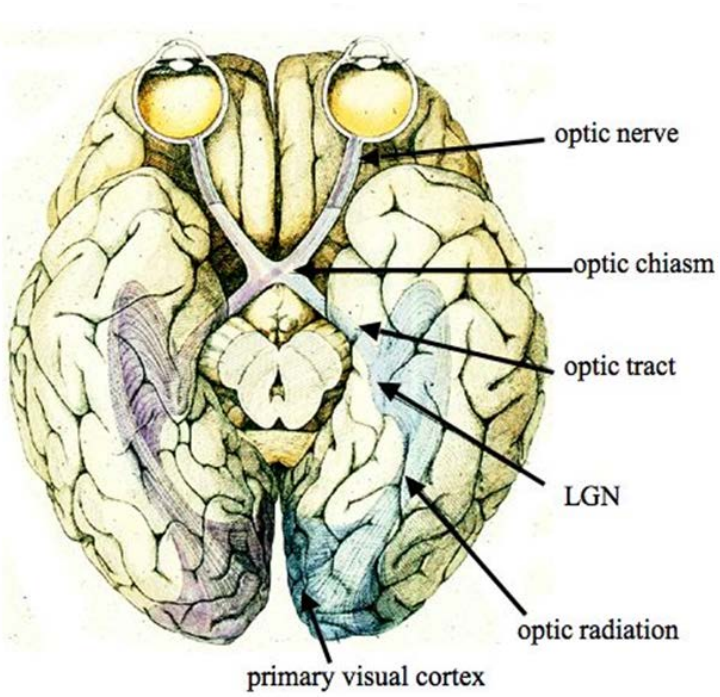


Figure 9: Representation of the anatomical pathways of the visual system from the optic nerve to the primary visual cortex. Taken from Clinical anatomy of the human eye; Snell and Lamp 2004)

Cortical cells in V1 are retinotopic, such that each cell in the early visual cortex responds to a specific area of the retina. Thus, the receptive fields of V1 form topographic maps of the visual field. The map in each hemisphere represents the contralateral visual field, that is, the right hemisphere maps the left visual field and vice versa (Kastner & Ungerleider, 2000). However, there is an intriguing property of the visual system that influences and distorts this organisational structure, the, "cortical magnification factor". From the retinal prospective this means that a large area of the cortex is devoted to a very small area of the retina. The retinal area corresponds to the fovea, the point on which the central visual field is positioned and functionally speaking allows for you to easily read this thesis (maintains high visual acuity).

One of the most striking organisational characteristics of cortical cells is their orientational selectivity. Each of the cortical cells has a preferred direction to which it is maximally

sensitive. Thus, if the orientation of a line deviates from this preferred orientation the cells firing rate dwindles and if it continues to deviate the cell eventually falls silent as shown in figure 10. In the early visual cortical there is a significant bias of orientation cells having a bias for a preferred direction to either horizontal or vertical vectors.

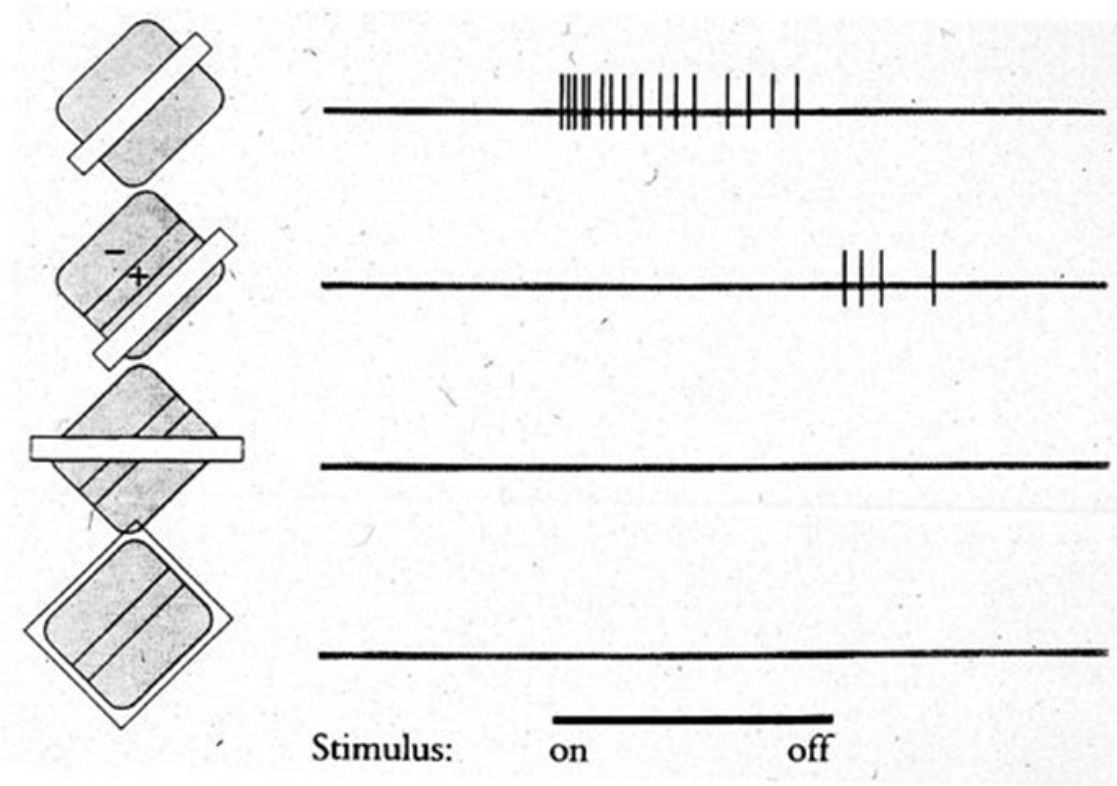


Figure 10: Diagrammatic representation showing orientation of V1 cells. In the top panel the cell responds optimally to that orientation and so when the stimulus is on there is maximal firing. When the orientation deviates the firing rate dwindles. Taken from Perception, Sekular and Blake 2004)

Now let us for a moment consider the property of orientation selectivity in more detail. Close your eyes and take your middle finger and point it in an upward direction. Let me guess that you are pointing to the ceiling. Now if I was to ask you do to the same whilst laying down or on your side you would still point to ceiling. This is because we interpret upward using gravitational co-ordinates as supplied by our vestibular system.

Thus the question arises, are these orientational selective cells in V1 capable of keeping track of changes in head position? In order to answer this question a monkey was implanted

with electrodes to record directly activity from orietational selective cells. Seated upright the monkey was presented in front of a computer screen with a vertical line and accordingly as expected the cells that were sensitive to the vertical orientation fired in an optimal fashion. Subsequently, the monkey (head and body) was tilted by 25 degrees whilst the line was kept vertical on the computer screen (i.e. same orientation). It was surprisingly observed that despite the visual stimulus remaining unchanged the cells firing rate diminished, demonstrating that changes in head position silences the cells firing rate (Marendaz et al., 1993). The implication of this experiment is that V1 cells cannot differentiate changes in orientation attributable to true visual orientational changes or head tilt. Hence, V1 cells do not have access to vestibular information in order to specifically map head position in gravitational co-ordinates (Marendaz et al., 1993).

It has been proposed from neuro-imaging studies that visual and vestibular cortical areas interact through reciprocal inhibitory mechanisms (Brandt et al., 1998). Such a mechanism is suggested to play the functional role of resolving sensory ambiguity that may arise when attempting to differentiate between self versus object motion. Neuro-imaging studies of vestibular cortical processing have also observed reduced visual cortical function. Moreover, vection inducing stimulation using full field visual stimuli, enhances visual cortical excitability with an associated attenuation of responses in the parietal lobe in the areas implicated in vestibular processing. Ecologically speaking such reciprocal mechanisms could be of potential functional relevance in order to attenuate disorientating visual and vestibular inputs (Brandt et al., 1998) (Refer to Figure 11 for a diagrammatic representation).

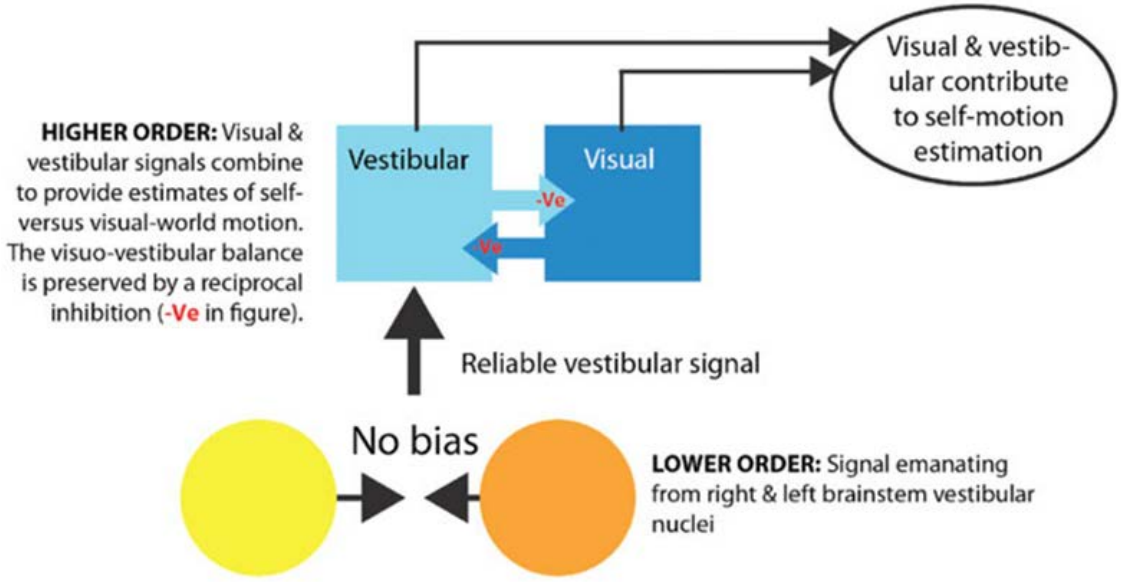


Figure 11: Block diagrammatic representation of visual-vestibular cortical interactions. Taken from Visual-vestibular Interaction: Basic Science to Clinical Relevance; Advances in clinical neuroscience and rehabilitation, Roberts et al., 2013)

We have recently demonstrated using direct measures of visual cortical excitability (single pulse TMS) a differential modulation during vestibular activation of visual cortical areas V5/ MT and V1/V2. We found that vestibular activation enhances early visual cortical excitability, whereas there is a reduction in excitability for visual motion areas (V5/MT) as shown in figure 12 (Seemungal et al., 2013).

Moreover disrupting activity using tDCS of the fronto-parietal areas implicated in both vestibular cortical processing and visuo-spatial processing results in modulation of V1 (Silvanto et al., 2009). Intriguingly these fronto-parietal areas additionally mediate the processing a special type of visual stimuli, namely bi-stable percepts.

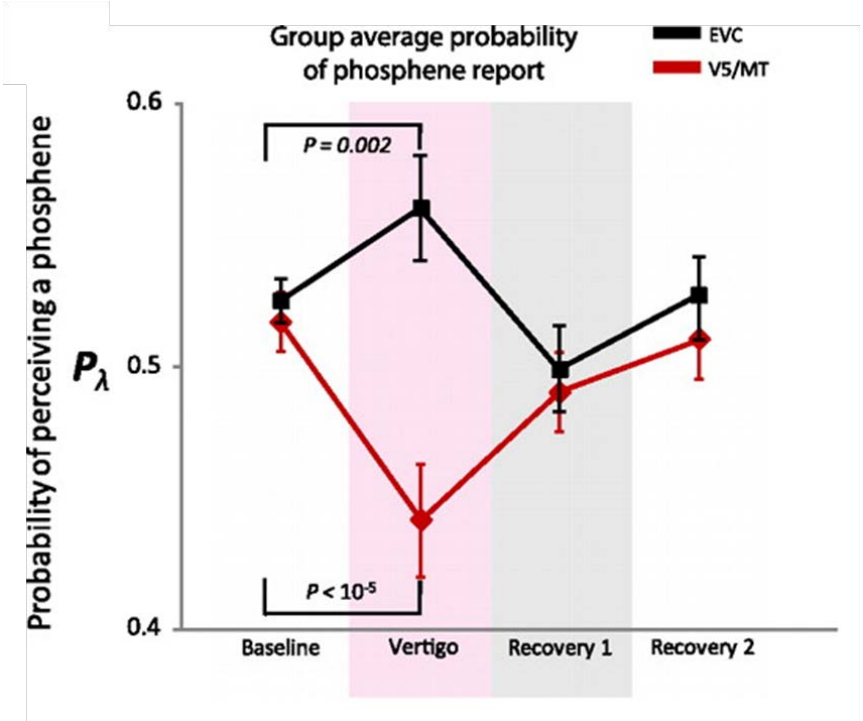


Figure 12: Effects of vestibular stimulation on visual cortical excitability. On the X axis the different conditions are represented with the purple striped condition representing vertigo (dizziness). On the Y axis is the direct measures of visual cortical excitability. As observed, during vertigo, V5 excitability drops whereas V1 excitability enhances. (Figure taken from Seemungal et al., 2013 Cerebral Cortex).

2.9 Bistable perception

When dissimilar images are presented to the two eyes simultaneously (e.g. rightward motion to the right eye and leftward motion to the left eye), normal binocular vision mechanisms breakdown giving rise to the beguiling phenomenon termed binocular rivalry. The consequence of viewing such visual stimulus is that the independent images from the two eyes compete for conscious awareness (perception). Each stimulus is seen alternately as perception switches between the two stimuli. The image that is seen is referred to as the, "dominant percept", whereby the invisible stimulus is referred to as the, "supressed image".

Dominance of rivalling images is determined by both ascending (bottom up) and descending (top down) influences. Ascending influences involve mainly stimulus properties such as luminance, contrast, contour density and spatial frequency. Descending influences include

influences of attentional nodes involving the intraparietal sulcus (Blake & Logothetis, 2002, Rees, Kreiman & Koch, 2002).

Neuroimaging and psychophysical studies are indicative that rivalry occurs at multiple neural loci including LGN and early visual cortical areas (V1/V2), higher visual areas including (V5/ MT) and more recently non visual areas in the fronto-parietal attentional network (Blake & Logothetis, 2002, Rees, Kreiman & Koch, 2002).

The exact neural basis that underpins rivalry is unclear, however three theoretical explanations exist to explain the phenomenon namely, eye rivalry (Tong, 2003), stimulus rivalry (Logothetis, Leopold & Sheinberg, 1996) (Leopold & Logothetis, 1996) and interhemispheric switching (Miller et al., 2000a). Eye rivalry assumes reciprocal inhibition between monocular neurones at the level of the lateral geniculate nucleus (LGN) and V1. Alternatively stimulus rivalry challenges eye rivalry by assuming that the rivalry occurs at higher cortical areas including V5, infero-temporal sulcus and the superior temporal sulcus as found in primate recordings. Finally a model of interhemispheric switching has been proposed to explain binocular rivalry which implicates the notion of competition between rather than within hemispheres (Tong, 2003, Miller et al., 2000a, Leopold & Logothetis, 1996, Logothetis, Leopold & Sheinberg, 1996).

2.10 Concluding remarks

Recently, the neuronal correlates of binocular rivalry have implicated strongly the role of non-visual brain regions namely the fronto-parietal attentional network (Lumer, Friston & Rees, 1998a). These cortical areas functionally overlap with those associated with vestibular cortical processing (Dieterich et al., 2003a). Further, modulating activity in the fronto-

parietal regions have been shown to disrupt perceptual transitions dynamics in binocular rivalry and alternatively lesions in these overlapping cortical areas lead to asymmetrical VOR responses. Moreover, artificially disrupting this parietal area using tDCS initiates top-down cortical modulation of V1(Kanai, Bahrami & Rees, 2010, Silvanto et al., 2009, Ventre-Dominey, Nighoghossian & Denise, 2003a).

Thus, it appears to be the case that cortical processing of binocular rivalry, visuo-spatial attention and vestibular signals overlap considerably. In doing so this affords a unique opportunity to probe possible parietal mediated behavioural manipulations of low level brain function (namely the VOR and early visual cortex) by applying concurrent vestibular activation and redirection of spatial attention either via performing visualised spatial attention tasks or viewing bistable perceptual visual stimuli. The potential practical applicability of this theoretical approach will now be tested in the experimental chapters of this thesis.

Chapter 3: Experiment 1- Modulating the vestibular-ocular reflex

3.1 Synopsis

Multisensory visuo-vestibular cortical areas are important for spatial orientation and facilitate the control of the brainstem mediated vestibular ocular reflex (VOR). Despite reports of visual input and cognitive tasks modulating the VOR through cortical control, it is unknown whether higher order visual stimuli such as bistable perception and attention tasks involving visual imagery have an effect upon the VOR. This is a possibility since such stimuli recruit cortical areas overlapping with those engaged during vestibular activation. Here, we used a novel paradigm in which subjects view bistable perceptual stimuli or perform complex attention tasks during concurrent vestibular stimulation. Bistable perceptual phenomena and attention tasks asymmetrically modulated the VOR but only if they involved a visuo-spatial component. Strikingly, the lateralisation effect was dependent upon the subjects' handedness, making this report support the hypothesis that vestibular cortical processing is strongly lateralised to the non-dominant hemisphere. Furthermore, it shows that perceptual transitions can modulate the dynamics of the vestibular system contingent upon the presence of a spatial component in the perceptual transition stimuli. Both perceptual transitions and attentional tasks are thought to invoke a redirection of spatial attention. We infer that such a redirection of spatial attention engages multisensory vestibular cortical areas, in turn initiating downregulatory control of low level vestibular function, which may contribute to spatial orientation.

Aims & Hypothesis

The aim of the experiments presented in this chapter is to consider visuo-vestibular interactions that have not previously been explored. That is the vestibular community has a long tradition of investigating the effects of visuo-vestibular interactions. However, to date, no study has looked at

the effects of binocular rivalry stimulus or motion induced blindness on the vestibular system. The specific reason for testing these visual stimuli on the vestibular system is due to the fact that they share overlapping neural circuits and therefore interact differently to other visual stimuli that do not invoke these overlapping neural circuits.

3.2 Background

The vestibular labyrinths detect head acceleration and integrate this input. Once integrated it is passed along the vestibular nerve to the vestibular nuclei. At the level of the vestibular nuclei this information is combined with input from other sources including visual input. Descending signals from the vestibular nuclei are passed to the spinal cord which are involved in postural control. Ascending signals from the vestibular nuclei are involved in aspects of oculomotor control and spatial orientation (Angelaki, 2004).

Conjugate eye movements faithfully represent the integrity of the vestibular system. What are conjugate eye movements? Conjugate eye movements occur when both eyes move together and include the VOR, optokinetic nystagmus, pursuit eye movements and saccades. The reason for why these eye movements reflect vestibular function is that the mechanisms generating these movements have reciprocal connections with the vestibular nuclei and other brainstem centres including the cerebellum that all contribute to aspects of oculomotor control.

As stated in the previous chapter, the key function of the vestibular system via the VOR is to compensate for head perturbations in order to stabilise gaze. This can be considered the pure VOR and is only active in complete darkness.

In light, the VOR combines with other eye movements to scan the environment, namely optokinetic eye movements (Brandt, Dichgans & Koenig, 1973). The optokinetic system generates a response to the entire movement of the visual surround and operates at

frequencies below 1Hz. For example, one uses this system when viewing the moving landscape from a train window. The stimulus for the optokinetic response is determined by the velocity by which the visual information travels across the retina which is termed retinal slip image velocity. Indeed, the optokinetic system does interact with the VOR in order to increase the sensitivity of movement in the visual world that we can detect.

The implication of this is that we are able to detect visual motion on the retina regardless of the origin i.e. whether initiated by head acceleration (vestibular), retinal slip (visual) or a combination of both (visuo-vestibular interaction).

Higher mammals and humans have pursuit and saccadic eye movements additionally. Pursuit eye movements are used to track and follow moving objects and the input is retinal slip and is stimulated by movement of a particular part of the visual scene, rather than the whole of the visual scene. For example, you would use the pursuit system to track a person walking down the street. The saccadic system involves rapid eye movements to scan and foveate stationary visual information such as for example reading this thesis.

However, if for example you are following the flight path of an aeroplane then the pursuit component is not sufficient as the plane is moving too fast to follow, therefore a combination of both saccadic and pursuit eye movements must be used. Indeed, eye movements may be combined to allow for more complex oculomotor movements as explained in the previous chapter (i.e. nystagmus).

As aforementioned in the previous chapter, pure vestibular nystagmus can be elicited during continuous self-rotation in the dark with the slow phase being generated in the opposite direction to that of the rotation followed by a quick saccadic resetting eye

movement. In contrast, OKN is generated by continuous movement of the entire visual field whilst the observer is stationary. For OKN, the slow phase is generated in the same direction as the moving visual scene followed by quick phases in the opposite direction by the saccadic system to reset the eye position. Hence, both the OKN and VOR systems can stabilise gaze in space.

Intriguingly, one can get the VOR and OKN to interact in specific laboratory settings. Consider a subject rotating inside a lighted optokinetic drum which can also be simultaneously rotated either in the same or opposite direction to that of the subject. So, if the OKN and VOR are in the same direction they add together, whereas if they are in opposite directions, they subtract in an algebraic fashion.

Brief, high frequency head movements lead to the optimal performance of the rotational VOR (Raphan, Matsuo & Cohen, 1979a). However, performance declines during sustained constant velocity rotations or low frequency movements. In fact in these situations, it is the optokinetic system which seemingly aids the declining ability of the VOR (Raphan, Matsuo & Cohen, 1979a).

The brain has a remarkable ability to adapt the VOR to the environmental circumstances that may prevail at any given time. For example, the VOR can compensate for sudden unilateral or bilateral loss due to disease or trauma as well as adapting to new spectacle prescriptions. In these scenarios the VOR must detect the errors in performance and correct for them appropriately in order to ensure calibrated compensatory eye movements in response to the head perturbation that are of the correct amplitude, direction and phase.

There are numerous examples of both short and long term adaptation that results in the recalibration of the VOR. For example, the VOR is able to habituate such that there is a reduction in the time constant and gain of the response in subjects whom are exposed to continuous spins; however the functional significance of such habituation is uncertain. Habituation is nicely exemplified in ballet dancers, whom perform long high speed spins, and when tested clinically have low VOR time constants (Nigmatullina et al., 2013).

More pertinent to the work to be presented in this thesis, is the context of visually induced adaptations of the VOR. A dramatic example of the effect of altered visual demand upon the VOR is exemplified by experiments where subjects view the world through head fixed optical devices such as mirrors or dove reversing prisms. For example, consider viewing the world through reversing prisms, as the head moves to the right, the visual world instead of moving to the left, will also move to the right, in the same direction as the head. It has been demonstrated that after just a few minutes of head rotation during reversed vision, the VOR gain measured in darkness declines. Removal of the optical devices results in the gain rapidly returning to the pre-inversion levels. Longer exposure to visual inversion results in more long term changes to the VOR. For example, subjects who wore reversing prisms for three to four weeks showed large changes in the VOR such that upon removal of the lens, head movements to the right would also cause eye movements to the right instead of the left. Notably however, the images would remain stable on the retina during these head movements (Gonshor & Jones, 1976a, Gonshor & Jones, 1976b).

An everyday example of the above scenario, albeit a less dramatic one, is the demand that is placed upon the VOR when adapting to a new spectacle correction. Spectacle lenses have a prismatic effect termed rotation magnification. So, for the correction of hypermetropia

(long sight) subjects wear positive lenses for the correction. However, this requires the subject to rotate their eyes more when they are moving their line of sight. Conversely, near sighted (myopic) individuals have negative corrective lenses, hence lower values for VOR gain than long sighted people as they have to move their eyes less. (N.B No such phenomenon occurs during the wearing of contact lenses as the contact lens rotates with the eye and so therefore no rotational magnification effect presents). Indeed adaptation to spectacle correction occurs rapidly with demonstrable changes in the VOR gain after fifteen minutes, however, slightly longer for presbyopic corrections.

Thus in summary, it is clearly apparent that the visual and vestibular systems are functionally complementary for gaze stabilisation to preserve visual acuity. Gaze stabilisation is partly mediated by retinal slip velocity signals and the vestibular ocular reflex (VOR). Also it is apparently clear that the VOR is a remarkably adaptive reflex as it fundamentally aims to achieve its main function which is to stabilise gaze. The vestibular system can compensate for head position in all the 3 dimensions of space and hence it is able to contribute functionally to maintaining spatial orientation during head perturbations (Suzuki et al., 2001). 3 dimensional interpretations of the world can be additionally formulated by the visual system.

Binocular vision encourages co-operation between the two eyes leading to stereopsis (3D vision). This allows for the visual system to judge depth and requires the use of both eyes. When the two eyes are viewing the world the images of the right and left eye are almost identical (central field overlap considerably) apart from the peripheral extremities. This is possibly in part due to the small difference caused by the lateral separation of the eyes in

the head; however despite this, the brain recognises the two visual images as identical and fuses them into a single coherent percept of the world.

Development of binocular foveate vision provided new challenges to the vestibular system and in particular to the VOR. Such challenges are that a requirement was necessitated to resolve potential conflict that came about by the requirement to concurrently stabilise images on the fovea and on the rest of the retina. For example, this may occur when fixing on a small object close to oneself whilst walking, i.e. looking at a mobile phone keypad whilst walking. In this situation the more distant background, i.e. the floor, moves on the retina in the opposite direction to the close object (Cheng & Outerbridge, 1975). Hence, the pursuit system with its superiority for attentional focus dominates visual following to resolve this predicament (Cheng & Outerbridge, 1975).

Intriguingly a beguiling predicament and phenomenon arises when one breaks down the normal co-operation between the two eyes (Blake & Logothetis, 2002). This can be done by separating the two eyes, so that different inputs can be concurrently presented to each eye individually. For example, a grating at 45 degrees can be presented to the right eye whilst a grating at 135 degrees can be presented to the left eye. What would be the result of such visual presentation? If the two images were combined by simply superimposing them upon each other a mosaic pattern would result, which doesn't faithfully represent the visual input. So instead what happens is that the two eyes engage in competition rather than co-operation in order to achieve perceptual dominance. The net result is that at one point in time one would observe the grating at 45 degrees and it would then switch to the 135 degrees grating. This phenomenon is termed binocular rivalry and is thought to be mediated by (non-visual) fronto-parietal cortical areas (Lumer, Friston & Rees, 1998a).

Additional cortical processing and higher-order integration of visual and vestibular velocity signals are critical for conscious perception of body position in space and are proposed to modulate lower brainstem vestibular reflexes such as the VOR (Karnath & Dieterich, 2006, Suzuki et al., 2001).

In healthy adults, VOR responses are symmetrical for right and leftwards rotations (Ventre-Dominey, Nighoghossian & Denise, 2003a, Raphan, Matsuo & Cohen, 1979a). The responses can be voluntarily modified bi-directionally by visual targets and non-visual tasks (e.g. VOR suppression is seen if subjects are asked to focus on a real or imaginary target rotating with them). Moreover, simple cognitive tasks such as mental arithmetic increase the subjects' attentiveness and, as a result, the gain of the VOR response is enhanced (Barr, Schultheis & Robinson, 1976).

However, the effects of higher order visual stimuli such as bistable perception (i.e. binocular rivalry and motion induced blindness (MIB) (Bonneh, Cooperman & Sagi, 2001) or attention tasks requiring visualised spatial manipulation are unknown.

The processing of such stimuli as discussed involves largely frontoparietal areas that have additionally been implicated in processing of complex cognitive attention tasks (that require visual imagery) and vestibular signals. Lesions or modulating activity in these overlapping cortical areas cause spatial neglect (Mesulam, 1998, Kinsbourne, 1977) by disrupting visuospatial attention, alter (bistable) perceptual transition dynamics(Kanai, Bahrami & Rees, 2010) and induce asymmetrical VOR responses(Ventre-Dominey, Nighoghossian & Denise, 2003a). Additionally it has also been shown that vestibular activation has been reported to alter perceptual dynamics of bistable perception(Miller et al., 2000a) by

modulating perceptual predominance of the rivalling images(Miller et al., 2000b), and to temporarily alleviate the symptoms of hemi-spatial neglect(Rubens, 1985).

Thus, it appears to be the case that processing of vestibular signals, visuospatial attention and bistable perception are intertwined.

As this has not yet been directly investigated, herein we attempt to modulate the VOR in subjects by exposing them to visuo-spatial attention tasks and perceptual transitions such as binocular rivalry during concurrent vestibular activation.

3.3 Materials and methods

The general experimental strategy consisted of assessing the effects of viewing bi-stable perceptual visual stimuli or performing visuospatial attention tasks during velocity step rotations upon the post-rotational VOR (stopping responses).

A vibration free, motorised rotating chair (Contraves, USA) fitted with restraints was used to deliver constant velocity rotations around an earth vertical axis (90^{o}/s). The chair was surrounded by a 1.44m diameter drum marked with vertical black and white stripes at 0.1 cycles/^{o} (Figure 13 and 14).

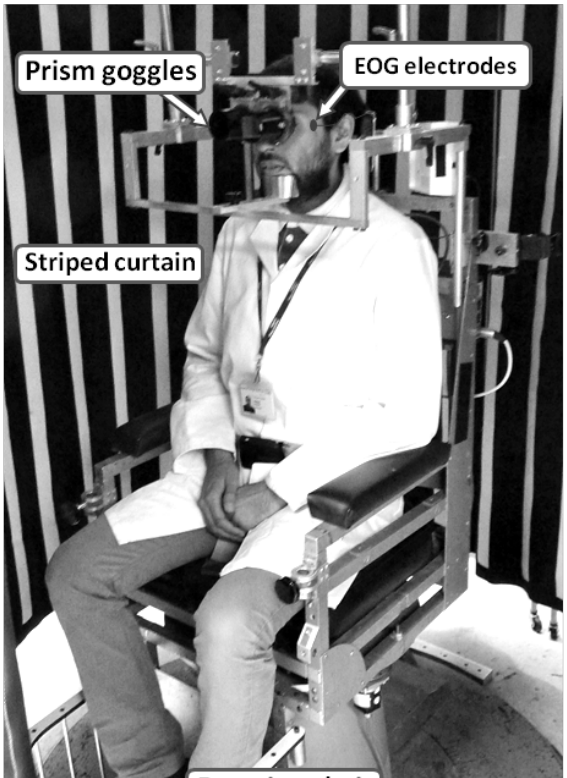


Figure 13: Subject seated upon the motorised rotating chair (Contraves, USA) used for the experiment with the visual stimulus attached in order to deliver the binocular rivalry stimulus.

Subjects were seated on a motorised chair inside an OKN drum viewed through a pair of Dove reversing prisms (Figure 14). Following 20s rotation (leftward blue arrow or rightward red arrow), the chair was always stopped in the dark and the VOR was measured (Figure 17a).

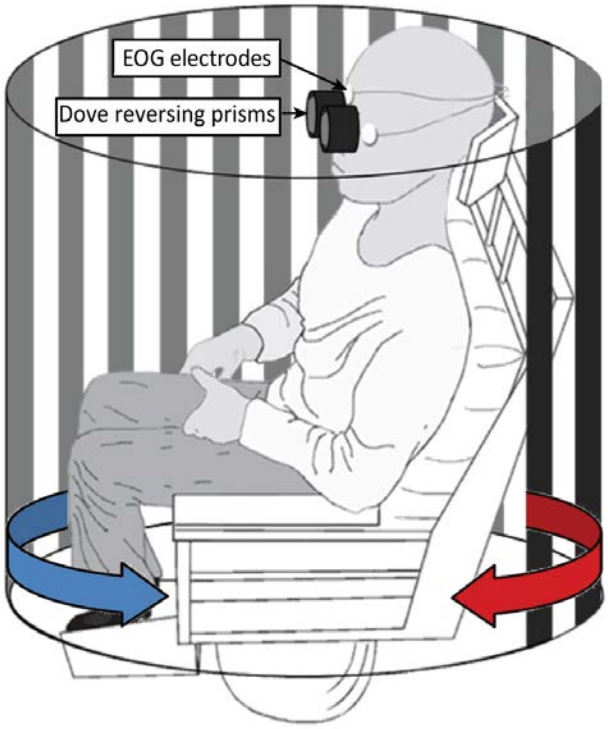


Figure 14: Experimental protocol for chair rotations. Subjects were seated upon the chair. Rotations were either rightward (red arrow) or leftward (blue arrows) Subjects were enclosed in the black and white OKN drum which consisted of vertical stripes which was viewed through the dove reversing prisms in order to generate different visual stimuli. Eye movements were recorded using DC EOG recordings.

3.3.1 Binocular rivalry

Viewing the striped background through the prisms whilst rotating, resulted in a differential grating motion in the two eyes and competition for the dominant percept. By altering the

orientation of the prisms in the two eyes rivalrous stimuli was created (i.e. “motion rivalry”) (Figure 15). A control non-rivalrous condition was implemented, which consisted of presentation of prisms in the same orientation (+45^{o}) to both eyes to ensure a single fused percept.

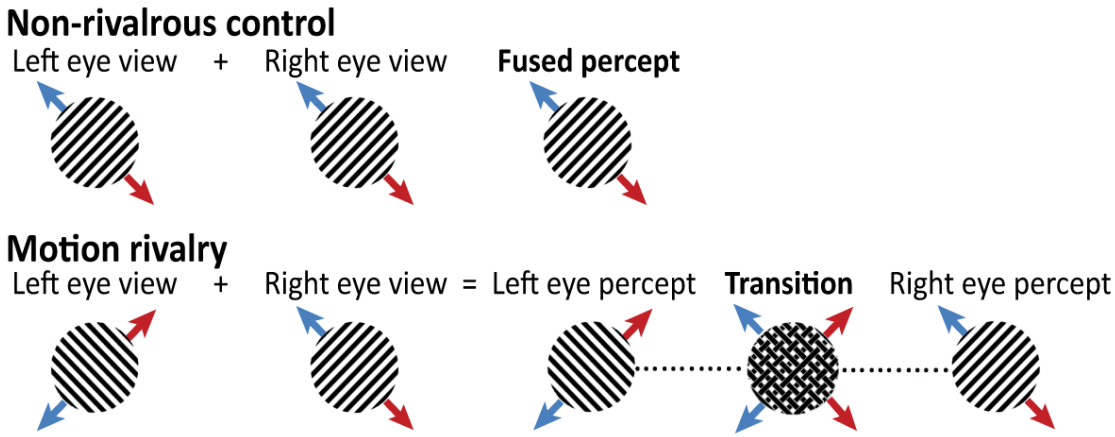


Figure 15: Example of visual motion stimuli used for the binocular rivalry experiment. For the non-rivalrous control conditions the dove reserving prisms placed in front of the left and right eye were orientated in the same direction so that subjects could fuse them into a single coherent percept as shown. During the motion rivalry condition the prism was tilted to the right (45 degrees) in front of the right eye and to the left in front of the left eye (135 degrees). Thus subjects could not fuse the two images and rivalry for the dominant percept presented (red arrows show perceived visual motion direction during rightward rotation and blue arrows for leftward rotation).

3.3.2 Motion induced blindness

For the motion induced blindness condition, subjects were seated with a screen monitor fixed to the chair at a distance of 40cm from the subjects’ eyes (Figure 16). The MIB stimulus consisted of three yellow dots (0.2^{o}) and a green fixation dot arranged along a 1^{o} radius circle forming a triangle, overlaid on a global clockwise moving pattern of blue dots on a black background. The subjects were instructed to fixate the central green dot during the 20s (leftward or rightward) rotations. The chair was stopped as the screen went black and the VOR was recorded (Figure 17b). A control condition was employed in which the background was stationary and, as a result, the subjects did not experience the

disappearance and reappearance of the yellow dots that is typical in MIB (Bonneh, Cooperman & Sagi, 2001).

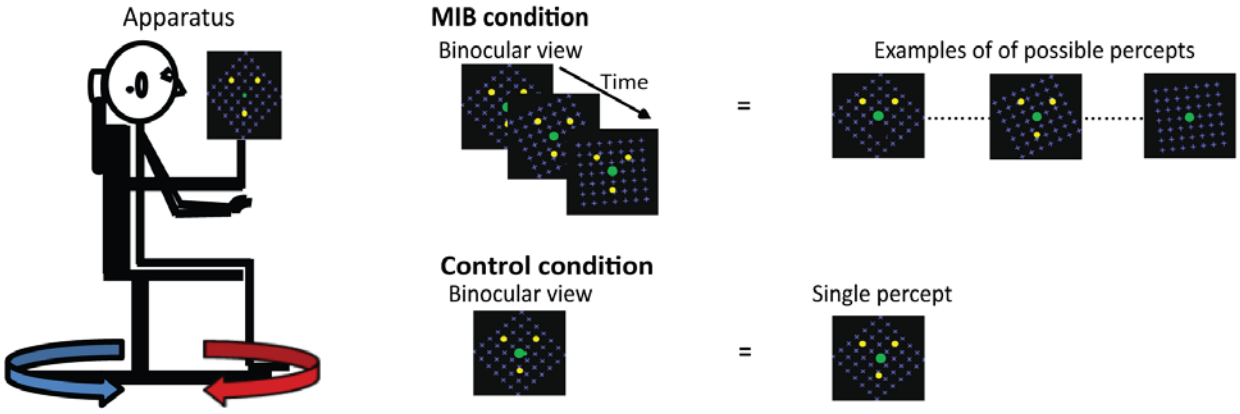


Figure 16: Motion induced blindness experimental set up. Subjects were seated upon a motorised chair (rightward rotation red arrow, leftward rotation blue arrow) with a screen monitor attached to the chair 40 cm away. Upon the screen was projected the MIB stimuli and subjects were instructed to fixate on the central green dot. Overtime they experienced the disappearance and reappearance of the yellow dots as shown. During the control condition the blue background remained stationary hence the subjects did not experience the disappearance reappearance of the yellow dots.

3.3.3 Visuospatial tasks

For the visuo-spatial attention tasks subjects performed a modified version of the Brooks visuospatial working memory task whereby 6 single digit numbers were randomly allocated to 6 specified locations in a visually imagined 3×3 grid (Brooks, 1967). A new digit was added to the imagined grid every 2.5s. This task was performed as the subjects rotated in the dark for 20s preceding the measurement of the VOR after the chair halt (Figure 17c). Subject's performance was assessed by asking them to draw the grid with all the remembered numbers after each recording. Any trial in which the subject failed to remember at least 4 numbers and their location in the grid was repeated. This ensured that the task employed provided sufficient attentional load (Lavie, 2005). In addition, we performed the same task

but altered the attentional load by giving subjects 3 numbers to remember in 3 different locations in the grid. In this low load task, the subjects were always able to recall all the numbers and their locations.

3.3.4 Non-visuospatial tasks

Finally, subjects also performed a modified version of a non visuospatial digit span memory task, which involved subjects repeating and memorising a string of single digit numbers with a new digit added to the string every 2.5s. This task was performed as the subjects rotated in the dark for 20s and the VOR was measured after the chair halt (Figure 17c). Subject's performance was assessed by asking the subject to verbally recall the numbers at the end of each trial. The subjects were asked to verbally recall a string of 7 numbers for the high load condition and 4 numbers in the low load condition (Axelrod et al., 2006). Any trial in in the high load condition in which the subject failed to recall at least 5 numbers was repeated. Pilot studies and the literature indicated that this purely verbal recall task is comparatively easier than the visuospatial task. Therefore, in order to ensure a comparatively equivalent attentional load in the two tasks (i.e. visuospatial and non visuospatial) a higher criterion was set (Kessels et al., 2008).

3.3.5 Experimental protocol

For the binocular rivalry and MIB conditions, each trial began in the light with the chair rapidly accelerating (0.5s) to a constant velocity of 90^{o}/s, whilst the trials with the attentional tasks were always performed in darkness. After 20s of chair rotation (rightwards or leftwards in a randomised order) either in the light (rivalry and MIB conditions) or dark (attentional tasks), the chair was always stopped in the dark (Figure 17). Eye movement

responses to the stopping stimuli were recorded using horizontal binocular DC-EOG recordings.

The duration of the vestibular stimulus was reduced to 20s in our experimental protocol to allow for maximal concurrent visual and vestibular activation, as the vestibular response during constant velocity rotations decays after 20 seconds (Refer to the appendix of this chapter and see details of supplemental experiment 3).

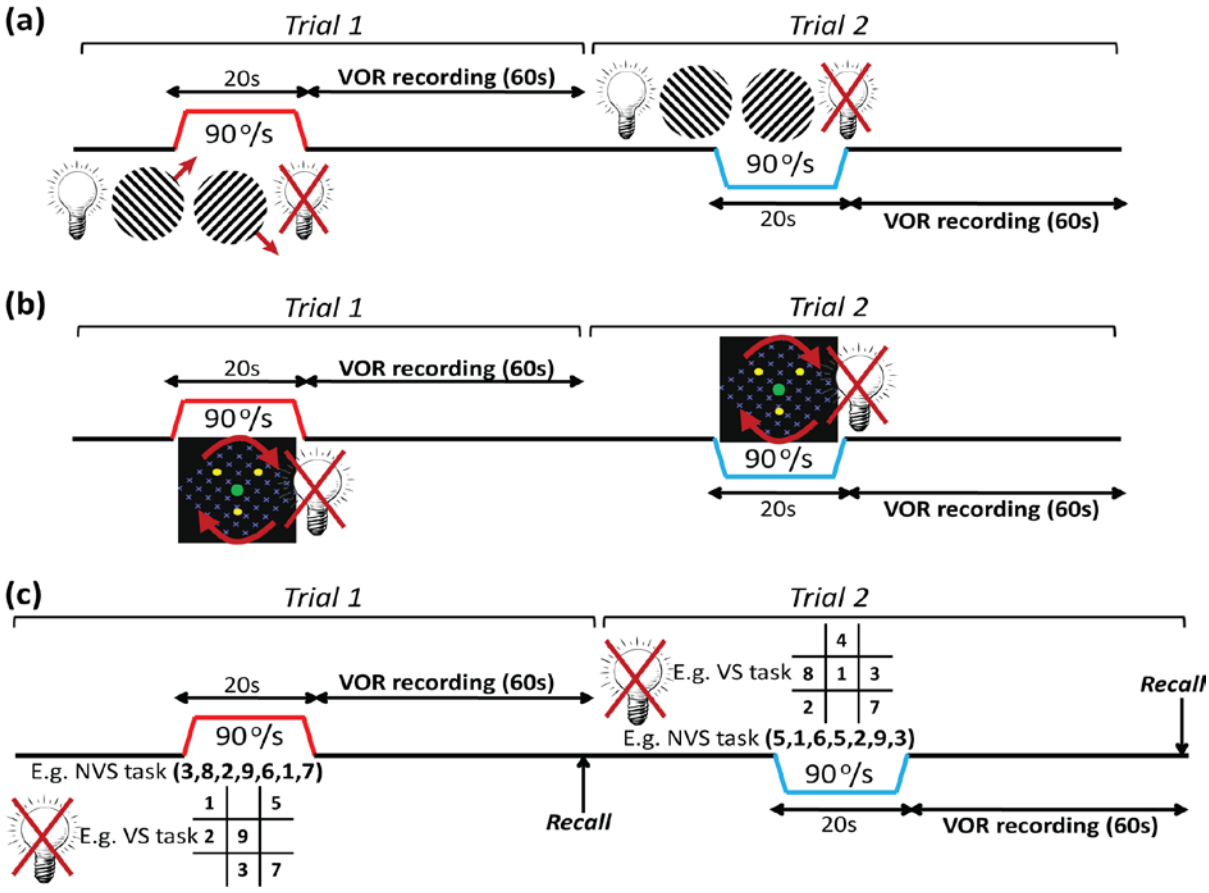


Figure 17: Experimental protocol: (a) Subjects viewed motion rivalry for either rightward (red displacement) or leftward (blue displacement) in light for 20 seconds. After 20 seconds rotation in either the rightward or leftward direction, subjects were always stopped in the dark. In the darkness the VOR was recorded following rightward and leftward rotations. (b) The same protocol was employed during the MIB condition. (c) For either the VS task or NVS task subjects performed the rightward and leftward rotations in darkness. At the end of the VOR recording, subject's task performance was assessed at recall.

3.4 Subjects and data analysis

Subjects were naïve, with no history of neurological, otological or ophthalmological disease. All had normal corrected vision and normal binocular and colour vision and we assessed this using the Titmus fly test and Ishihara colour plates. One set of subjects completed all binocular rivalry experiments, a separate set the MIB study and a further separate set the attention tasks. Eight subjects participated in more than one set of experiments but since these 8 subjects were tested 6 months apart and hence there was no potential of carry over effects, repeated measures statistics were not employed. 10 right handed subjects were recruited for the rivalry conditions (6M/ 4F), 10 right handed subjects for the motion induced blindness (4M/ 6F), 10 right handed subjects for the visuospatial attention task (6M/4F) and 10 right handed subjects (5M/5F) for the non visuospatial attention task. For the lateralisation experiments involving motion rivalry 12 right handers (7M/5F) and 8 left handers (7M/1F) were recruited. For the visuospatial task 12 right handed (6M/6F) and 8 left handed subjects were recruited (6M/2F).

Participants completed an Edinburgh handedness inventory questionnaire and all had a handedness score of >40 (considered as right handed) or <-40 (considered as left handed)(Oldfield, 1971).

Subjects successfully confirmed the presence of perceptual transitions during bistable perceptual stimuli. The switching rate for perceptual transitions was not measured, as a mosaic (mixed percept) is reported predominantly in the motion rivalry condition. An important point to note, is that there is no difference in the duration of perceiving rightward motion as opposed to leftward motion during binocular rivalry (Hayashi & Tanifuji, 2012).

Binocular EOG and chair motion signals were saved on a computer at a sampling rate of 250 Hz. After calibration of eye position, EOG signals were differentiated to obtain eye velocity curves. Fast phases of nystagmus were removed and slow phase eye velocity curves were averaged from the chair halt whilst keeping the right and left stopping responses separate. Averaged eye velocity curves were fitted with an exponential function to determine the main time constant (TC) of decay of the VOR. [Nb: VOR TC in man is approximately 16s as a result of the velocity storage mechanism in the brainstem, which prolongs the vestibular nerve signal (Okada et al., 1999).

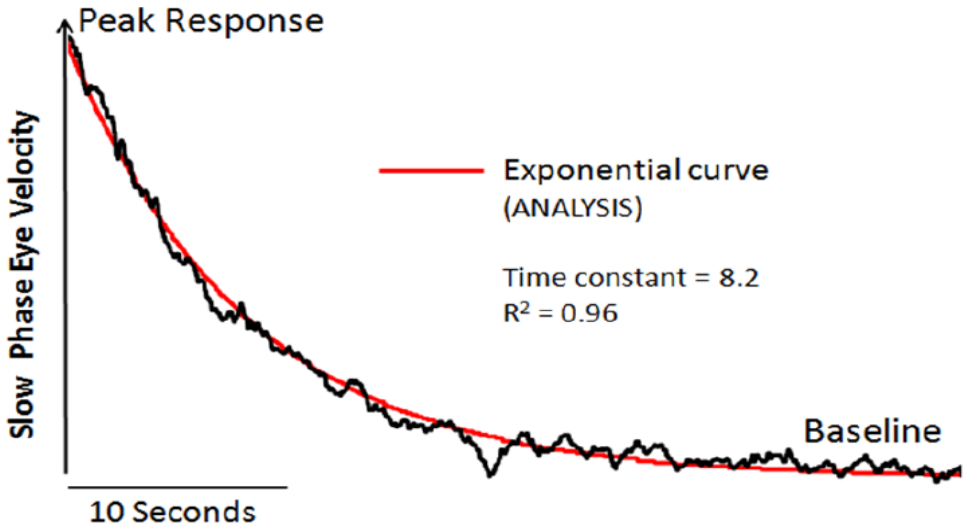


Figure 18: Eye velocity curve: X axis represents time in seconds; Y axis represents slow phase eye velocity. Upon chair stopping (time 0.5 seconds) the maximal SPV is observed which decays exponentially over 30 seconds. An exponential curve can be fitted to the eye velocity curve to determine the time constant of the response.

To quantify the VOR asymmetry, we calculated the VOR_{TC} Asymmetry Index alternatively referred to as directional preponderance:

$$VOR_{TC}\ Asymmetry\ Index\ (\%) = \frac{(Left\ stop\ TC - Right\ stop\ TC)}{(Left\ stop\ TC + Right\ stop\ TC)} \times 100$$

(NB: Positive Asymmetry Index denotes shortened VOR response following the rightward rotation whilst negative Asymmetry Index represents shortened VOR following the leftward rotation.)

3.5 Results

3.5.1 Motion Rivalry results

Motion rivalry in the 10 right handed subjects caused asymmetric VOR responses in the dark. VOR time constants following the rightward rotations were significantly reduced compared to VOR_{TC} following the leftward rotations ($p<0.001$, paired t-test; Figure 19) with a mean positive VOR_{TC} Asymmetry Index of 25.4%.

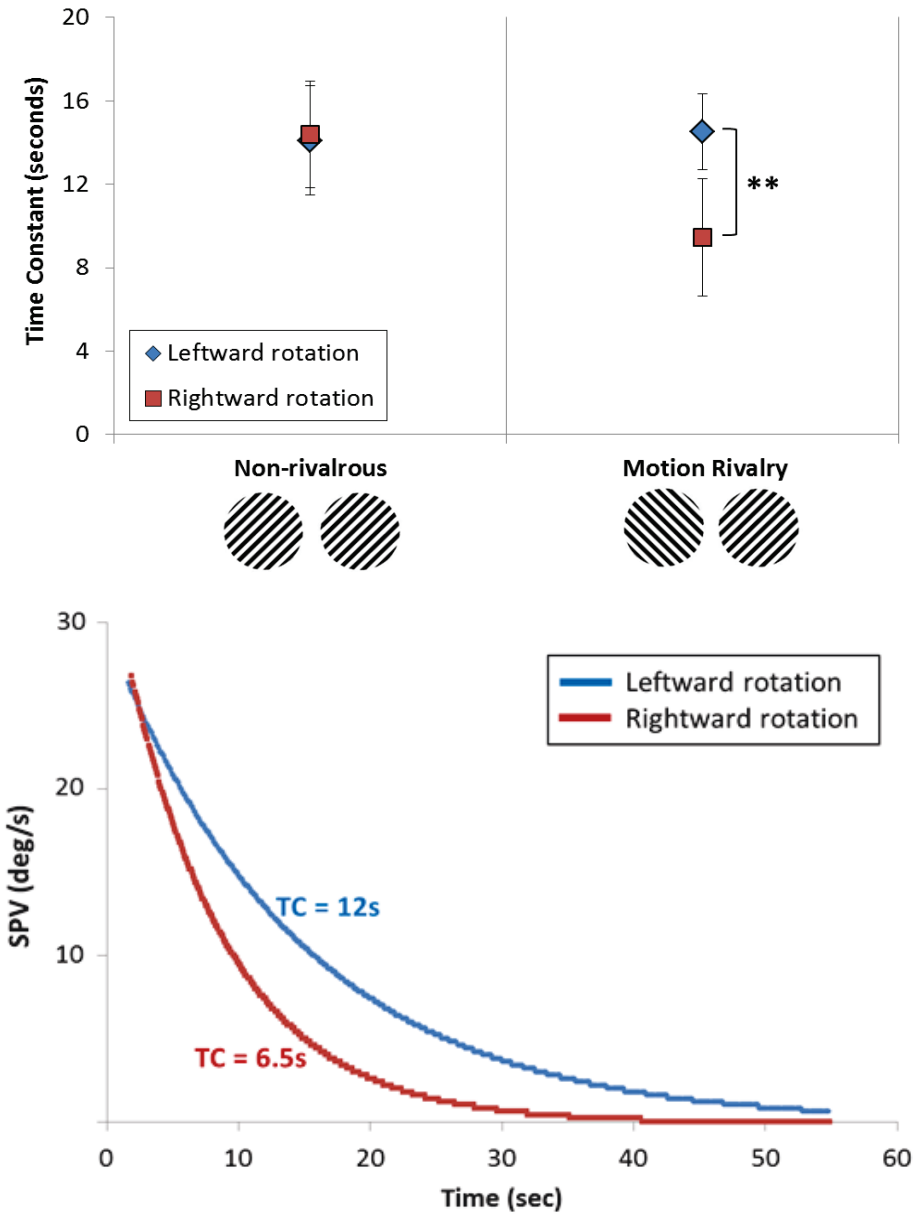


Figure 19: Results for motion rivalry condition. Top figure shows the group results. On the x axis the two conditions used, either the non-rivalrous control stimuli or the motion rivalry. Y axis represents the time constant in seconds. Red squares represent the group average VOR time constant following rightward rotation, whilst the blue diamond's represent the group average time constant following leftward rotation. Following the viewing of the control stimuli the VOR is symmetrical. Following the viewing of rivalry the VOR following rightward rotation is suppressed. Lower figure shows time on the x axis and the slow phase eye velocity on the Y axis. The curves represent the exponential eye response curve from an individual subject following the viewing of binocular rivalry (red representing the VOR following rightward rotation, blue following leftward rotation). As can be seen from the eye curves the VOR time constant following the rightward rotation is almost half that of the VOR following leftward rotation.

3.5.2 Motion induced blindness results

All 10 right handed participants demonstrated reduced TC ($p<0.001$, paired t-test; positive asymmetry index; Figure 20) following rightward rotations with a mean positive VOR_{TC} Asymmetry Index of 17.9%. In the control condition the VOR responses were symmetric ($p>0.05$, paired t-test; Figure 20). The subjects were instructed to maintain steady fixation at the centre of the screen during the 20s (leftward or rightward) rotations in both the test and control condition.

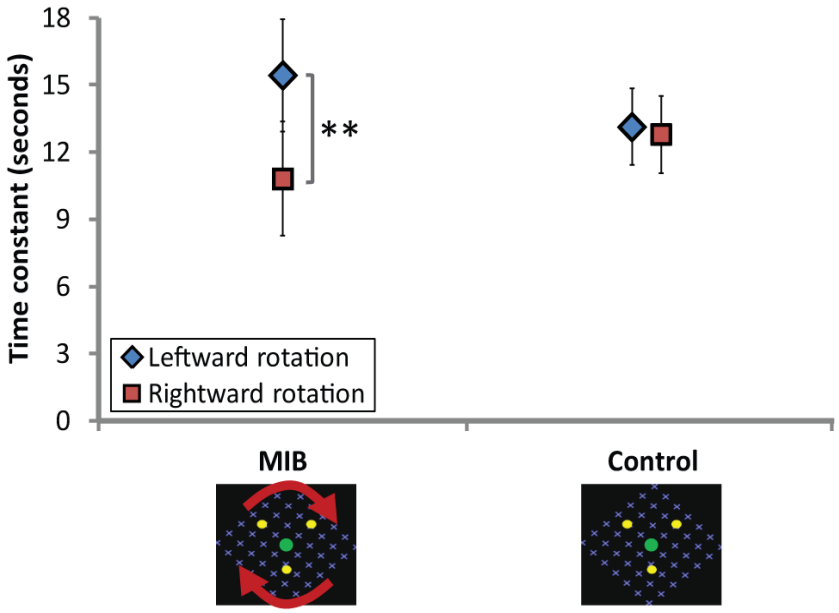


Figure 20: Results from the MIB condition. On the X axis are the two conditions, either the motion induced blindness or the control. On the Y axis are the time constant values (mean for the whole group). Blue diamond's represent the group average VOR time constant following leftward rotation and red squares represent average VOR time constant following rightward rotation. As expected the VOR time contact for the control are symmetrical following either rightward or leftward rotation. During the MIB condition we observe an asymmetrical reduction in VOR time constant following the rightward rotation.

3.5.3 Visuospatial attention task results

The control condition, in which the subjects received no task and rotated in the dark for 20s, showed symmetric VOR responses ($p>0.05$, paired t-test; Figure 21). Both high and low load visuospatial attention tasks induced asymmetric VOR TCs following rightward rotations with a mean positive VOR_{TC} Asymmetry Index of 17.5% and 4.6% respectively ($p<0.001$; $f = 126.7$; df= 1 direction; Repeated measures ANOVA). The asymmetries induced by the low load attention compared to high load were however significantly smaller ($p<0.001$, $f = 247.4$; df = 1 Load×Direction interaction; Figure 21). Inspection of the eye movement traces did not detect voluntary or 'scanning' eye movements during the attentional tasks, irrespective of the attentional load. In all traces the responses were dominated by robust patterns of vestibular nystagmus.

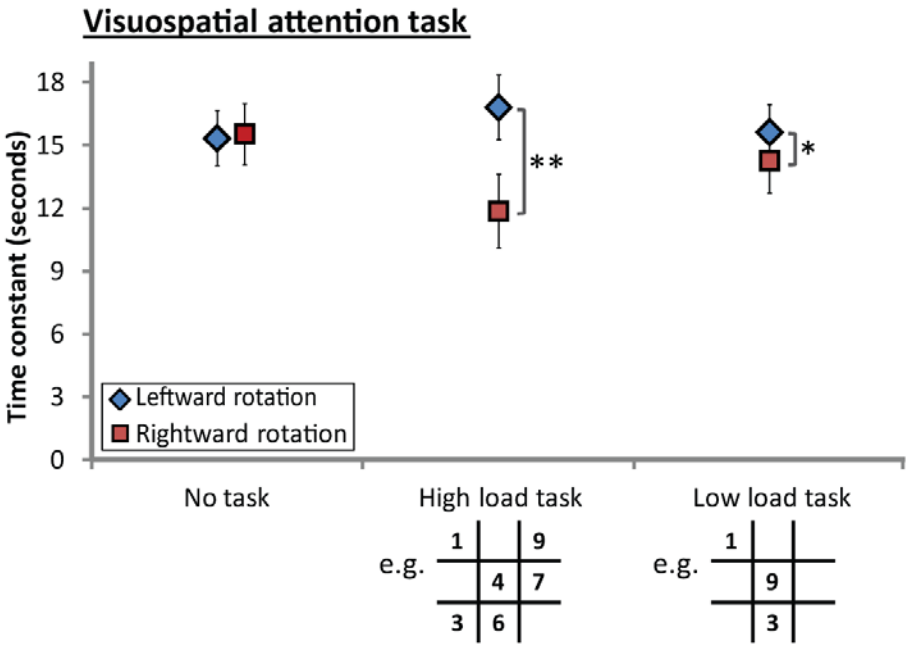


Figure 21: Results for the visuospatial attention task. On the X axis the three conditions are represented, i.e. no task, high-load task and low-load task. On the Y axis the VOR time constant is represented. In the no task condition as expected the VOR is symmetrical. In the high and low load visual spatial task condition the VOR time constant following rightward rotation is suppressed.

3.5.4 Non Visuospatial attention task results

As expected, the control condition in which no task was given showed symmetric VOR responses and neither high nor low load digit span task asymmetrically modulated the VOR p>0.05, f = 3.3; df =1; direction) and the data did not differ from the control condition (p>0.05, f = 2.5; df = 2 Repeated Measures ANOVA; Figure 22). Thus, the presence of a visuospatial component in the attentional task is a vital factor in the asymmetric modulation of the VOR; hence attention per se is not responsible.

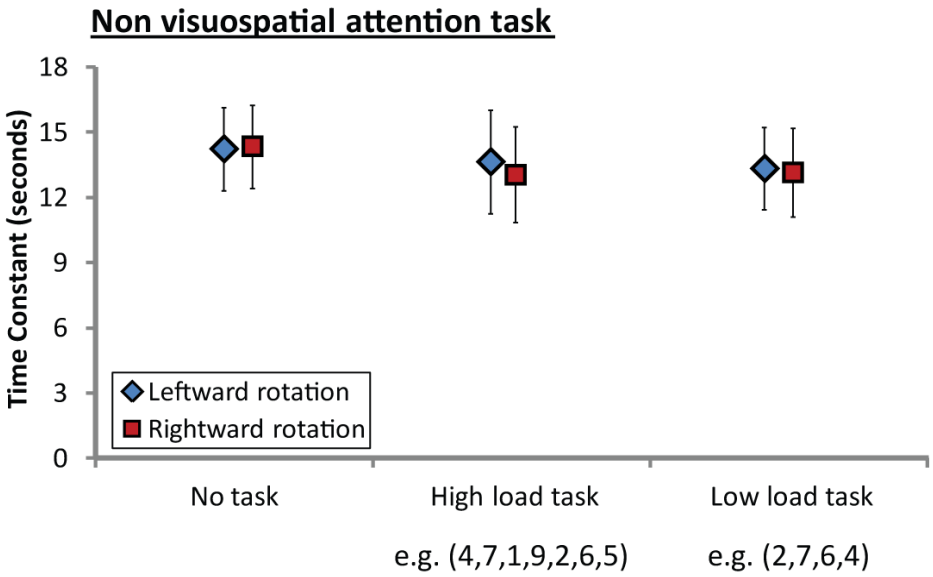


Figure 22: Results for the non visuospatial task. On the X axis the three conditions are represented. On the Y axis the VOR time constant is represented. As observed the VOR is symmetrical in all three conditions.

3.6 Lateralisation study

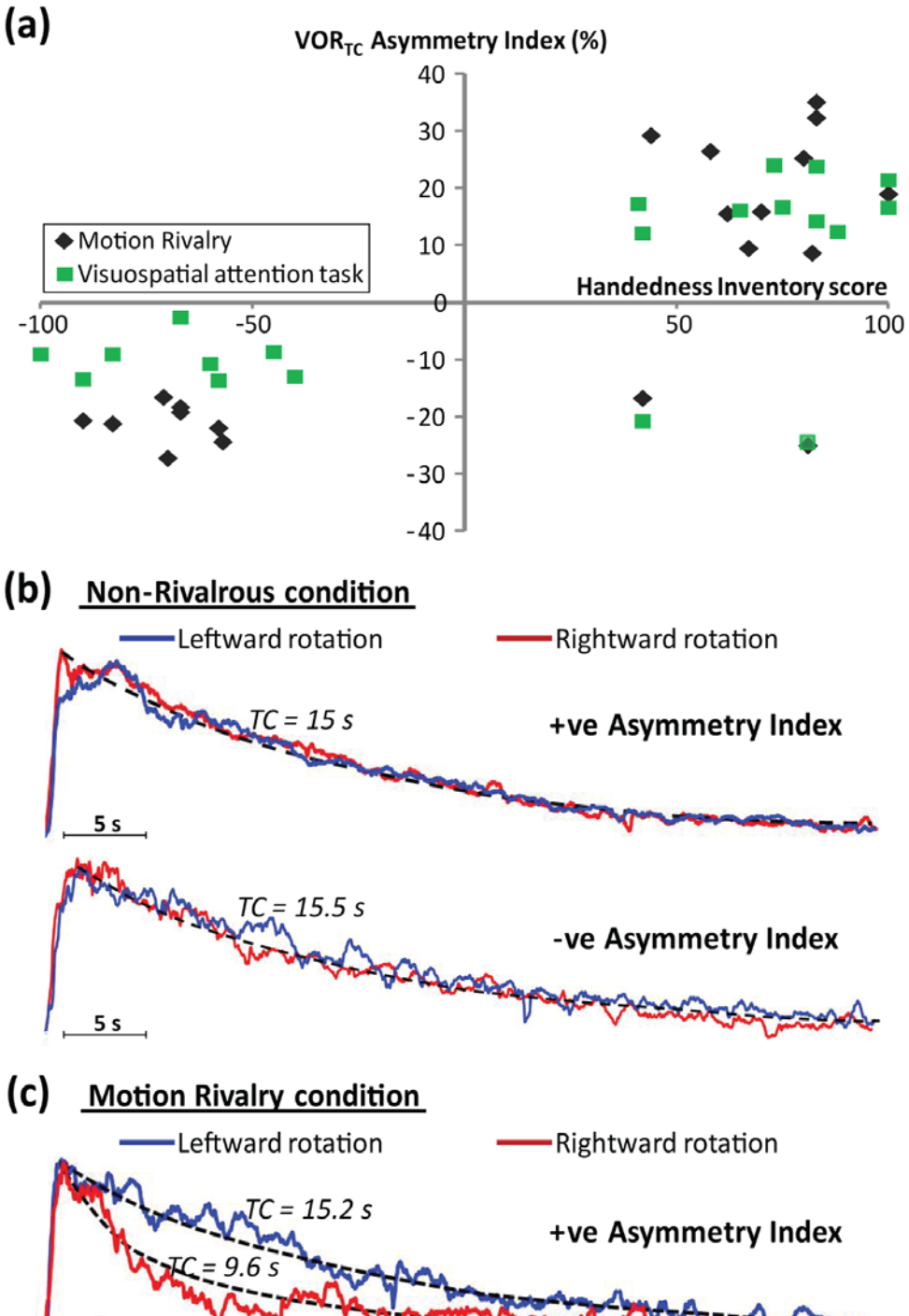
The above results show that contingent upon both perceptual transitions and attentional tasks entailing a spatial component, that they are able to modulate the oculomotor response by reducing the VOR time constant of decay following the rightward rotations compared to leftward rotations in right handed individuals. We performed a further study

using binocular motion rivalry and visuospatial attention stimuli to investigate the possible effect in left handed individuals.

Subjects participated in the motion rivalry experiment with the same experimental set up as before (Figure 15 and 17a). Two conditions were performed: motion rivalry and a control non-rivalrous condition described above (Figure 15). As expected the non-rivalrous control condition produced symmetric VOR responses ($p>0.05$, paired t-test; Figure 23b). In the rivalrous condition, the VOR was asymmetrically modulated with TCs reduced following the rightward rotations in 10 out of 12 right handed individuals ($p<0.001$, paired t-test; Figure 23C) with a mean positive VOR_{TC} Asymmetry Index of 21.7% (Figure 23 A and C). The VOR_{TC} Asymmetry Index was negative in all 8 left and the 2 right handed participants with a mean asymmetry index of -21.2%, implying that the VOR was reduced following the leftward rotations ($p<0.001$, paired t-test; Figure 23a). In the high load visuospatial task condition, the VOR was asymmetrically modulated with TCs reduced following the rightward rotations in 10 out of 12 right handed individuals ($p<0.001$, paired t-test; Figure 23a) The VOR_{TC} Asymmetry Index was negative in all 8 left and the 2 right handed participants with a mean asymmetry index of -13.5% ($p< 0.001$, paired t-test; Figure 23a). The two right handers with the negative asymmetry index were retrained left handers.

Grouping all participants in these experiments, laterality with handedness was found in 34/36 (94.1%) of subjects. In all conditions (bistable perception and attentional tasks) there was no effect on the gain of the VOR ('p' values ranging between 0.064 and 0.78; paired t-tests).

Figure 23: Results for the lateralisation study (next page). (a) X axis shows subject individuial handedness inventory scores (-100 left handed to +100 right handed). On the Y axis is represented the VOR time constant asymmetry index in percentage terms. As can be seen those individuals whom are right handed have a postive asymmetry index and those who are left handed have a negative assymmetry index. (b) Results for control condition. X axis represents time in seconds and Y axis represents the slow phase eye velocity. The red curve is the VOR exponential eye velocity curve following rightward rotation, blue curve is the VOR exponential velocity cuirve following leftward rotations. These curves represent the group grand average eye velocity curves (n=10). As expected for the control condition the VOR time constant (curves) following rightward and leftward rotations overlap.(c) In the motion rivalry condition it can be observed that suppression of the VOR time constant following rightwards rotation presents in those with a positive asymmetry index (right handers) and leftward rotation in those with a negative asymmetry index (left handers).



3.7 Discussion

Both perceptual transitions (binocular rivalry and MIB) and attention tasks that entailed a spatial component asymmetrically modulated VOR responses. The modulation observed was dependent upon the subject's handedness.

The VOR is not a rigid reflex. Its characteristics are dynamic and can be altered bi-directionally by habituation to repeated rotations, and asymmetrically in unilateral labyrinthine or CNS disease (Cohen et al., 1992, Barr, Schultheis & Robinson, 1976). Moreover, bi-directional modulation can be attributable to visual input, mental imagery and pursuit eye movements impacting upon the central velocity storage mechanism (Raphan, Matsuo & Cohen, 1979b, Barr, Schultheis & Robinson, 1976).

Both visuospatial attention and perceptual transitions (with a spatial component; see appendix of this chapter and supplemental experiment 1) asymmetrically suppressed the VOR close to the vestibular nerve time constant. This implies that these phenomena result in downregulation of the central velocity storage mechanism (Raphan, Matsuo & Cohen, 1979b). However, as both phenomena modulated the VOR in a similar manner it rules out

the possibility that pursuit eye movements or visual motion caused the downregulation of the velocity storage mechanism (for further details refer to appendix and supplemental experiments 2 and 5 respectively). Furthermore, as both phenomena are known to be processed in the cortex and, additionally, with the observed handedness dependent effect it is suggestive that higher order mechanisms are likely to be responsible for this downregulation (Dieterich et al., 2003a, Corbetta & Shulman, 2002c, Lumer, Friston & Rees, 1998a, Logothetis, Leopold & Sheinberg, 1996).

During concurrent visuospatial and vestibular activation it is likely that the brain networks involved overlap considerably for two reasons (Rees, Kreiman & Koch, 2002, Sharpe & Lo, 1981). Firstly, voluntary non-visual modulation of the VOR requires visuospatial mental imagery (Barr, Schultheis & Robinson, 1976) and such ability is particularly reduced in parietal cortical lesions (Sharpe & Lo, 1981). Secondly, spatial mental imagery and perceptual transitions generate activity in overlapping parietal areas to those that mediate prolongation of VOR responses in the non-dominant hemisphere.

Hence, irrespective of the stimulus employed the lateralised fronto-parietal attentional network is activated, in accord with the view that visuospatial attention and bistable perception call upon a common neural mechanism (Rees, Kreiman & Koch, 2002, Lumer, Friston & Rees, 1998a). Resolving bistable perception or performing visuospatial attention tasks during vestibular activation results in functional overloading of the non-dominant hemisphere with utilisation of considerable processing resources, leading to disruption of parietal interhemispheric balance (Sparing et al., 2009b). An alternative hypothesis is that the concurrent activation of the right and left fronto-parietal attentional network (right - via the rivalry viewing and/ or visuo-spatial working memory tasks, and the left hemisphere via

the left vestibular acceleration in right handers) results in conflict regarding the redirection of spatial attention with the net result being the right hemisphere suppressing the left and reducing the processing of the vestibular nystagmus.

Disruption of interhemispheric balance by the attentional demand placed upon the non-dominant parietal lobe renders it less able to contribute to the vestibular nystagmus as it continues to co-process the attentional or bistable perceptual tasks. Notably, this happens despite the absence of any physical visual stimulus, a process previously observed during binocular rivalry termed "perceptual memory"(Sterzer & Rees, 2008). The end result reduced left beating nystagmus in right handers and right beating nystagmus in left handers, which may be mediated by ipsilateral parietal descending projections to the vestibular nuclei (Ventre & Faugier-Grimaud, 1986). It would then follow that by reducing the attentional load, as in the visuospatial attention task (Lavie, 2005), more resources in the non-dominant hemisphere can be allocated to vestibular processing and, hence, the asymmetries in the VOR responses should be reduced. Indeed, we have shown this to be the case. However, this attentional load theory can still explain the conflict theory in that there is less right hemisphere activation and hence accordingly less conflict and hence less suppression of the left hemisphere and reduced asymmetries.

These results provide novel evidence that those bistable perceptual stimuli that contain a motion and hence a spatial component are able to modulate the function of a separate sensory-motor system (VOR). Furthermore, they demonstrate that the VOR is subject to handedness-related cortical modulation (Refer to appendix and supplemental experiment 6) and suggest that the central velocity storage mechanism and visuospatial processing draw upon common cortical processing resources, strongly lateralised to the non-dominant

hemisphere (i.e. 94%). Previous suggestions of lateralisation of vestibular cortical processing were based on functional imagining (Dieterich et al., 2003a) or lesion studies (Ventre-Dominey, Nighoghossian & Denise, 2003a). The latter reported suppressed time constants in the direction of the non-dominant hemisphere but normal gain (Refer to appendix and supplemental experiment 4), in line with the results reported herein. Therefore, parietal disruption either via a lesion (Ventre-Dominey, Nighoghossian & Denise, 2003b) or functional overloading (as in the work reported here; (Arshad, Nigmatullina & Bronstein, 2013a), or conflict regarding the redirection of spatial attention (this study) can down regulate the velocity storage mechanism; however the gain of the VOR can remain unchanged.

Functionally speaking, vestibular cortical processing facilitates the control of the VOR and spatial orientation. Critical for maintenance of spatial orientation is spatial attention. Insights into the neuronal mechanisms that sub-serve spatial attention have been greatly aided by observations following right parietal lesions that lead to spatial neglect (Mesulam, 1998, Kinsbourne, 1977). Following parietal disruption through functional overloading of the right hemisphere as we speculate occurs in the present study, one observes a similar inability to process the vestibular stimulus as found in right hemisphere brain damaged individuals (i.e. leftward acceleration in right handers and a more pronounced inability to process if the parietal lesions invokes visuo-spatial neglect) (Ventre-Dominey, Nighoghossian & Denise, 2003a).

Finally, it remains for us to ascribe a useful function to the VOR modulation observed above. We propose that as perceptual transitions involve a redirection of spatial attention and as spatial attention and vestibular processing share cortical resources, the conflicting

hemispheric redirection of spatial attention during concurrent visual viewing and vestibular activation may potentially disrupt spatial orientation. In order to prevent disorientation the VOR is suppressed. The asymmetrical nature of the modulation is attributable to the fact that both spatial and vestibular processing show at a cortical level dominance in the right hemisphere (Dieterich et al., 2003a, Corbetta & Shulman, 2002b, Lumer, Friston & Rees, 1998b) with these findings providing the first behavioural demonstration of this.

3.8 Appendix: Supplemental control conditions

Supplemental experiment 1: Colour rivalry and combined motion and colour rivalry

Binocular motion rivalry was found to asymmetrically modulate the vestibular ocular reflex (VOR). The aim of this supplemental experiment was to further explore this novel finding and try to ascertain whether different types of binocular rivalry (i.e. motion vs. colour) equally affect vestibular processing. In order to address this question we compared the effects of different forms of binocular rivalry upon the VOR. Here we demonstrate that motion rivalry asymmetrically modulates the VOR, whereas colour rivalry has no effect. This finding suggests that in order to asymmetrically modulate the VOR a spatial component is required for the binocular rivalry stimulus.

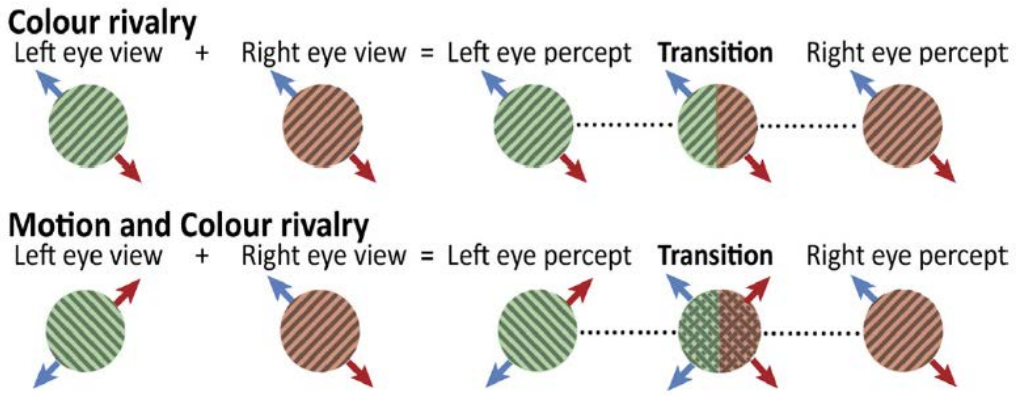


Figure S1: Visual stimuli for the colour rivalry and combined motion and colur rivalry stimulus. For the colour rivalry a blank lens of equal optical density was housed in the eyepieces to ensure no changes in spatial frquency when viewing the drum. A red filter was placed over the right lens and a green filter over the left lens. This allowed for colour rivary and examples of possible percepts during the rivalry are shown. A second visual stimulus was employed additinally wherein we combined motion and colour rivalry. As per the motion rivalry experiment a prism was set at 45 degrees in front of the right eye with an additional red coloured filter overlaid, whilst a prism was set at 135 degrees in front of the left eye with a green filter overlaid.

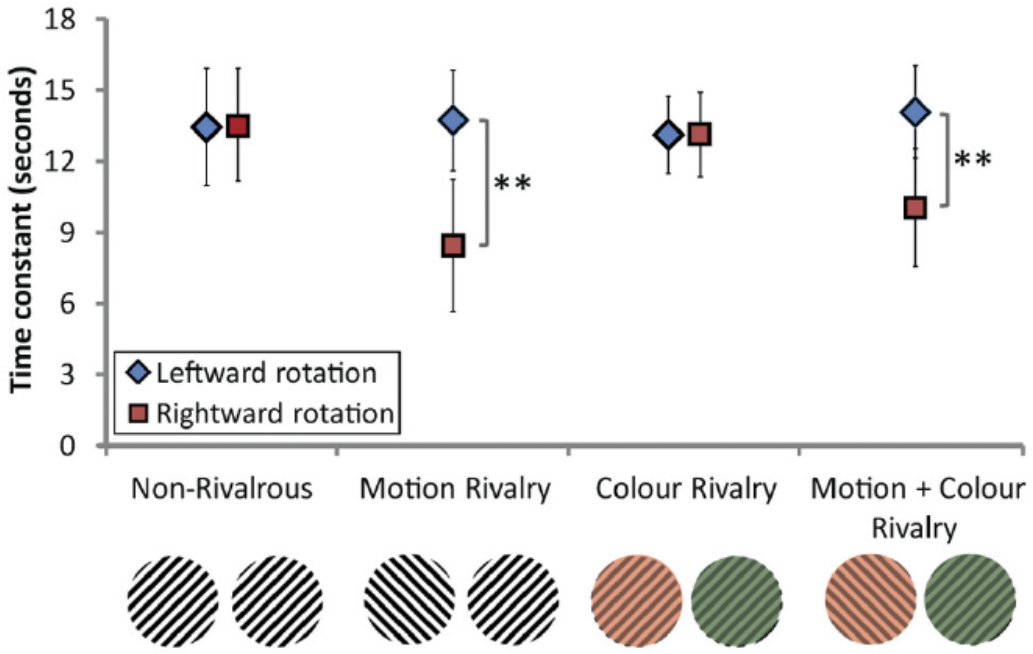


Figure S2: Results from the colour rivalry and combined motion and colour rivalry experiments. The experimental paradigm was identical to that illustrated in Figure 17A. On the x axis are represented the different conditions, whilst on the y axis is the time constant of the VOR responses. 10 new right handed participants were recruited for the colour and motion+colour rivalry condition with 5 subjects performing the colour rivalry first. As it can be observed the colour rivalry did not modulate the VOR, as demonstrated by the group average VOR time constants following either rightward (red square) or leftward (blue diamond) rotation ($p>0.05$ paired t-test).However, when motion+colour rivalry were combined we observed an asymmetrical modulation of the VOR with the VOR following rightward rotation suppressed ($p<0.001$ paired t-test). This modulation was similar to that observed in the motion rivalry alone condition as shown in the above figure. Hence, we infer that the rivalry stimulus requires a spatial component in order to asymmetrically modulate the VOR.

Supplemental experiment 2: Effects of altering visual input upon the VOR

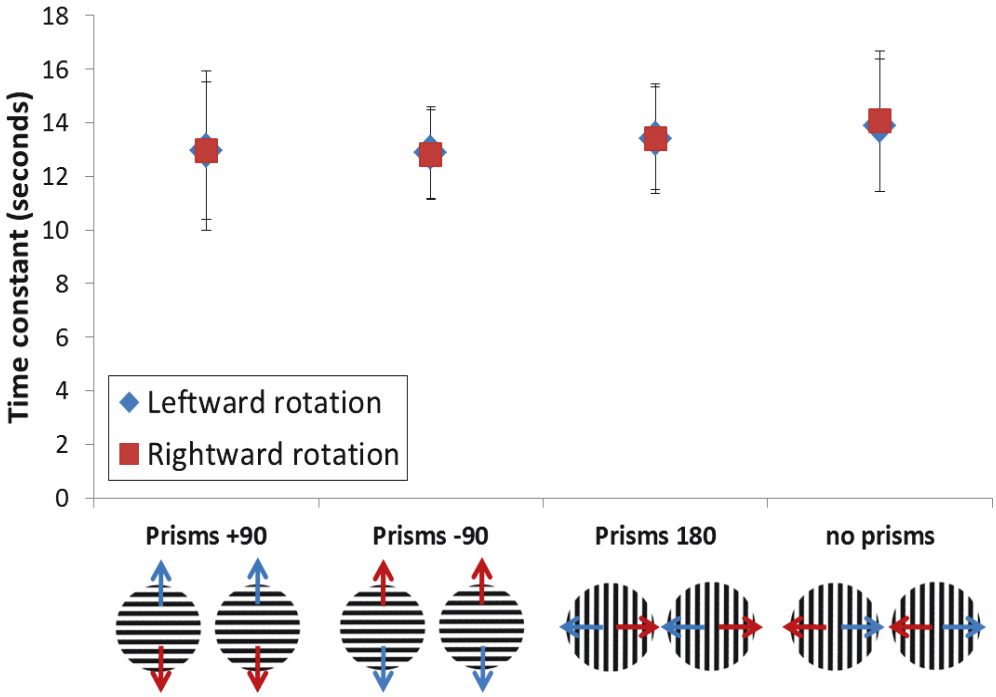


Figure S3: We performed a series of additional control experiments as per the experimental protocol outlined in Figure 17A in a new set of 20 right handed subjects to investigate the effects of altering visual input upon the VOR. However there was no binocular rivalry as both eyes received the same input, hence subjects could fuse the two images into a single coherent percept of the visual world. 4 different visual conditions were employed as shown by the X axis. In the condition when the prisms were set at 90 degrees subject perceived vertical motion (direction of vertical visual motion was dependent upon the direction of subject rotation as referenced by the red and blue arrows (red rightward rotation and blue leftward rotation)). There was a condition whereby subjects rotated with no prisms but with two blank lens of equal optical density no ensure no changes in spatial frequency of the visual stimulus and one where the reversing prisms were set at 180 degrees (i.e. visual world horizontal but inverted). On the Y axis is represented the time constant of the VOR. Red squares represent the group average of the VOR following rightward rotations (n=20) and blue diamonds represent the group average of the VOR following leftward rotations. As demonstrated (overlapping of the red

squares and blue diamonds) following 20 seconds rotation viewing the altered visual input resulted in no modulation of the VOR)P> 0.05 Repeated measures ANOVA (i.e. Symmetrical VOR). Hence, altered visual input per se or pursuit eye movements impacting upon the central velocity storage mechanism was not responsible for the modulation of the VOR.

Supplemental experiment 3: Effects of altering vestibular stimulus parameters

I performed various pilot experiments in 15 right handed subjects in order to determine the optimal vestibular parameters for rotation.

For different chair velocities employed the mean asymmetry index for the right handers was as follows for 25 second duration rotation:

For 30 deg/s = 22.7% (SD=6.6)
For 60 deg/s = 30.7%(SD=4.6)
For 90 deg/s = 35.8 % (SD=6.1)
For 120 deg/s = 29.1% (SD=6.2)
For 150 deg/s = 12.1% (SD=6.9)

Table 1: Results showing the mean asymmetry indexes that resulted by altering the chair velocity. The duration of the rotation was kept constant at 25 seconds for each of the different velocities.

Altering the duration of the rotation the mean asymmetry index for right handers was as follows for constant velocity rotations of 90 degrees/second:

For 10 seconds = 12.2% (SD=4.9)
For 20 seconds = 25.4 %(SD=6.6)

For 40 seconds = 20.9 % (SD=7.9)
For 60 seconds = 18.4 % (SD=6.1)

Table 2: Results showing the mean asymmetry indexes that resulted by altering the duration of the rotation during constant velocity rotations of 90 degrees/second.

Hence the stimulus employed for the final experiments described in chapter3 (main experiments) was a duration of 20 seconds, with a velocity of 90 degrees/second as this yielded the optimal asymmetries.

Supplemental experiment 4: Effects upon other parameters

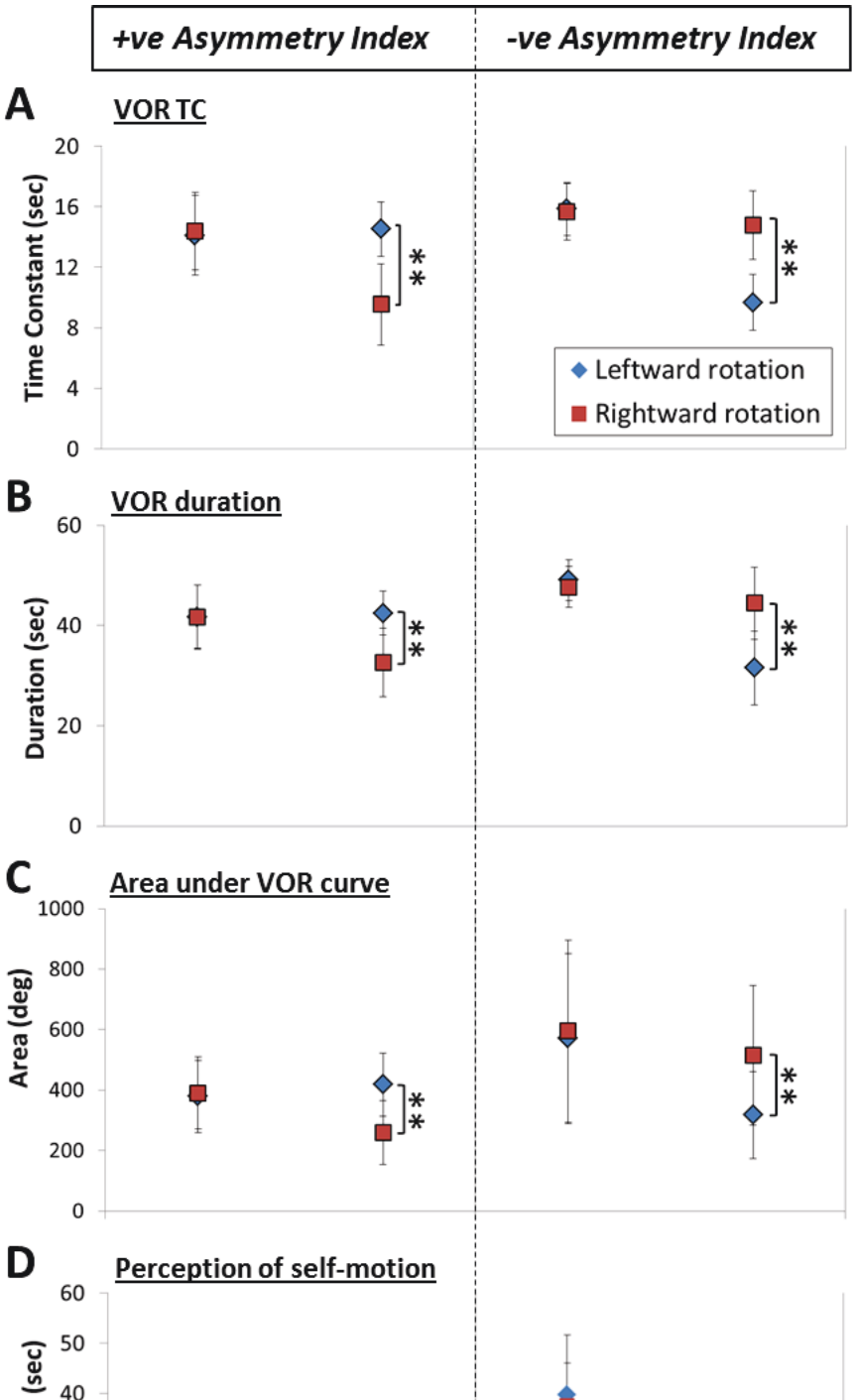


Figure S4 (previous page): A separate study in 10 right handers (positive asymmetry index) and 8 left handers (negative asymmetry index). Two conditions were employed either, a non-rivalrous control condition and rivalry. However, this time in addition to investigating the effects upon the VOR, additional analyses were performed such that we also analysed the VOR for changes in both the duration of the response and the area under the exponential curve which reflects the duration, time constant and gain. The motion rivalry asymmetrically modulated the VOR with respect to the time constant, duration and area under the curve. The modulation was such that for the right handers it was supressed following rightward rotation and following leftward rotations in left handed subjects. Notably, despite the supressed VOR, self-reported duration of perception of dizziness remain unaffected in both right and left handed subjects.

Supplemental experiment 5: Effects of fixation

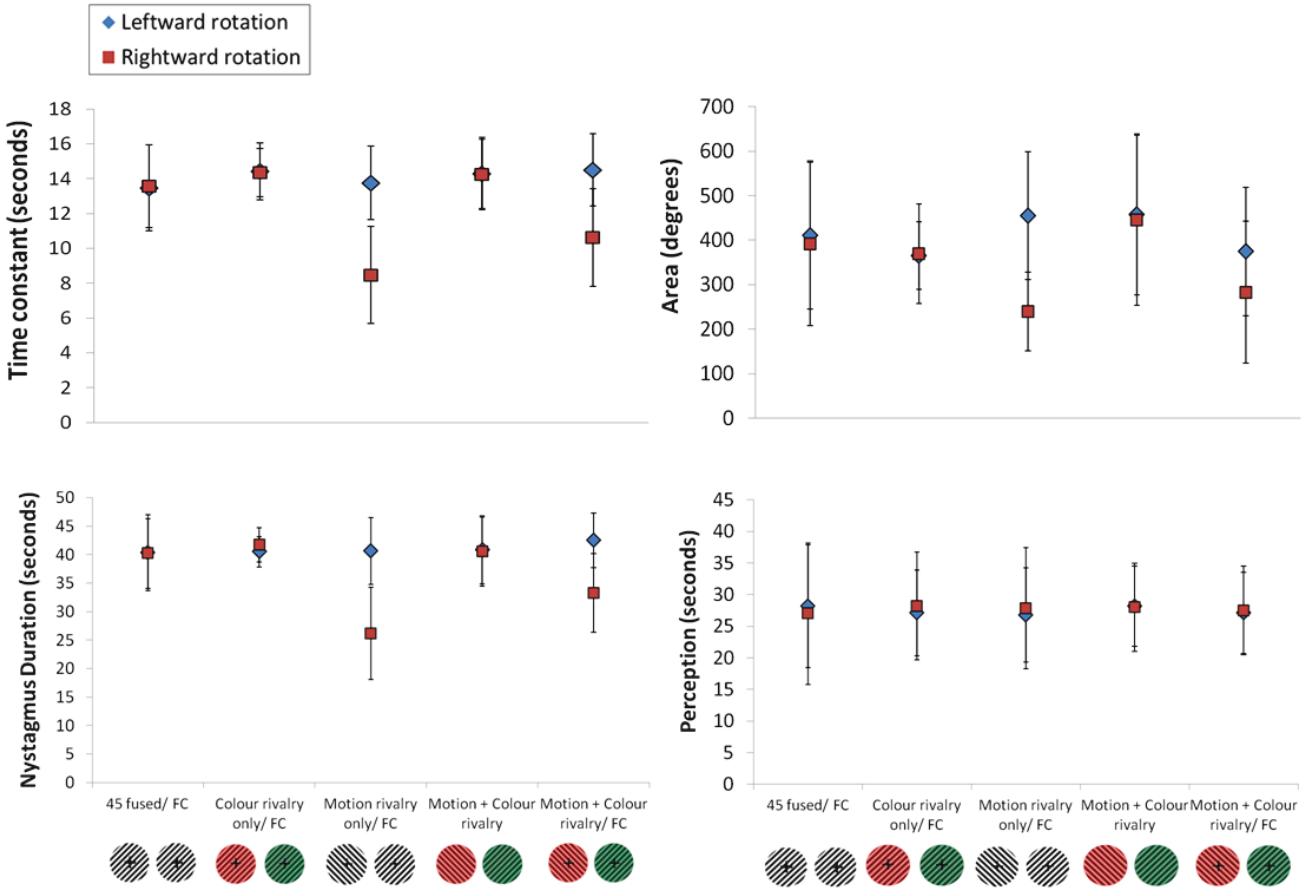


Figure S5: In order to assess the possible effects of fixation we repeated the above experiments a new set of 10 right handed subjects using a control fused condition, motion rivalry, colour rivalry and motion+colour rivalry. The experimental protocol was identical to that employed for the motion rivalry condition as outlined in Figure 17A. Additional analyses of the eye movement recordings were made such that we also analysed the VOR for changes in both the duration of the response and the area under the exponential curve as outlined in supplemental experiment 4. The results were comparable to those without fixation in that binocular rivalry+cross condition and motion+colour rivalry+cross asymmetrically modulated the VOR. Formal measures

of vestibular perception remained unchanged across all conditions, as measured by self-reported lengths of perceived rotation. .

Supplemental experiment 6: Computational model of the velocity storage mechanism

The above experimental results indicate that disruption of cortical interhemispheric balance leads to an asymmetric response of the vestibular-ocular reflex. In this section we propose a minimal modification of velocity integrator model (Figure 6) to account for the asymmetric response.

Let's recall the modelling approach used in figure 6 (or refer to figure S8) (Raphan, Matsuo & Cohen, 1979b).For simplicity we will only consider the case of rotation in complete darkness eliminating the need for accounting for visual input (indeed this is the case in the experiment as the suppressed VOR that is recorded, is measured in darkness). The task of the model is to predict the slow phase eye velocity as a function of time during rotation of the subject at a particular velocity. The rotation of the subject results in the stimulation of the eye via two pathways: direct stimulation by the cupular signal and indirect stimulation via the "velocity storage". The model was formulated in terms of the following equations

$$y(t) = x(t) + cf(t) \quad (1)$$

$$\frac{dx}{dt} = -ax + f(t), \quad (2)$$

$$f(t) = b\exp\left(-\frac{t}{T_c}\right). \quad (3)$$

Here y(t) is the eye velocity; it is a sum of the signals from the direct pathway cf(t) and from the velocity integrator, x(t). The variable x is referred to as the VOR (Raphan, Matsuo & Cohen, 1979b). f(t) is a function proportional to the cupula signal, a is a parameter

influencing the velocity storage, b is a parameter related to the velocity of rotation of the subject and Tc is a decay constant for the cupula signal. The solution to the differential equation (2) is

$$x(t) = \frac{T_c b}{aT_c - 1}\left(e^{-at} - e^{-t/T_c}\right), \qquad (4)$$

And hence the evolution of eye phase velocity is given by

$$y(t) = cb\exp\left(-\frac{t}{T_c}\right) + \frac{T_c b}{aT_c - 1}\left(e^{-at} - e^{-t/T_c}\right). \quad (5)$$

Figure S6 shows a plot of the cupula dynamics, the VOR state and the phase eye velocity (equations (3),(4) and (5)). As shown, initially the slow phase eye velocity is mainly due to the direct stimulation from the cupula. The cupula signal also “charges” the integrator. As time progresses the cupula stimulation decreases and the slow phase eye velocity is mainly due to the stimulation from the velocity storage integrator.

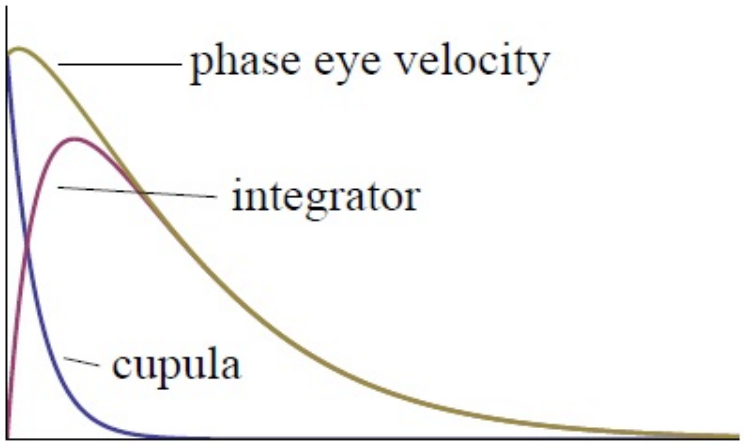


Figure S6: Velocity storage model. Phase eye velocity represented as a function of time, with the parameters implemented as follows, a= 0.06, b =2.2, Tc =4 and c=1.

Now we consider the modification to the velocity integrator that leads to a response which depends on the direction of the rotation of the subject i.e. on the sign of the cupula signal. Physically, this modification could be a result of the interaction between the brainstem and the cortex. The modification involves an addition of a quadratic term to the velocity storage differential equation. The model is expressed using the following equations

$$y_L^R(t) = x(t) + cf_L^R(t), \quad (6)$$

$$\frac{dx}{dt} = -ax + \alpha x^2 + f(t), \quad (7)$$

$$f_L^R(t) = \pm\, b\exp\left(-\frac{t}{T_c}\right), \quad (8)$$

where $f_L^R(t)$ is the cupula signal in the case of clockwise/anticlockwise rotation, $y_L^R(t)$ is the eye phase velocity in the case of clockwise/anticlockwise rotation and α is the "handedness" parameters. When α = 0 then the model reduces to the symmetric case described in the previous section. When α > 0 the phase eye velocity for the rotation to the left decays more slowly than for the rotation to the right. For α < 0 it is exactly the reverse phase eye velocity for the rotation to the right decays more slowly than for the rotation to the left. Figure 2 shows the results of the simulations for several different values of α and the phase eye velocities (note that on the graph the magnitude of the phase eye velocity is shown; naturally, responses for the clockwise and anticlockwise rotations have opposite signs). The analytic solution of the differential equation (7) is possible, but has a rather complicated form so it is probably just as instructive to solve the equation numerically and plot the solution on a graph as shown in figure S7 below.

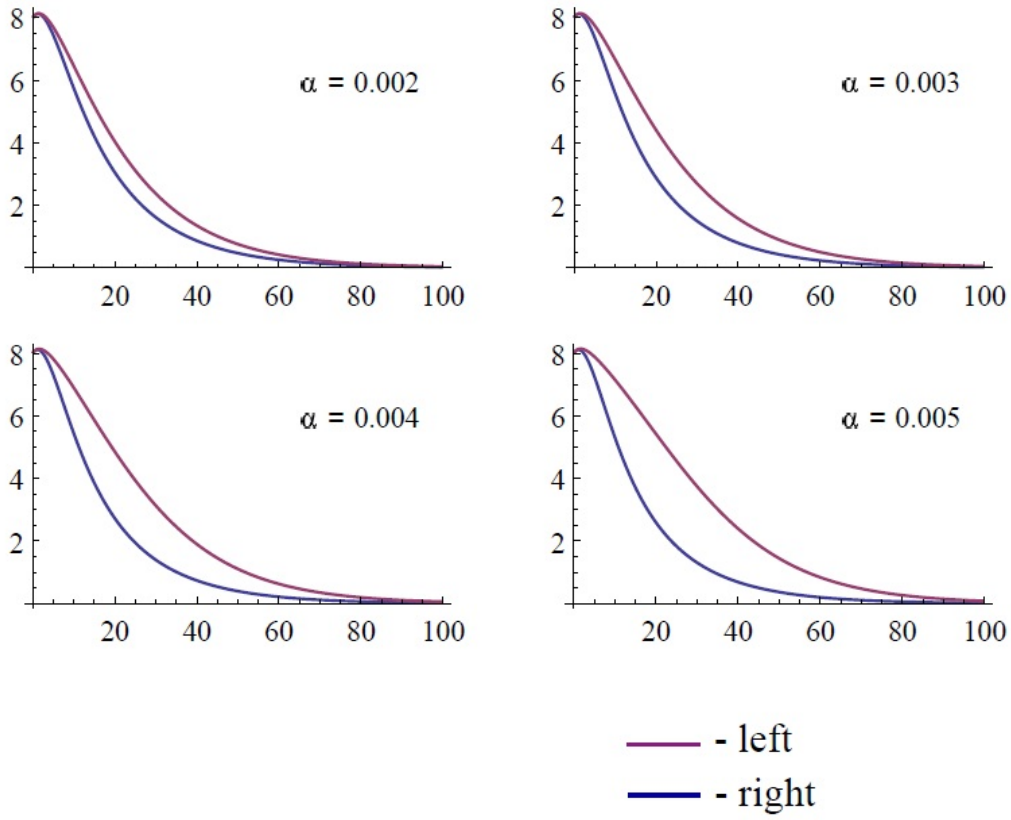


Figure S7: Computation simulation (modelling the asymmetric VOR response in right handed individuals). Magnitude of the phase eye velocity is shown by the curve as a function of time for the cases of rotation to the right (blue line) or to the left (purple line). The 4 different tables show the change in the phase eye velocity as a results of changing the "handedness" parameter i.e. the alpha values as shown from values ranging from 0.002 to 0.005. All other parameters were kept in accord with the original model (Figure 7) and as shown in Figure S6 (i.e. a=0.06, b=2.2, Tc=4 and c=1.

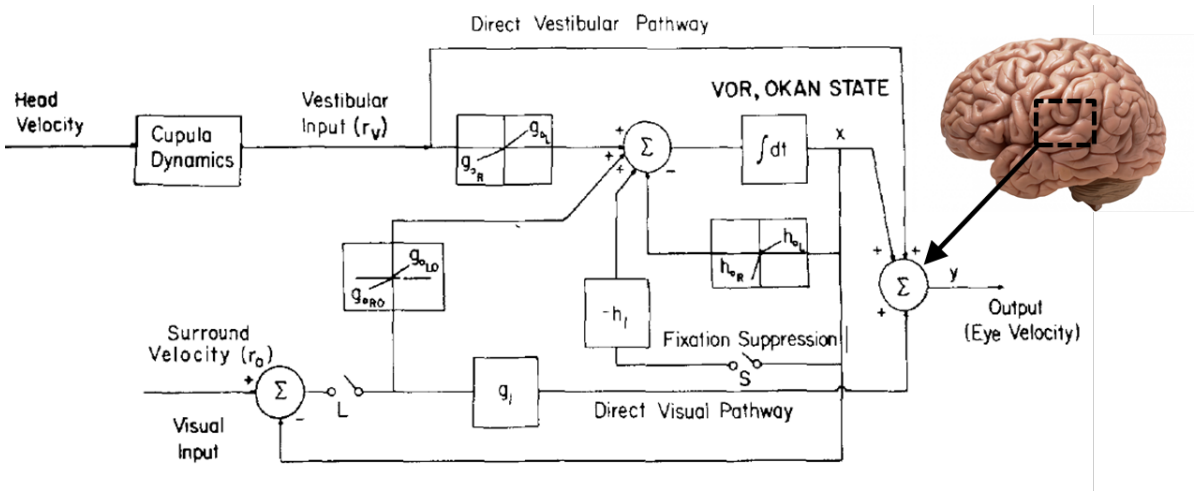


Figure S8 (previous page)**:** A revised model for the velocity storage mecahnism including the new "handedness" input represented by the black line which correspondingly recieves input from the parietal lobe.

Chapter 4: Experiment 2- Neuro-modulation of the vestibular-ocular reflex: Role of inter-hemispheric parietal balance

4.1 Synopsis

Multi-sensory visuo-vestibular cortical areas within the parietal lobe are important for spatial orientation and possibly for modulation of the brainstem pathways of the vestibular-ocular reflex (VOR). Functional imaging and lesion studies suggest that vestibular-cortical processing is localised primarily in the non-dominant parietal lobe. However, the role of inter-hemispheric parietal balance in vestibular processing is poorly understood. Indeed, the previous experimental chapter suggested a possible role of parietal balance in vestibular cortical processing. Therefore, we tested whether experimentally induced asymmetries in right versus left parietal excitability and thus disrupting parietal balance would modulate vestibular function. VOR function was assessed in right-handed normal subjects during caloric ear irrigation (30^{o}C), before and after transcranial direct current stimulation (tDCS) was applied bilaterally over the parietal cortex. Bilateral tDCS with the anode over the right and the cathode over the left parietal region resulted in significant asymmetrical modulation of the VOR, with highly suppressed responses during the right caloric irrigation (i.e. left beating nystagmus). In contrast, we observed no VOR modulation during either cathodal stimulation of the right parietal cortex or SHAM tDCS conditions. Application of unilateral tDCS revealed that the left cathodal stimulation was critical in inducing the observed modulation of the VOR. We show that disruption of parietal inter-hemispheric balance can induce asymmetries in vestibular function.

Aims & Hypothesis

In the previous experimental chapter we speculated that concurrent visual and vestibular stimulation overloaded the right hemisphere and induced an asymmetric modulation of the vestibulo-ocular reflex. In this chapter we directly test the hypothesis that overloading is directly responsible for the modulation. We modulated cortical excitability using tDCS to boost the right hemisphere and supress the left hemisphere and subsequently ascertain if this montage impacts upon the vestibulo-ocular reflex to support or disprove our hypothesis formulated at the end of the third experimental chapter.

4.2 Background

In the previous experimental chapter, we demonstrated that concurrent vestibular activation and redirection of spatial attention resulted in a handedness related asymmetrical modulation of the VOR (Arshad, Nigmatullina & Bronstein, 2013a). It was postulated that the asymmetry observed was attributable to a disruption of parietal inter-hemispheric balance via overloading of the right hemisphere. However, as the previous experiment was purely a behavioural experiment the hypothesis that we proposed was merely speculative.

Indeed the observation that the supressed VOR was found when rotating in the direction of the non-dominant hemisphere, tallied nicely with the results presented in the single case report of the observed changes in the VOR of patients with posterior parietal lesions (Ventre-Dominey, Nighoghossian & Denise, 2003a). Moreover the fact that we observed a handedness related modulation is highly indicative of higher order parietal mechanism likely to be responsible for the modulation.

In order to directly test the hypothesis that disruption of parietal balance induced asymmetrical VOR responses, one must manipulate directly parietal function (Ventre & Faugier-Grimaud, 1986). One can modulate relative excitability of the brain via non-invasive application of low density current applied to the scalp.

Trans-cranial direct current stimulation (tDCS) has previously been shown to modulate cortical excitability through the induction of transient changes in local field polarity (Cohen Kadosh et al., 2010), thus has emerged as an effective technique in order to induce bi-directional polarity dependent alterations in excitability (Nitsche & Paulus, 2000), with demonstrable changes in neurophysiology and motor function.(Nitsche et al., 2005, Nitsche & Paulus, 2000). Moreover, concurrent application of opposite polarity stimulation over parietal regions has been reported to alter the parietal balance between the two hemispheres (Cohen Kadosh et al., 2010, Sparing et al., 2009a).

Attempts to investigate the effects of electrical stimulation upon brain function is not a new phenomenon, as there are reports of eminent Roman and Arab scientists (Kellaway, 1946) placing electric fish over the scalp in order to relieve headache and epilepsy respectively. However with the advent of electricity (more specifically the electrical battery) it allowed the possibility to investigate the potential effects of direct current stimulation upon brain function. Indeed the first demonstration of a vestibular cortical area in humans corresponding to the anterior tip of the intra-parietal sulcus was demonstrated via electrical stimulation, albeit through direct invasive stimulation during brain surgery (Penfield, 1957).

An important differentiation needs to be drawn between tDCS from other neuro-modulation techniques such as Trans-cranial magnetic stimulation (TMS). tDCS does not induce neuronal firing unlike TMS, which is attributable to supra-threshold neuronal membrane depolarisation (Priori, Hallett & RothIll, 2009, Nitsche et al., 2008). Rather tDCS acts by modulating the spontaneous activity of the neurones (Priori, Hallett & RothIll, 2009, Nitsche et al., 2008). In the main anodal stimulation excites and cathodal stimulation supresses excitability, conclusions which have been drawn from animal studies. These

studies demonstrate changes in excitability which can be linked to the modulation of the spontaneous firing rate of neurones and their responsiveness to afferent synaptic inputs (Bikson et al., 2004, Jefferys, 1981). Thus, it is thought that it is this primary polarisation mechanism that underlies the effects of low-intensity direct current stimulation upon cortical excitability during tDCS (Priori et al., 1998).

Application of tDCS for a duration of 15 minutes can produce lasting effects upon cortical excitability with a temporal duration in the magnitude of around one hour (Wagner et al., 2007). Thus such relative long lasting effects cannot solely be explained by changes in spontaneous firing rates of neuronal populations. tDCS studies have demonstrated that stimulation can also modulate synaptic strength of MMDA receptors and/or alter GABAergic activity (i.e long term potentiation) (Stagg et al., 2009, Nitsche et al., 2004, Liebetanz et al., 2002). An alternative explanation to explain the long term effects of tDCS is that it can be considered to result as a consequence of the electric field displacing the polar molecules thus affecting neurotransmitters and receptors in the brain that possess electrical properties. Thus, it may well be the case that tDCS additionally influences brain activity (excitability levels) by inducing alteration to the neuro-chemical balance (Stagg et al., 2009).

The above mechanisms of action are direct mechanisms by which tDCS is possibly acting. It is additionally proposed that there exists indirect mechanism such that connectivity driven alterations of distant cortical and subcortical areas results (Matsunaga et al., 2004) (Stagg et al., 2009). Additionally, tDCS does not merely modulate excitability by modulating spontaneous activity of neuronal activity but intriguingly it is able to modulate neuronal oscillations. For example, changes in neuronal oscillations have been found to occur

beneath the cathodal electrode with changes in slow EEG activity presenting as an increase in activity in the theta and delta band range (Nitsche et al., 2005).

Much of the work using tDCS has been used to probe motor cortical function (Nitsche et al., 2005, Nitsche & Paulus, 2000), although it has also been shown that tDCS can also induce long-lasting alterations in somato-sensory potentials and visual-evoked potentials (Accornero et al., 2007, Antal et al., 2004, Matsunaga et al., 2004).

Recently it has been successfully shown that application of bi-hemispheric parietal tDCS temporarily alleviates spatial neglect in patients following posterior parietal lesions (Sparing et al., 2009a). The top-down modulation of the VOR that was observed in the previous experimental chapter was speculated to be attributable to disruption of parietal hemispheric balance (Arshad, Nigmatullina & Bronstein, 2013a). We now seek to modulate relative excitability levels directly in the parietal lobes of left and right hemispheres with tDCS. Such application will induce parietal lobe imbalance and subsequently it will allow me to assess any potential effects upon the VOR.

4.3 Material and Methods

4.3.1 tDCS Stimulation

Stimulation was applied using a battery driven stimulator (neuroConn GMBH, ilmenau, Germany). The current had a ramp up time of 10 seconds at which point a constant current of an intensity of 1.5mA was applied for a total duration of 15 minutes, after which the current ramped down in a 10 second fade out period, in line with current safety guidelines.

For anodal stimulation of the right parietal cortex the anodal electrode was placed over P4 (international 10-20 system for EEG electrode placement, area 25 cm^2), whilst the cathode

(area 25 cm^2) was placed over the left P3 (right-anodal/left-cathodal condition). Reciprocally, anodal stimulation of the left parietal cortex involved the anodal electrode placed over the left P3 and the cathodal electrode placed over the right P4 (left-anodal/right-cathodal condition). This montage has previously been shown to be successful in inducing parietal asymmetries (Bardi et al., 2013). For the SHAM condition the electrodes were placed over analogous target areas as for the tDCS condition (right anodal over P4) (Figure 24). However, in the SHAM stimulation condition the stimulator was ramped down after 30 seconds ensuring that the initial sensation of the tDCS and SHAM condition did not differ without providing any actual stimulation.

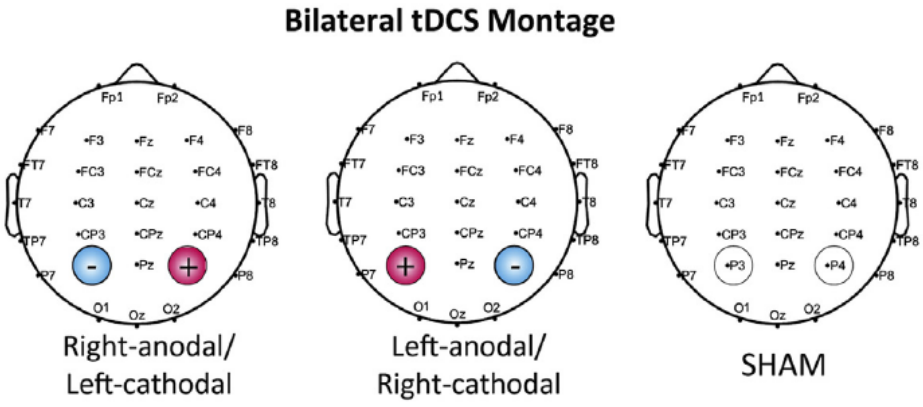


Figure 24: tDCS montage for the bilateral experiment. Three conditions were employed. Right parietal anodal stimulation, left parietal anodal stimulation and SHAM.

In order to isolate any potential active electrode in any possible modulation of the VOR by the bilateral tDCS stimulation (concurrent application of opposite polarity stimulation) we employed a unilateral tDCS condition. This involved application of either right anodal or right cathodal stimulation over P4, or left anodal or left cathodal stimulation over P3 (i.e. right-anodal, right-cathodal, left-anodal, left-cathodal conditions; Figure 25). The reference electrode in all four conditions was placed on the ipsilateral shoulder (deltoid muscle) (Bardi et al., 2013). In order to reduce irritation and maximise subject comfort a larger reference

electrode was used (area 35 cm^2). Otherwise, the stimulus parameters for the tDCS were the same as for the bilateral stimulation.

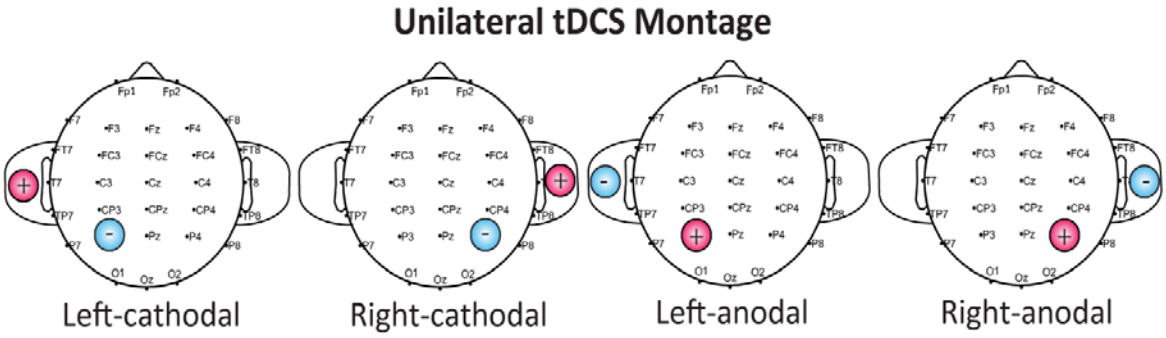


Figure 25: tDCS montage for the unilateral experiment. Four conditions were employed. Right anodal, left anodal, right cathodal and left cathodal parietal stimulation. Note in all conditions the reference is placed on the ipsilateral deltoid muscle (shoulder).

4.3.2 Vestibular stimulation

Following otoscopy, to exclude local contra-indications, subjects underwent caloric irrigation. The participants lay supine on a couch with the head tilted at 30^o to obtain maximal activation of the horizontal semi-circular canals (Barnes, 1995). The external auditory meatus was irrigated with water at 30^oC (cold water) at a rate of 500 ml/min for 40 seconds (CHARTR VNG; ICS medical) (10). The onset of vertigo occurs approximately 20 seconds after the start of the irrigation reaching a peak at around 60 seconds. The total duration of the response lasted on average 3 minutes (Barnes, 1995).

In response to the caloric vestibular activation an oculomotor response (VOR in the form of 'vestibular nystagmus') is elicited: e.g. the right cold caloric results in left beating nystagmus with a rightwards slow phase and vice versa (Figure 27).

4.4 Subjects and Data analysis

Twenty right handed subjects (14 male, mean age 25.6 years, range 19-35) without any brain stimulation contra-indications, nor history of labyrinthine or neurological disorder and naive to the purpose of the study provided written consent to take part in the study as directed by the local ethics research committee. The 20 subjects were equally split into two groups. The first set of 10 subjects (8 males) participated in the bilateral tDCS experiment whilst the fellow set of 10 subjects (6 males) took part in the unilateral tDCS experiment.

Eye movements were recorded using a head mounted infra-red binocular video-oculography (VOG) system (CHARTR VNG; ICS medical). Analyses of eye movements were performed using a computerised automatic analysis programme (CHARTR VNG; ICS medical) that removes the quick phases (saccades) of the nystagmus and plots the slow phase velocity of the eye movement over a period of 100 seconds (rightwards slow phase for right cold caloric and vice versa). The automated analysis programme required subjects to initially perform an eye movement calibration by following a pursuit target. Response intensity was determined by the peak slow phase eye velocity (SPV). Right cold water induces left beating nystagmus, whilst left cold water induces right beating nystagmus respectively (Barnes, 1995).

4.5 Experimental protocol

In the bilateral experiment each participant underwent 3 randomised sessions (right-anodal/left-cathodal, left-anodal/right-cathodal or SHAM), separated by a minimum of 4 days to minimise any potential tDCS carry over effects and any possibility of vestibular habituation. Each session began with two caloric tests (right and left ear randomised), in order to establish the pre-stimulation oculomotor response. The irrigations were separated

by a period of 5 minutes to allow for after effects to subside. After the pre-stimulation caloric response, tDCS was applied for 15 minutes. Following tDCS, two further caloric irrigations (one per ear) were performed in order to obtain the post-tDCS caloric response. Thus, each subject was tested on 3 separate occasions and within each session each subject underwent 4 caloric irrigations (two per ear) in total.

In the unilateral experiment each participant underwent 4 randomised sessions in accord with a balanced experimental design (right-anodal, right-cathodal, left-anodal or left-cathodal), with each condition separated by a minimum of 4 days. Otherwise, the experimental procedure was identical to that implemented in the bilateral tDCS experiment.

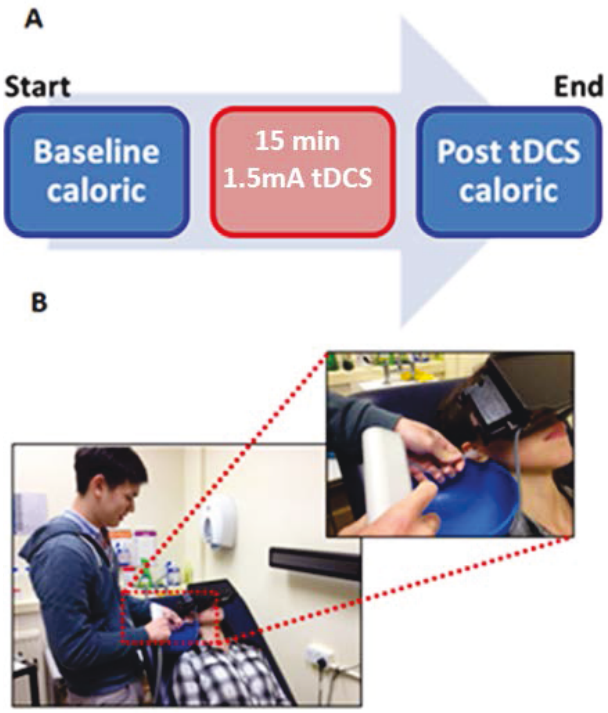


Figure 26: tDCS Experimenetal protocol. We firstly established baseline measures of the VOR using a caloric and then applied 15 minutes of tDCS. Following the application of direct current we measured again the VOR in response to a caloric.

4.6 Statistical analysis

The analysis was a within-subject repeated measures (ANOVA), using the peak of the slow phase velocity (SPV) of the VOR response. The ANOVA comprised the within-individual

factors tDCS (right-anodal/left-cathodal, left-anodal/right-cathodal, SHAM); laterality of caloric (left, right) and time (before, after tDCS).

I used the percentage change in baseline SPV to perform a within-subjects repeated measures ANOVA with factors tDCS (cathodal or anodal); laterality of caloric (left or right), and stimulation side (left or right).

For both stimulation conditions, post hoc tests were applied using Bonferroni corrections for multiple comparisons, differences were considered significant at a level of $P<0.05$. Sphericity in the ANOVA model was examined for using Mauchley's test. For non-spherical data the Greenhouse–Geisser correction was used. Statistical analyses were performed using SPSS 20.

Across all participants in both tDCS conditions and the SHAM condition the baseline peak VOR response for the caloric was symmetrical (i.e. right versus left) as expected ($p>0.05$).

4.7 Results for the bilateral condition

Post hoc paired t-tests demonstrated a significant reduction in rightwards slow phase velocity (right caloric) following right-anodal/left-cathodal tDCS condition ($t(9)=6.2$, $p<0.001$, corrected; Figure 27). We observed a marked suppression of the VOR response in all 10 participants with a mean percentage reduction of 40% in the slow phase velocity (Figure 27 A.B and C). There was no significant change in the VOR response attributable to the left caloric following right-anodal/left-cathodal parietal stimulation ($p>0.05$). The VOR response was symmetrical following either SHAM or left-anodal/right-cathodal tDCS stimulation ($p>0.05$). Thus, bilateral right-anodal/left-cathodal tDCS stimulation of the parietal cortex

induced an asymmetrical VOR response with reduction of the rightward slow phase velocity in response to the right caloric (Figure 27 A,B and C).

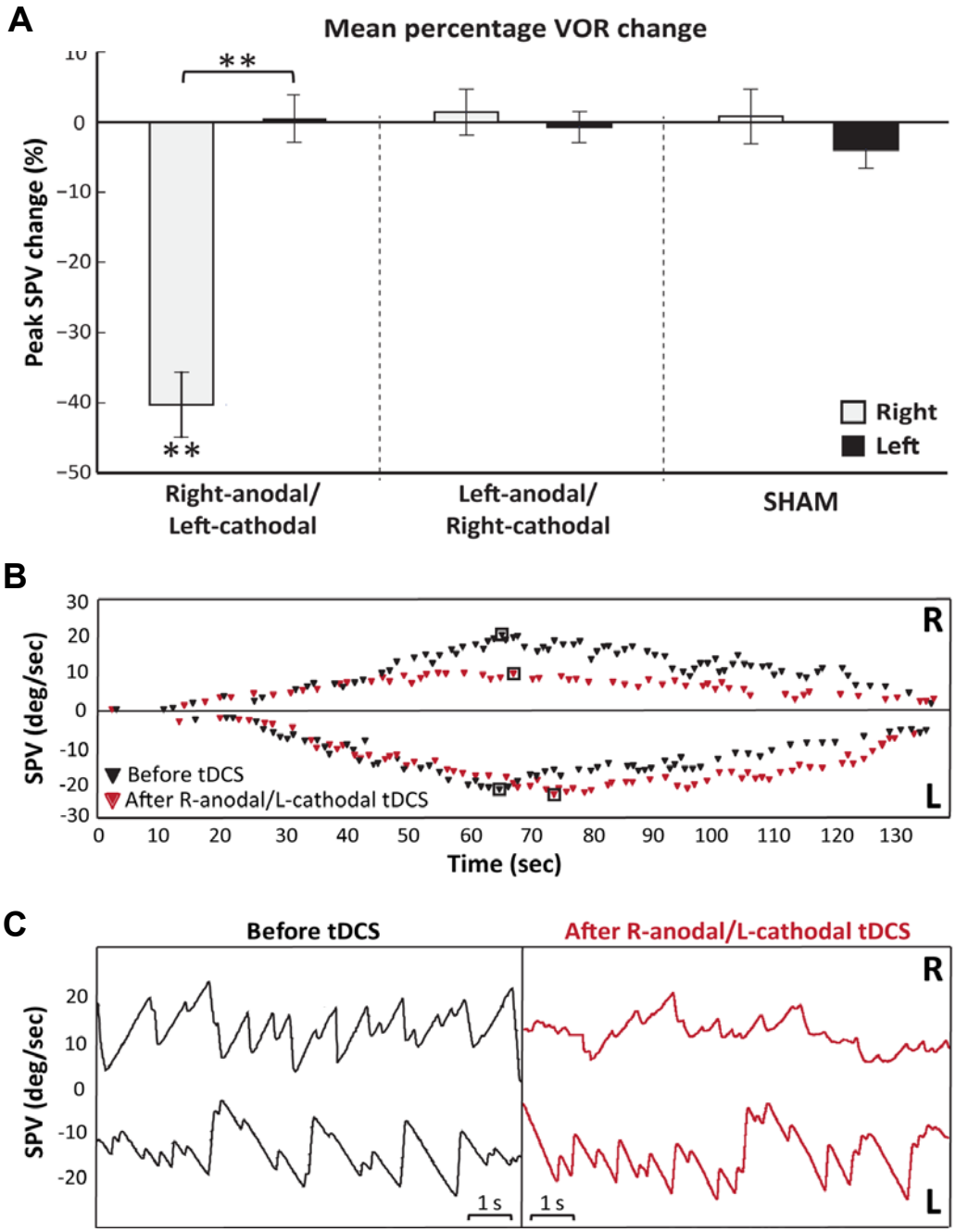


Figure 27: Results from the bilateral tDCS experiment. Panel (A) on the x axis we have the three conditions right anodal, left anodal and SHAM. On the y axis is the % change in peak SPV in the VOR following

application of tDCS. As one can observe, neither left anodal nor sham modulated the VOR. However, following right anodal stimulation a marked reduction was observed for the right cold caloric. Panel (B) X axis shows the time and on the y axis is the slow phase eye velocity; positive values rightwards slow phase and negative values leftwards slow phase. Red and black dots represent the slow phase velocities; black dots before tDCS and red dots after tDCS. The lower panel represents the response for the left caloric and as we can see the red dots and black dots overlap (i.e. no modulation). However for the right caloric we can see the response of the red dots is suppressed in comparison to the black dots representing suppression of the VOR. Panel (C) Raw traces of vestibular nystagmus. The response following right caloric and tDCS (red trace upper panel) is markedly suppressed.

4.8 Results for the unilateral experiment

In the unilateral stimulation conditions, cathodal stimulation of the left parietal region (left-cathodal) induced a reduction of VOR response to both left and right caloric. ANOVA with tDCS (two levels), tDCS stimulation side (two levels) and laterality of caloric (two levels) showed a significant main effect of tDCS type ($F[1,7]=32.9$, $p<0.001$) and stimulation side $F[1,7]=30.2$, $p<0.001$). There was a significant interaction of tDCS type*stimulation side ($F[1,7]=57.5$, $p<0.001$), stimulation*laterality of caloric ($F[1,7]=9.49$, $p<0.018$) and tDCS type*stimulation side*laterality of caloric ($F[1,7]=38.4$, $p<0.001$). A post hoc paired t-test (2-tailed) showed a larger suppression of VOR response for the right caloric versus left caloric in left-cathodal condition ($t(7)=-3.3$, $p=0.013$, Figure 28 A, B and C). Thus, unilateral left-cathodal tDCS stimulation of the parietal cortex resulted in bilateral reduction of VOR response following the right and the left caloric. This reduction was asymmetric with greater suppression of the rightward slow phase (i.e. Right cold caloric) (Figure 28 A, B and C).

4.9 Discussion

Although not formally measured, all participants reported a subjective reduction in dizziness following the tDCS conditions which elicited a significant reduction in VOR response (i.e. in bilateral right-anodal/left-cathodal and unilateral left-cathodal conditions). In all the other stimulation conditions whereby no modulation of the VOR was observed, participants reported the similar intensity of dizziness as in the baseline condition.

Herein we demonstrate that disruption of the inter-hemispheric parietal balance (Bardi et al., 2013, Cohen Kadosh et al., 2010, Sparing et al., 2009a) through bilateral application of tDCS (right-anodal/left-cathodal) results in the asymmetrical modulation of the VOR, such that the VOR was suppressed following the right caloric irrigation. In order to delineate the

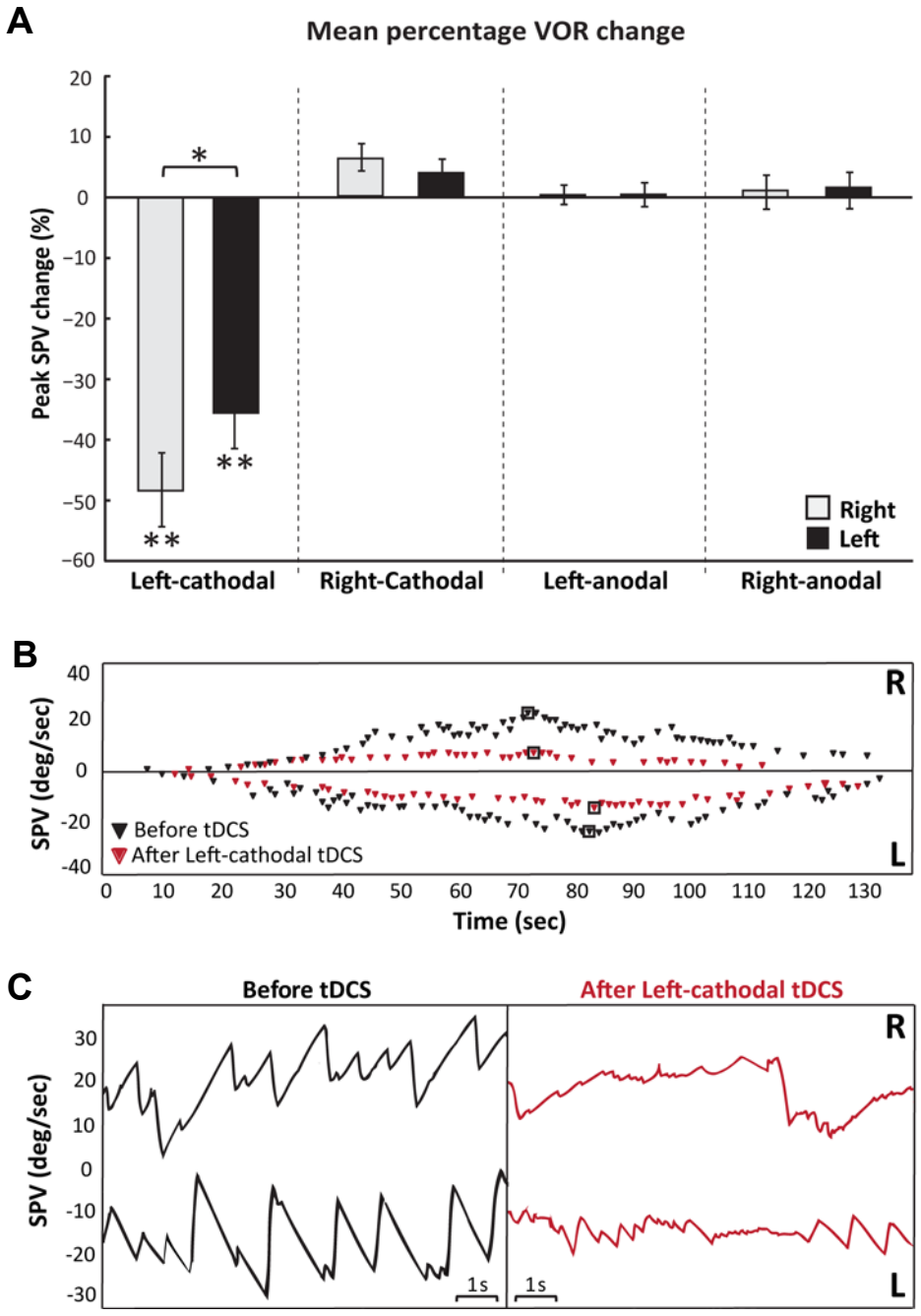


Figure 28: Results from the unilateral tDCS experiment. Panel (A) on the x axis we have the four conditions right anodal, left anodal, right cathodal and left cathodal. On the y axis is the % change in peak SPV

in the VOR following application of tDCS. Neither the right or left anodal stimulation; nor the right cathodal stimulation affected vestibular processing. However, following left cathodal stimulation a marked reduction was observed for the right and left cold caloric, albeit significantly more supressed for the right caloric. Panel (B) X axis shows the time and on the y axis is the slow phase eye velocity; positive values rightwards slow phase and negative values leftwards slow phase. Red and black dots represent the slow phase velocities; black dots before tDCS and red dots after tDCS. The lower panel represents the response for the left caloric and upper panel for right caloric and as we can see for both the right and left caloric following left cathodal stimulation we can see the response of the red dots are suppressed in comparison to the black dots representing suppression of the VOR. Panel (C) Raw traces of vestibular nystagmus. The response following tDCS (red trace) is markedly suppressed.

"active electrode" during the bilateral condition we applied unilateral tDCS stimulation. Cathodal stimulation of the left parietal cortex alone resulted in bilateral albeit asymmetrical reduction in VOR slow phase velocities (i.e. greater reduction for the right compared to the left caloric).

We rule out the possibility that the modulation of the VOR observed was due to the tDCS impacting upon vestibular afferents, via galvanic stimulation, since we observed an asymmetrical VOR modulation and, furthermore, since galvanic stimulation induces predominantly torsional vestibular-ocular responses. Moreover, this possibility has been further ruled out as in a recent study it was demonstrated that application of tDCS (as per the experimental protocol in this study)(Kyriakareli et al., 2013) does not induce torsional VOR eye movements as observed with 3D-VOG. Moreover, the specific asymmetric nature of the VOR modulation observed suggests that higher order mechanisms may be responsible for the apparent down-regulation.

Previous neuroimaging studies suggest that the insular parietal cortical regions are implicated in processing vestibular signals (Dieterich et al., 2003a). Cold water caloric irrigation appears to result in bilateral activation of the cortical areas however with a preponderance of activating the contralateral parietal cortex to the side of the irrigated ear. Moreover, right hemisphere dominance in right handed individuals has been suggested for

vestibular cortical processing as evidenced from neuroimaging studies (Dieterich et al., 2003b). Thus, in our baseline pre-tDCS VOR measurements, the cortical processing of the right ear caloric takes place predominately in the left hemisphere with some in the right hemisphere. For left ear caloric the vast majority is processed in the right hemisphere (due to the right hemisphere dominance) with little processing on the left (Schematic model; see Figure 29).

Both bilateral right-anodal/left-cathodal or unilateral left-cathodal tDCS stimulation caused reduction of VOR rightward slow phase velocity following right caloric irrigation. We identified that cathodal stimulation over the left parietal cortex is the “active” electrode that induces the observed VOR modulation. We suggest that left cathodal stimulation inhibits the left parietal lobe and renders it less able to process the vestibular signals from the right caloric resulting in VOR suppression (Figure 27, 28 and 29). Interestingly, for left ear caloric, the “active” electrode produced differential effects in the bilateral compared to the unilateral condition. In unilateral left-cathodal condition, a reduction in the VOR for left caloric was additionally observed, albeit the reduction was smaller to the one observed for right caloric (Figure 28). However, in bilateral right-anodal/left-cathodal condition the left caloric produced normal VOR responses, which were similar to the responses observed pre-tDCS (Figure 27). We propose that the introduction of anodal stimulation over the right hemisphere in bilateral right-anodal/left-cathodal condition results in a facilitatory effect increasing the processing capacity of vestibular information in the right parietal cortex. Thus, the right hemisphere is able to compensate for the loss of processing power in the left hemisphere and a normal VOR response is observed (Figure 29).

No modulatory effect upon the VOR was observed with any of the other tDCS stimulation conditions. Lack of a modulatory effect in right cathodal condition is somewhat surprising since inhibition of right parietal cortex should hypothetically result in disruption of inter-hemispheric balance (Sparing et al., 2009a) and in alteration of vestibular cortical processing. We propose that the right hemisphere may be able to compensate better than the left hemisphere for the induced inhibition (Sparing et al., 2009a, Dieterich et al., 2003a, Mesulam, 1998, Kinsbourne, 1977) via cathodal tDCS stimulation, thus sufficiently be able to process the vestibular information. This is based on the previously suggested right hemisphere dominance for vestibular cortical processing. Moreover, an alternative but not a mutually exclusive explanation is the proposed ongoing functional asymmetry between the two parietal cortices (Koch et al., 2011). For visuo-spatial abilities, the right hemisphere appears to exert a stronger inhibition over the left hemisphere suggesting that weighting of function connectivity between the two hemispheres are asymmetric (Koch et al., 2011). Hence, cathodal tDCS stimulation may cause less inhibitory effect when applied over the right hemisphere compared to the left hemisphere as a result of the ongoing functional asymmetry between the parietal cortices(Koch et al., 2011, Mesulam, 1998, Kinsbourne, 1977).

These findings are supported by two studies where it was observed that disruption of parietal function either via a lesion(Ventre-Dominey, Nighoghossian & Denise, 2003a) or possible overloading of the right hemisphere or conflict regarding the redirection of spatial attention between the hemispheres (Arshad, Nigmatullina & Bronstein, 2013a) resulted in suppressed VOR time constants whilst rotating in the direction of the non-dominant hemisphere. However, no effects of any change in the VOR gain were reported in either

study (Arshad, Nigmatullina & Bronstein, 2013a, Ventre-Dominey, Nighoghossian & Denise, 2003a). Hence, it was speculated that parietal disruption could down-regulate the central velocity storage mechanism without affecting the VOR gain.

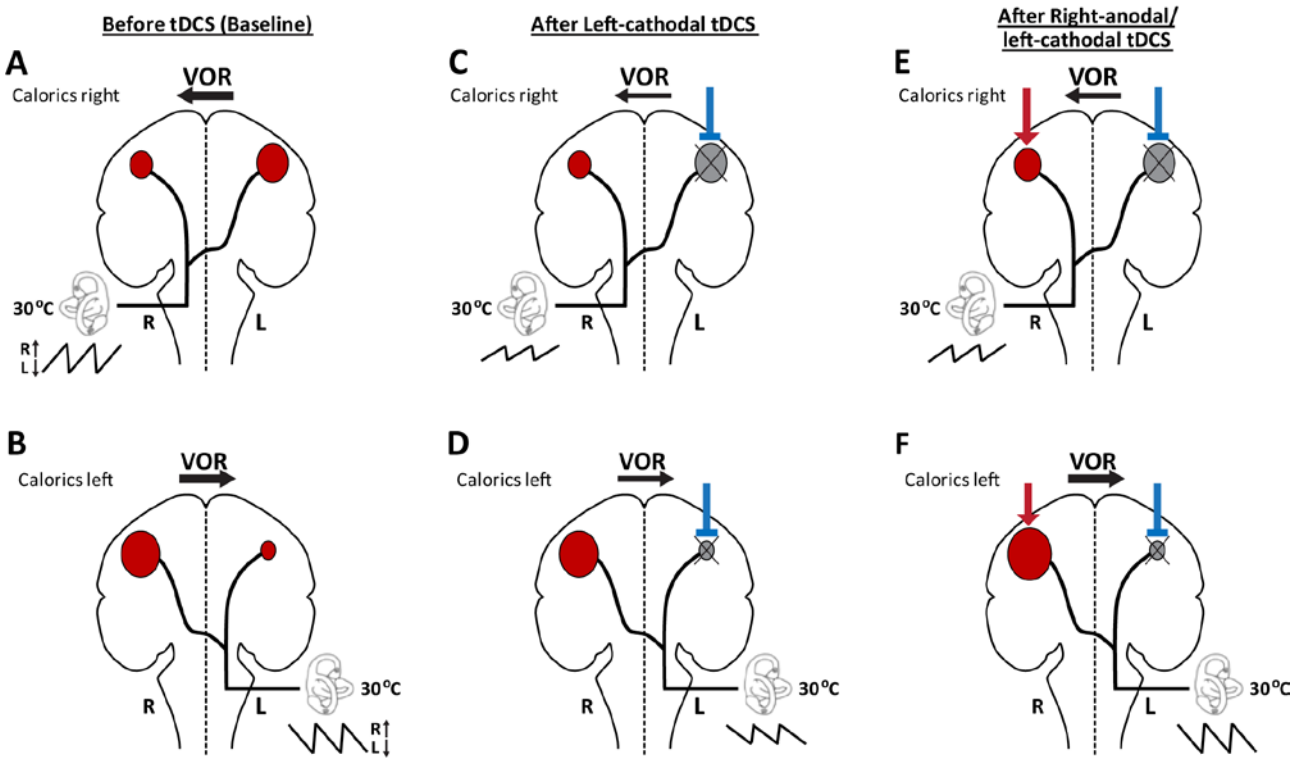


Figure 29: Schematic model of vestibular processing during baseline cold caloric irrigation (A, B) and hypothesized modulation of VOR response after left-cathodal (C, D) and right anodal/left-cathodal (E, F) tDCS stimulation. The intensity of the cortical activation is represented by the size of the red areas. The direction of slow phase eye movement generated by caloric irrigation is shown by black arrows with the thickness of the arrows indicating eye velocity magnitude. The VOR response following a caloric is exemplified by a short nystagmic trace (inserted below the semi-circular canals), the relative amplitude of which reflects the changes in mean SPV observed (A and B). In the baseline condition, activation of semi-circular canals by caloric irrigation results in stronger projections to contralateral parietal cortex with right hemisphere dominance. C, D, E, and F. Left-cathodal stimulation results in inhibition of the underlying cortex as represented by blue blunt arrow and gray areas; Right-anodal stimulation causes facilitation of the underlying cortex as represented by red arrow and expansion of red areas (E and F). After unilateral left-cathodal inhibitory stimulation, the left parietal lobe may have insufficient resources to process right and left caloric responses, resulting in the bilateral but asymmetric reduction of the slow phase eye velocity (C and D). After bilateral left-cathodal/right-anodal tDCS stimulation, right caloric is insufficiently processed due to inhibition of the left parietal lobe. Left caloric is sufficiently processed with normal VOR response since application of the right-anodal stimulation may compensate for the lack of processing resources in the left parietal lobe.

However, a parsimonious explanation for why we now specifically observe a modulation of slow phase velocity (i.e. the gain) but not the duration of the response (i.e time constant) is most likely related to critical differences between the two vestibular stimuli used. The rotational stimulus previously used lasts <1s (steps) whereas the temperature gradient created by caloric irrigation lasts several minutes (Barnes, 1995). Slow phase velocity during step velocity rotations, as employed in the two previous studies(Arshad, Nigmatullina & Bronstein, 2013a, Ventre-Dominey, Nighoghossian & Denise, 2003a) where a modulation of the VOR time constant (but not gain) was observed, is measured during the high frequency component of the rotational stimulus - typically within 1-2s of the high acceleration delivered and when the slow acting velocity storage mechanism is not involved. In the present study a caloric stimulus was deployed and the peak velocities reported are reached 60-80 seconds after stimulus onset (see Figures 27 and 28) are almost certainly under the influence of the velocity storage integrator. Thus, disruption of parietal inter-hemispheric balance either via a right hemisphere lesion(Ventre-Dominey, Nighoghossian & Denise, 2003a), possible overloading of non-dominant hemisphere(Arshad, Nigmatullina & Bronstein, 2013a) or by neuromodulation (as in this study)(Arshad et al., 2013) can result in the down-regulation of maximal slow phase VOR velocities either by affecting the time constant or gain component of the central velocity storage mechanism.

In summary, these results provide novel evidence using neuromodulation that disruption of parietal balance via tDCS inhibition of the left hemisphere in right handed subjects results in an asymmetrical suppression of the VOR. Moreover, these results provide support for the presence of functional asymmetry between the two parietal lobes and imply right

hemisphere dominance for vestibular cortical processing and show that it is subject to dynamic interhemispheric competition.

Chapter 5: Experiment 3- Behavioural manipulation in order to induce Top-down cortical control of V1

5.1 Synopsis

It was demonstrated in the first experimental chapter of this thesis (Chapter 3) the ability of a novel behavioural/physiological technique (i.e. concurrent vestibular activation and redirection of spatial attention) to induce a handedness related top-down cortical control of the brainstem mediated VOR. We proposed that this modulation was attributable to a disruption of parietal function (possibly via disruption of parietal balance) and we subsequently directly tested this hypothesis in the second experimental chapter (4) by directly altering parietal hemispheric balance using trans-cranial direct current stimulation (tDCS). Such an intervention was found to induce an asymmetrical VOR in response to caloric stimulation. Herein, we apply the same technique as in the first experimental chapter (i.e. concurrent vestibular activation and redirection of spatial attention (via performance of a spatial attention task)) to examine the possibility of whether one can use this technique to additionally modulate other low-level brain/ sensory structures, namely the early visual cortex. We found that the combination of right ear cold caloric (i.e. left beating nystagmus) and the concurrent performance of a visuo-spatialworking memory task modulated the early visual cortical excitability. However, no modulation of cortical excitability was observed with left ear cold caloric (i.e. right beating nystagmus) and the concurrent performance of a visuo-spatial working memory task. This results suggests that the combination of left beating nystagmus and a concurrent spatial task or

viewing a bistable task is able to induce top-down modulation of both the VOR and the early visual cortex.

Aims & Hypothesis

The aim and hypothesis behind this experiment was to assess whether concurrent visual and vestibular activation that was demonstrated to asymmetrically modulate the VOR in the third experimental chapter of this thesis would extend to modulate other lower brain level structures, namely the primary visual cortex. If the technique was able to modulate the primary visual cortex then the technique induces top down control of low level brain structures. If it failed to do so, then the technique was specifically acting on the vestibular system alone.

5.2 Background

Attention improves processing of the attended target whilst simultaneously reducing processing to simultaneously presented distractors (Kastner & Ungerleider, 2000). This bias of neural responses toward the target is thought to be mediated by the frontoparietal network (Corbetta & Shulman, 2002a). Evidence for this arises from the following observations. Firstly, parietal lesion patients who present with neglect and extinction show a characteristic lack of attention to stimuli on the contralateral side despite the presence of normal visual fields (Mesulam, 1998, Kinsbourne, 1977). Secondly, neuroimaging (Ruff et al., 2008) as well as neuro-modulation studies (Kanai et al., 2011) provide further evidence for the role of frontal and parietal networks in attention.

More specifically, evidence supporting the notion that the frontoparietal network is responsible for top down modulation of visual system is supported by the following studies. Taylor and colleagues asked subjects to perform a covert orienting task while applying transcranial magnetic stimulation over the frontal eye fields and measured changes in

occipital visually evoked potentials (Taylor, Nobre & Rushworth, 2007). Silvanto and colleagues similarly found that stimulation of frontal eye fields alters activity of the visual cortex, however instead of using visual evoked potential, phosphene threshold measures of excitability were implemented (Silvanto, Lavie & Walsh, 2006). Ruff and colleagues applied TMS over frontoparietal regions during functional magnetic resonance imaging (Ruff et al., 2008). Their findings did indeed confirm those earlier findings of Silvanto and Taylor (Taylor, Nobre & Rushworth, 2007, Silvanto, Lavie & Walsh, 2006).

Furthermore, disruption of the right lateralised fronto-parietal attentional network using tDCS has been shown to induce both functional and perceptual modulation of the early visual cortex (Silvanto et al., 2009). Such modulation is suggested to be mediated by a disruption of interhemispheric competition (Silvanto et al., 2009). Hence, if the technique we have developed in this thesis of concurrent vestibular activation and either viewing bistable percept's or performance of a visuo-spatial working memory task does indeed disrupt inter-hemispheric parietal balance then we should also observe a modulation of the early visual cortex. In this study, we stimulated the vestibular system during performance of an attentional task, a technique which has previously been shown to result in the asymmetrical modulation of the brainstem mediated vestibulo-ocular reflex (VOR) (i.e. first experimental chapter; Chapter 3) (Arshad, Nigmatullina & Bronstein, 2013a). The modulation of VOR was suggested to occur as a result of activating overlapping cortical networks responsible for processing both vestibular information and the attentional task in the right parietal lobe (Dieterich et al., 2003a, Corbetta & Shulman, 2002a, Miller et al., 2000a), and hence disrupting parietal function. Thus in this study, we employed the same technique to disrupt parietal function in normal subjects and measured the possible effect

upon V1 excitability. Moreover, we attempt to delineate the specific contributions of spatial versus non-spatial attentional networks in modulating the early visual cortex.

5.3 Materials and Methods

5.3.1 Trans-cranial magnetic stimulation (TMS)

Application of a single TMS pulse over the occipital cortex elicits the illusionary percept of a brief flash of light termed a phosphene (Boroojerdi et al., 2000). Elicitation of a phosphene is reflective of the underlying visual cortical excitability (i.e. such that if low intensities of TMS can elicit phosphenes it represents a high underlying visual cortical excitability and vice versa) (Romei et al., 2007). Subject phosphene threshold was determined by implementing a modified binary search (MOBS) paradigm (Tyrrell & OIns, 1988). This paradigm can potentially allow me to determine the TMS intensity required to elicit phosphenes 50% of the time (i.e. threshold) during a trial sequence (e.g. 10 yes responses out of 20 TMS pulses). The paradigm is an adaptive procedure whereby the initial stimulus value (TMS pulse) is presented at a value which represents the bisection of an initial upper and lower boundary pair. These boundary pairs are continually updated based upon the subjects prior response to each TMS pulse (e.g. a positive subjective response will shift the boundary downwards and vice versa). The actual threshold was determined after subjects made 3 consecutive alternate choices in order to minimise variability (Johnson & Shapiro, 1989). TMS was applied at phosphene threshold + 20% in all subjects as this would allow for any potential effect in the rate of phosphene perception (i.e. any possible enhancement or reduction) to be easily observed, despite the supra-threshold nature of the stimulus following the intervention. Subjects were trained in a prior session to rate the intensity of the perceived

phosphene on a scale from (0-5; 0 no phosphene, 5 maximal brightness- i.e. 100% of the maximal stimulator output).

Biphasic TMS pulses were administrated with a Magstim 200 stimulator (Magstim Co, UK). The coil was a 70 mm figure of eight shaped coil, always held with the handle turned laterally. V1 stimulation site was localised using a functional method by placing the coil centrally over the inion then moving it in 1 cm steps dorsally until the brightest stationary phosphene percept in the centre of the visual field is observed. The participants were asked during the localisation phase of phosphenes to verbally describe the phosphenes and their perceived location in terms of its position, superimposed on an imagined clock face in order to determine whether they were midline and hence V1. The coil position was recorded for every participant with an average position of 1.9 cm above the inion. Initially, the intensity of the stimulation was set at 70% of maximum TMS output, but this was increased if the participants did not perceive phosphenes.

This functional approach has been implemented in the majority of phosphene studies (Silvanto, Lavie & Walsh, 2005, Juan & Walsh, 2003); for localisation and stimulation of area V1 but stimulation of nearby areas such as area V2 cannot be ruled out. However, V1 is the most likely site of stimulation to produce phosphenes in the centre spanning both visual fields (Kammer, 1999) and furthermore perception of phosphenes is not possible without involvement of V1 (Coly & Walsh, 2001). Hence, we infer that any effects observed in this study are attributable to changes in V1 excitability. Moreover, it has been shown that this functional approach of V1 localisation produces comparative results to those obtained using neuro-navigation techniques (Soto, Llellyn & Silvanto, 2012).

5.3.2. Vestibular Stimulation

Following otoscopy, to exclude local contra-indications, subjects underwent caloric irrigation. The participants lay supine on a couch with the head tilted at 30^{o} to obtain maximal activation of the horizontal semi-circular canals (Barnes, 1995). The external auditory meatus was irrigated with water at 30^{o}C (cold water) at a rate of 500 ml/min for 40 seconds (CHARTR VNG; ICS medical). The onset of vertigo occurs approximately 20 seconds after the start of the irrigation reaching a peak at around 60 seconds. The total duration of the response lasted on average 3 minutes (Barnes, 1995).

In response to the caloric vestibular activation an oculomotor response (VOR in the form of 'vestibular nystagmus') is elicited: e.g. the right cold caloric results in left beating nystagmus with a rightwards slow phase and vice versa.

5.3.3 Experimental protocol

We assessed V1 excitability using phosphenes, elicited by briefly stimulating the visual cortex using single pulse transcranial magnetic stimulation (TMS). Subjects were blindfolded and were seated on a chair fitted with a fixed magnetic coil and head restraint system. The head was inclined 30 degrees from the horizontal plane for maximal horizontal canal caloric stimulation. Firstly, V1 stimulation site was localised using a functional method by placing the coil centrally over the inion then moving it dorsally until the brightest stationary phosphene percept is observed in the centre of the visual field (Figure 30). Secondly, the threshold was established according to a modified binary staircase algorithm previously described. Subjects were trained to rate the intensity of the perceived phosphene on a scale from 0 (no phosphene, below threshold) to 5 (maximum brightness, 100% max stimulator output). We then used the established clinical approach for cold water (30^{o}C) caloric

irrigation (left or right ear, randomised order) for 40s to activate the vestibular system. The irrigations were separated by a period of 5 minutes to allow for any after effects to subside (Barnes, 1995).

Following irrigation, we immediately measured visual cortical excitability using 20 single TMS pulses (Seemungal et al., 2013) applied at 20% above phosphene threshold for each individual, with each pulse separated by 3s. Subjects responded verbally and rated each phosphene on a scale (0-5) based on the intensity of the perceived phosphene.

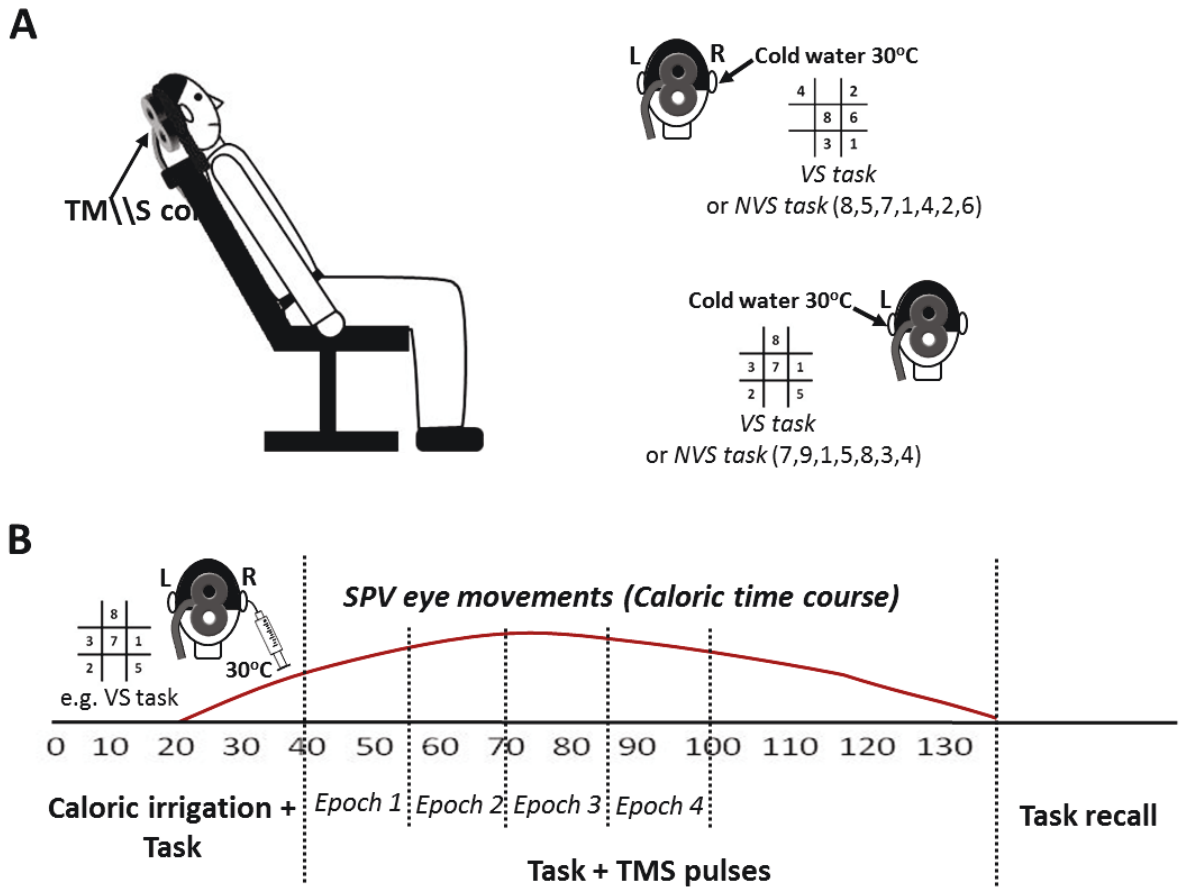


Figure 30: The TMS experimental protocol (A) shows the subjects position and TMS coil position and the task employed. (B) Shows the time course of the vestibular response.

Subjects and Data analysis

Eighteen right-handed participants (male 14, mean age = 24; range 20-33) gave written informed consent as approved by the local research ethics committee. 9 subjects completed the spatial attention task and 9 were used for the non-spatial task. The task employed were exactly the same as those used in the previous experimental chapter (3) when we investigated the effects of the tasks upon the VOR (Refer to Chapter 3; Figure 17 C). The numbers for the task were presented at the start of the trial during the caloric, and participants were then required to recall the numbers at the end of trial (Figure 31 A). Participants were required to recall at least 4 out of 6 numbers in the correct position on the grid.

For the purpose of data analysis, subjects were required to rate the brightness of the phosphenes on a scale of between 0-5. I noted the subject's responses and calculated the mean phosphene intensity for the run of 20 TMS pulses for each of the conditions.

5.3 Results

The intensity of phosphenes was similar (not significantly different, $p > 0.05$ paired t-test) following either right or left ear caloric irrigation alone.

We then examined whether performing a visuo-spatial attention task *during* vestibular activation would modulate V1 excitability. We repeated the procedure described above (i.e. caloric + TMS), however this time participants performed the attentional tasks.

We found that the intensity of phosphenes was significantly reduced *only* when participants performed the visuo-spatial working memory task during *right* ear caloric. In a repeated measures ANOVA, factors Caloric side (left, right), Task (visuo-spatial, no task), there was a significant Caloric side x Task interaction ($p < 0.05$, $df = 3$, $F = 7.05$ Repeated measures

ANOVA). Post hoc t-tests confirmed that this effect was seen in epochs 1 and 2 (Figure 31 B), thus the effect lasted around 30s ($p < 0.01$, $t = 3.7$ for epoch 1; $p < 0.05$, $t = 2.77$ for epoch 2; paired t-tests). However, no significant changes were observed in V1 excitability following left caloric ($p>0.05$ Repeated measures ANOVA), (Figure 31 B); nor during the low load visuo-spatial attentional task for either the right or left ear caloric ($p> 0.05$ Repeated measures ANOVA).

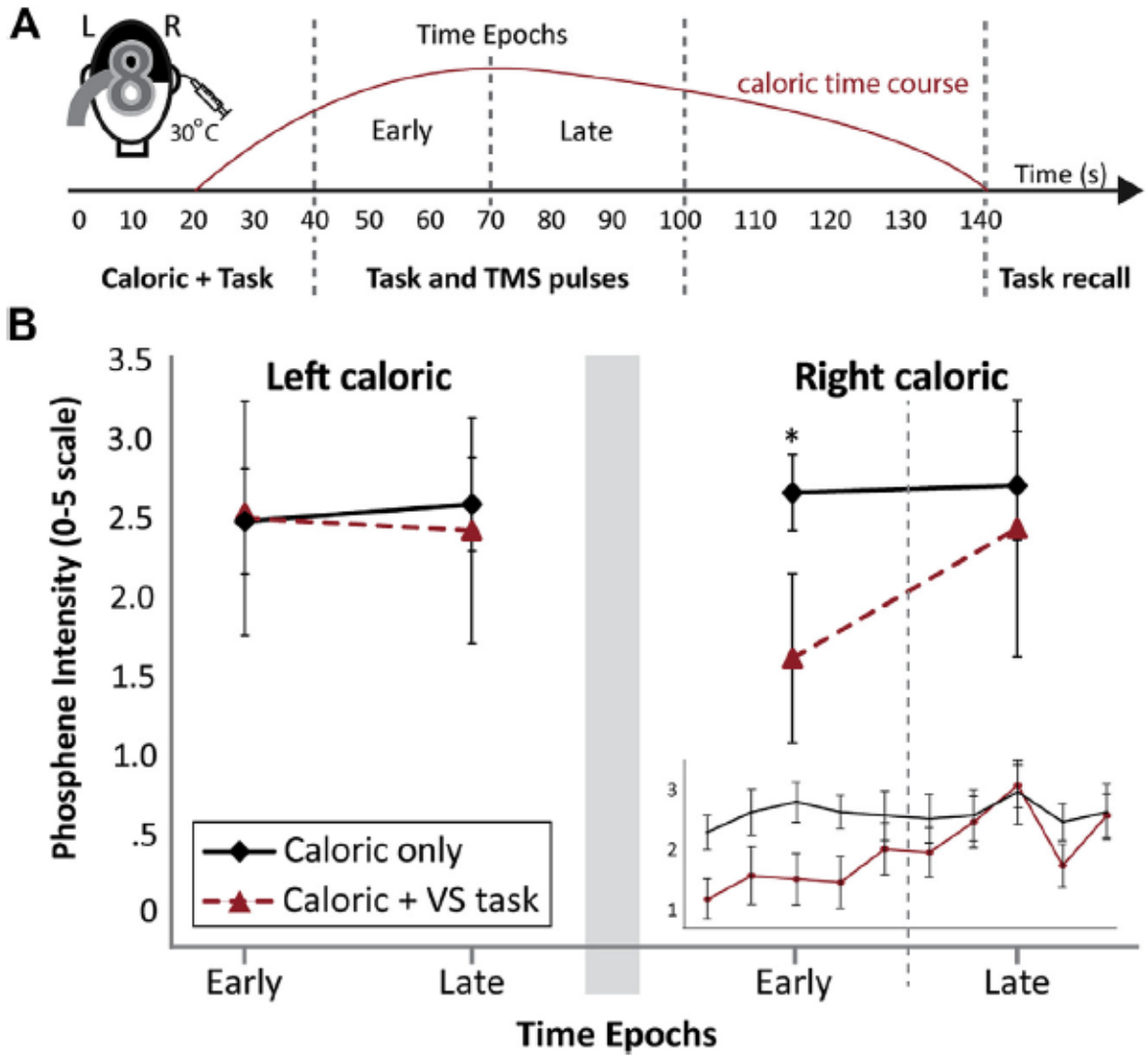


Figure 31: Results from the TMS experiment (A) Time course of the experiment. The caloric was applied for 40 sec (x axis) at which time either the spatial or non-spatial task was given to the subject (x axis).

The first TMS pulse coincided with the end of the irrigation at 40 sec (x axis). In total 20 pulses were delivered (from 40-100 seconds), with each pulse separated by 3 sec. Thus, the TMS was applied for a total duration of 60 sec, divided into two time epochs; each representing 30 sec (early and late). These epochs represent in part the decaying caloric-induced activation represented by the oculomotor response (red curved line). (B) Results for the EXPERIMENT. As shown visual cortical excitability changes either following right ear or left ear caloric alone (black solid line) or visual cortical excitability following concurrent vestibular activation and visuo-spatial attentional task for left or right ear (red dashed line). (B inserts right-hand side). Plot of the temporal dynamics of the modulation, and as can be observed there was specifically a difference of excitability between caloric alone (black line) and caloric+ visuo-spatial working memory task) only in the early epoch. This shows that the modulation of the early visual cortex only lasted 30 seconds after the end of the caloric irrigation.

To test whether this effect could be simply explained by an increase in cognitive load, we repeated the experiment in a separate group of 9 subjects using a non-visuo spatial task. Here participants were required to remember a string of seven numbers (modified digit span) (Axelrod et al., 2006), a task used previously as it carries a relatively equivalent attentional load (Arshad, Nigmatullina & Bronstein, 2013a). We analysed performance using the same ANOVA approach described above, but this revealed no significant interactions or effect of task performance on phosphene perception ($p>0.6$).

5.4 Discussion

The data shows that asymmetrical modulation of visual cortical excitability presents *only* during the specific interaction of a mental visuo-spatial working memory task and right ear caloric irrigation. It has been previously shown that the interaction between visuo-spatial working memory task during vestibular activation results in disruption of parietal function as evidenced by the failure of vestibular cortical processing of the rightwards slow phase vestibular nystagmus (i.e. right cold caloric) (Arshad et al., 2013, Arshad, Nigmatullina & Bronstein, 2013a). Herein we show that disrupting parietal balance or inducing conflict between the right and left hemispheres regarding the redirection of spatial attention using the above interaction modulates the early visual cortex (Arshad et al., 2013). Another novel aspect of the findings reported herein is that we were able to separate the attentional

component of the visual cortex modulation by showing that specifically visuo-spatial attention (but not non-spatial attention) provides the modulatory effect. We propose that the cortical networks subserving specifically visuo-spatial attention and the central velocity storage mechanism (required to prolong the vestibular nystagmus) overlap(Arshad, Nigmatullina & Bronstein, 2013a, Ventre-Dominey, Nighoghossian & Denise, 2003a) in the right fronto-parietal attentional network(Dieterich et al., 2003a, Corbetta & Shulman, 2002a). This results in disruption of the normal parietal function and leads to top down modulation of the early visual cortex (Arshad et al., 2013, Silvanto et al., 2009, Sparing et al., 2009a).

In summary these findings provide a demonstration that this technique of concurrent vestibular activation and performance of a visuo-spatial working memory task modulates not only the VOR but additionally the early visual cortex, and that this modulation is specific to visuo-spatial attention (Arshad et al., 2013).

Chapter 6: Conceptual discussion and concluding remarks

6.1 Overview of the experimental approach implemented

Vestibular processing, bistable perception and spatial attention appear to share neuronal correlates within the right lateralised fronto-parietal attentional network (Dieterich et al., 2003a, Corbetta & Shulman, 2002a, Lumer, Friston & Rees, 1998a). In light of these

suggested overlapping neuronal networks, we developed a novel behavioural technique which entailed concurrent vestibular activation and redirection of spatial attention either via viewing bistable visual stimuli or performing imagined visualised spatial attention tasks to examine whether this could be used potentially to disrupt parietal function in neurologically intact individuals.

Following the possible disruption of parietal function we subsequently wanted to ascertain any potential impact upon the VOR and the early visual cortex (refer to results in Chapter 3 and 5) (Arshad, Nigmatullina & Bronstein, 2013a). We confirmed the role of the parietal lobe during the modulation of the VOR via the application of tDCS (refer to experimental chapter 4).

The rationale for the specific approach implemented above is twofold. Firstly, it has been demonstrated that disruption of parietal function following a lesion has been shown to induce an asymmetrical VOR (Ventre-Dominey, Nighoghossian & Denise, 2003a). Secondly, there are the findings in the literature that show disruption of parietal inter-hemispheric balance using tDCS is able to induce top down modulation of the early visual cortex (Silvanto et al., 2009).

Thus, based upon the results of these previous findings coupled with pre-existing and validated techniques readily available to measure visual cortex excitability and the VOR, jointly provided the rationale for specifically choosing the visual cortex and VOR as measures for the possible disruption of parietal function induced by our novel behavioural/physiological technique.

We show that the dual stimulation paradigm (i.e. that of concurrent vestibular activation and viewing bistable percept's or performance of visualised spatial attention tasks) can induce an asymmetrical modulation of both the VOR (assessed via eye movement recordings) and the early visual cortex excitability (measured via the perceptual phenomena of phosphenes).

However, it remains unknown what is special about this interaction that occurs during this concurrent dual stimulation paradigm that results and in turn mediates these modulations observed. In part, this is attributable to the fact that we used purely behavioural/physiological manipulations in the experimental work presented in this thesis. Hence, we are only able to speculate about what is occurring at the cortical level and thus presents a definitive limitation of the work that is presented in this thesis.

Having said this, we can use evidence from the literature from lesion studies, functional imaging and behavioural experiments with neuronal correlates to infer possible mechanism (s) for the modulations that we report herein. Moreover, we can use the findings to support or challenge existing theoretical frameworks in the literature as we use a novel technique to probe parietal function. For example, we gain new insights into how the velocity storage mechanism can be modulated, the interaction that exists between spatial attention and vestibular mechanisms and more generally insights into vestibular cortical processing. We shall now proceed to discuss each of these in more detail below starting with the insights this data set provides with respect to the issue of vestibular cortical processing.

6.2. Vestibular cortical processing

Regarding firstly the issue of vestibular cortical processing, it has been almost a decade since the first report using neuro-imaging that suggested that it is strongly lateralised to the non-dominant hemisphere, and that handedness was the strongest predicting co-variant (Dieterich et al., 2003a). The findings presented in chapter 3 (i.e. that viewing bistable precepts or performing visualised attentional tasks results in an asymmetrical modulation of the VOR) are the first set of behavioural experiments to support these neuro-imaging findings from a decade ago (Arshad, Nigmatullina & Bronstein, 2013a).

Recall that we showed that the viewing of bistable perceptual stimuli with a motion aspect and hence a spatial component and /or performing a imagined (mentally) visualised spatial attention task during concurrent vestibular activation resulted in a handedness related top-down cortical modulation of the VOR (Arshad, Nigmatullina & Bronstein, 2013a).

That is, in right handed subjects the VOR following rightward rotations was supressed (i.e. left beating nystagmus), whereas, no modulation was observed following leftward rotations (i.e. right beating nystagmus) (Refer to the results section in chapter 3). Conversely, in left handers we observed a supressed VOR following leftward rotations (i.e. right beating nystagmus), whereas, no effect was observed following rightward rotations (i.e. left beating nystagmus) (Refer to results section Chapter 3) (Arshad, Nigmatullina & Bronstein, 2013a).

Hence, in this study we found lateralisation of the vestibular cortex in association with an individual's handedness in 94% of the subjects (Arshad, Nigmatullina & Bronstein, 2013a). The reason for this value is that that two of the right handers in the lateralisation experiment (refer to chapter 3 results; section lateralisation experiment) showed the same trend as left handers, in that we observed a suppressed VOR following leftward

accelerations (i.e. suppression of the right beating nystagmus not left beating nystagmus, hence the opposite trend to that found in the rest of the right handed cohort).Upon, further questioning it was revealed that these two right handed subject were in fact re-trained left handed individuals.

Previous figures for the degree of lateralisation found for vestibular cortical processing from functional imagining data suggested that the association with handedness stands at 80% (Dieterich et al., 2003a). Partly, the difference in values between the two studies can be potentially explained by the subject selection and moreover in that handedness is a self-reported measure. Alternatively the difference can be potentially attributed to the sensitivity and or specificity of the two different technical parameters employed between the two contrasting experimental approaches (i.e. imaging data versus eye movement recording).

Indeed there has been much contention in the literature regarding this issue of laterality of vestibular cortical processing in the non-dominant hemisphere. For example, earlier studies showed bilateral and symmetrical activation patterns in response to caloric stimulation (Fasold et al., 2002, Suzuki et al., 2001, Bottini et al., 1994). However, these earlier findings were challenged by those provided by the study published in 2003 that clearly showed right hemisphere dominance (Dieterich et al., 2003a). However, since then only two recent studies have provided strong evidence to suggest or support the hypothesis that the vestibular cortex is lateralised to the non- dominant hemisphere. Firstly, a comprehensive meta-analysis of 28 functional imaging studies investigating the neuronal correlates of vestibular cortical processing implicates right hemisphere dominance and suggests that the core region to be involved is the parietal opercular (OP2) (Lopez, Blanke & Mast, 2012). The

second study is our behavioural demonstration of modulating the VOR and its association with handedness, which is reported in the 3rd experimental chapter of this thesis (Arshad, Nigmatullina & Bronstein, 2013a). Taken together, the strong evidence provided by the comprehensive meta-analysis (Lopez, Blanke & Mast, 2012), the initial report (Dieterich et al., 2003a), the parietal lesion effects upon the VOR (Ventre-Dominey, Nighoghossian & Denise, 2003a) and our behavioural results (reported in chapter 3) (Arshad, Nigmatullina & Bronstein, 2013a) provide strong evidence to support the hypothesis that vestibular cortical processing is lateralised to the non-dominant hemisphere.

Moreover, the specific manner in which we show that the vestibular cortex is lateralised is by the concurrent method of vestibular activation and redirection of spatial attention, demonstrates a curious relationship between vestibular and spatial attention mechanisms that we will now discuss in further detail below.

6.3 Interaction between spatial attention and vestibular mechanisms

The report (i.e. results presented in the 3rd chapter) shows a novel interaction in that bistable percept's are able to modulate the function of a separate sensory system (e.g. binocular ***visual*** rivalry can modify ***vestibular*** function). The converse interaction, such that ***vestibular activation*** can alter the ***perceptual dynamics*** during the viewing of ***visual rivalry*** has been reported (Miller et al., 2000a). However, in conjunction with the findings reported herein, it suggests that this relationship between bistable percept's and the vestibular system is bi-directional (Arshad, Nigmatullina & Bronstein, 2013a).

Hence, the bi-directional relationship between these two seemingly independent processes is intriguing. Bistable visual perceptual stimuli have been shown to have neuronal correlates

in fronto-parietal areas that are co-associated with spatial attention (Rees, Kreiman & Koch, 2002, Lumer, Friston & Rees, 1998a).Further, such areas are additionally implicated for the cortical processing of vestibular signals (Dieterich et al., 2003a).

Hence, considering the shared neural architecture for these three entities (i.e. binocular rivalry, visuo-spatial attention and vestibular cortical processing) it is entirely a possibility that a degree of reciprocal interaction would present between them. As a side note to the point made above, it is apparent that there is also a degree of specialisation in the interaction between these three entities.

That is, although it has been shown that the neuronal correlates of binocular rivalry shares areas of non-visual fronto-parietal attentional network (Lumer, Friston & Rees, 1998a), we found no modulatory effect upon either the VOR or the visual cortex when either the visual bistable percepts (i.e. colour rivalry) or attentional task (i.e. non-spatial task) did not possess a motion / spatial component (Refer to results in experimental chapters 3 and 5).

Hence, the presence of a spatial and or motion component is critical in order to observe the modulation (i.e. an interaction between these visual or attentional tasks and the vestibular system) possibly due to the fact that specifically the redirection of spatial attention may engage mutlisensory vestibular cortical areas (including vestibular) within the same network in order to modulate low-level vestibular function, which in turn may contribute to maintaining spatial orientation (Dieterich et al., 2003a).

Furthermore, following this line of thought, such an arrangement may provide a possible explanation for why vestibular cortical processing is lateralised to the non-dominant hemisphere, which we will now turn to and discuss in further detail.

6.4 Postulation for why the vestibular cortex shows lateralisation

With regards to why an ancient function (i.e. the vestibular ocular-reflex) should present with such a strong hemispheric specialisation is curious. Such a hemispheric preference that is handedness related could well be a by-product of human evolution.

Hence, due to the lack of a clear distinct cortical area solely devoted to vestibular cortical processing, the dominance of vestibular cortical processing cannot be considered in isolation as alluded to in the above section (i.e. in the pure vestibular sense).

Rather it should be considered with respect to the functionality of the vestibular system and the anatomical location of the vestibular cortex. One of the key functions of vestibular systems is the provision of spatial orientation such that it contributes to a complex multi-purpose network for the detection, integration and motor planning and execution of reactions to changes in egocentric space (Dieterich et al., 2003a).Indeed, a key contributor to the maintenance and provision of spatial orientation is the allocation of spatial attention (Dieterich et al., 2003a) which shares neuronal correlates in the parietal lobe and is additionally lateralised to the right hemisphere (Mesulam, 1998).

Hence, as both processes are functionally and anatomically related it may have been the case that both processes in evolution became lateralised together in an attempt to increase neuronal efficiency and reduce computational cost. Having considered the possible reasons for the lateralisation of the vestibular cortex in man, we will now turn to the possible neural mechanisms mediating the modulations reported herein.

6.5 Possible mechanisms for the behavioural modulation of the VOR

Specifically turning back to the behavioural modulation of the VOR observed (as reported in the 3rd experimental chapter; in that viewing bistable percepts or performing spatial tasks induced an asymmetrical VOR), there are two alternative possible explanations to explain the effect from the existing evidence available that can be drawn from the literature.

Firstly, there is the possibility that the modulation of the VOR is secondary to overloading of the right hemisphere. That is, concurrent vestibular activation and either viewing bistable percept's or performing visualised spatial attention tasks call upon a common neural network within the right lateralised fronto-parietal network (Kanai, Bahrami & Rees, 2010, Silvanto et al., 2009, Ventre-Dominey, Nighoghossian & Denise, 2003a), hence overloading the right hemisphere.

In accord with this viewpoint, the left beating nystagmus that is supressed in right handers is processed mainly in the left hemisphere but also the right hemisphere (Arshad, Nigmatullina & Bronstein, 2013a).However, as the right hemisphere is additionally engaged with the processing of bistable percepts (Kanai, Bahrami & Rees, 2010) (even in the dark due to the presence of a phenomena termed perceptual memory) (Sterzer & Rees, 2008) or engaging in an attentional task, that renders the right parietal lobe less able to contribute to the processing of the left beating nystagmus.

Accordingly then, if we reduced the processing demand upon the right hemisphere by reducing the attentional load in accord with Lavies attentional load theory (Lavie, 2005) we should theoretically free up processing resources and observe reduced asymmetries in the VOR. By altering the attentional load we showed this to be the case, as presented in the 3rd

experimental chapter of this thesis. In sum, this experimental evidence adds supports to the overloading hypothesis of the right hemisphere.

Alternatively, a secondary hypothesis is that the modulation is secondary to the disruption of parietal balance. For example, lesions of the posterior parietal cortex that can lead to development of spatial neglect may do so by disrupting right-left parietal balance (Sparing et al., 2009b). Restoring parietal balance in these parietal lesion patients using tDCS has been shown to be effective in reducing the neglect (Sparing et al., 2009b). Moreover patients with posterior parietal cortical lesions and that have an additional spatial neglect component associated with the lesion have been reported to (hence potentially present with a disruption of parietal balance) have asymmetrical VOR responses following velocity step rotations (similar to the ones we employed in the 3rd experimental chapter of this thesis (Ventre-Dominey, Nighoghossian & Denise, 2003a).

Hence, in order to directly test this hypothesis (i.e. the role of right-left parietal balance), we performed the tDCS experiment to directly manipulate parietal excitability between the right and left hemispheres in order to ascertain any potential impact upon the VOR as reported in Chapter 4 of this thesis (tDCS modulation of the VOR).

6.6 Disruption of Parietal balance mechanism

We showed that disruption of parietal balance using tDCS in the bilateral montage results in an almost identical asymmetrical modulation of the VOR to that observed during the behavioural manipulations (Refer to results section of chapter 4). That is, right anodal/left cathodal stimulation in the bilateral montage resulted in suppression of the right cold caloric in right handed subjects (i.e. left beating nystagmus). In doing so, these results

provides support for both the overloading of the right hemisphere hypothesis and also supporting the disruption of parietal balance hypothesis for the behavioural modulation of the VOR reported in the 3rd experimental chapter of this thesis.

However, the results from the unilateral tDCS montage experiment yields results that challenges both the overloading hypothesis and disruption of parietal balance. The reason that we performed this specific montage (unilateral tDCS) was in order to determine the active electrode in the bilateral montage. We demonstrated that the left cathode electrode was the more "active" electrode in producing the modulation observed in the bilateral condition, however the right anodal electrode (in the bilateral montage) did play a role in the modulation observed (refer to discussion of chapter 4) (Arshad et al., 2013).

However, the point remains that the results from the unilateral montage experiment yields conflicting conclusions to those outlined above regarding the possible mechanisms of the modulation observation and challenges the above conclusions (i.e. right hemisphere overloading and disruption of parietal balance) formulated.

That is the results from the unilateral montage tDCS experiment show, that inhibition of the left hemisphere supresses both the processing of the left beating nystagmus and right beating nystagmus (albeit significantly greater suppression of the left beating). The implication of this result is that the right hemisphere can and does exert a strong inhibition over the left hemisphere.

Hence, during the behavioural manipulation presented in Chapter 3 an alternative explanation is that the modulation is caused by the attentional tasks or bistable percept's activating the right hemisphere (i.e. overloading) which in turn due to the relative greater

activation of the right hemisphere in turn supresses the left hemisphere, rendering it less able to process the left beating nystagmus. Reducing the attentional load could in theory reduce the relative excitability and lessen the inhibition exerted, as demonstrated.

However, the argument against such an explanation is twofold. Firstly, application of unilateral anodal stimulation of right hemisphere with tDCS stimulation did not modulate the VOR and, secondly, that the behavioural modulation observed during velocity step rotations was unilateral as opposed to the bilateral yet still asymmetrical suppression that would be expected in line with the tDCS findings.

Moreover, there was no modulation of the VOR when the right hemisphere was selectively suppressed using tDCS. The possible reason for a lack of modulation observed during right cathodal stimulation (i.e. during suppression of the right hemisphere) could potentially be explicable by the two following possibilities. Firstly, it could be attributable to the fact that right hemisphere dominance exists for vestibular cortical processing (Dieterich et al., 2003a). That is, the application of the same amount of current to both the right and left hemisphere does not produce comparable effects due to the preponderance (greater devotion of resources) of the right hemisphere compared to the left for vestibular processing. Secondly, it could be attributed to the fact that asymmetric connections present between the right and left parietal lobes in order to place each hemisphere under reciprocal inhibition. The result of these asymmetric connections is that the right hemisphere is able to exert a stronger inhibition over the left hemisphere than the left hemisphere is able to exert over the right hemisphere. Accordingly, following inhibition of the left hemisphere the right is able to exert a greater suppression of the left hemisphere (hence supressing the VOR)

compared to that what the left hemisphere is able to exert over the right following application of right cathodal stimulation (Koch et al., 2011).

Moreover, in light of the above arguments we feel that in totality of the evidence available, that a simplistic explanation of disruption of parietal balance, as initially postulated in this thesis, is not responsible for the modulation. The reasons for such a viewpoint are outlined below.

Firstly, in all the tDCS conditions a disruption of parietal balance is created, yet no modulation is observed in all the conditions when theoretically they all disrupt parietal balance. Secondly, a recent report showed that application of bilateral parietal tDCS did not modulate the VOR in response to velocity step rotation (i.e. specifically ruling out a disruption of parietal balance hypothesis for the behavioural modulation of the VOR; i.e. Results presented in Chapter 3) (Kyriakareli et al., 2013).

To further clarify the role of parietal balance we performed the experiments presented in chapter 5. We assessed whether this novel behavioural/physiological technique was specifically acting upon the vestibular system or whether it could generalise and extend to modulating other low-level sensory structures, namely the early visual cortex.

As the hypothesis was drawn from a previous demonstration, namely that disruption of parietal balance using tDCS can induce top down modulation of the early visual cortex (Silvanto et al., 2009), it follows then that, if indeed this novel behavioural technique (i.e. concurrent vestibular activation and redirection of spatial attention) was disrupting parietal balance then accordingly it should modulate the early visual cortex in line with the earlier tDCS findings.

As we show in the final experimental chapter (Chapter 5), this novel behavioural technique did induce top down cortical modulation of the early visual cortex (Arshad et al., 2013). However, as these findings differ from those of earlier findings using tDCS to disrupt parietal balance and subsequently assessing the effects upon visual cortex (Silvanto et al., 2009), it casts further doubt that the modulation of either the VOR or the visual cortex following the behavioural/physiological manipulations is secondary to disruption of parietal balance.

That is, as only during the combination of right but not left cold caloric and a visuo-spatial working memory task modulated the excitability of the visual cortex. In both cases (right or left cold + visuo-spatial working memory task) a disruption of parietal balance exists, yet modulation of the visual cortex excitability does not occur in both cases.

As right cold irrigation activates mainly the left hemisphere and the attention task the right hemisphere, a potential conflict may exist with regards to the re-direction of spatial attention. No such conflict is occurring during left caloric as both the vestibular stimulus and the attentional task signal a re-direction of spatial attention in a congruent manner.

Hence, it could well be the case that the conflict regarding the re-direction of spatial attention induced disruption of parietal function (and thus asymmetrical modulation of both the VOR and the visual cortex) in an independent manner to that caused by the tDCS.

Thus, one cannot rule out the possibility that the effects of tDCS upon the parietal lobe function to be different to the effects of the behavioural manipulations used in experimental chapters 3 and 5, hence to draw comparisons between the two is of limited significance. The finding that we specifically showed that tDCS is able to act upon the gain

component of the velocity storage but not, as the behavioural manipulations can, upon the long-time constant component of the velocity store, further supports this view.

Moreover, the findings reported in chapter 3 and 4 do have functional implications regarding how we consider the velocity storage function, which we shall now discuss.

6.7 Implications for the concept of the velocity storage mechanism

Regardless of the mechanism that may be responsible for the results reported in both Chapter 3 and 4, important implications arise from the findings. That is, the conventional and well accepted model of the velocity storage mechanism should be revised to consider an input from the parietal cortex.

Recall from the introduction that the velocity storage mechanism is involved in neural integration. In vestibular processing the semi-circular canals mechanically integrate the initial head acceleration input into a velocity signal (Raphan, Matsuo & Cohen, 1979b), as recorded from the vestibular nerve (Buttner & Waespe, 1981). Direct recordings have demonstrated that this canal integration has a time constant of between 5-7 seconds, termed the direct vestibular pathway (Buttner & Waespe, 1981).

However, the canals can drive the eyes by activating both direct and indirect pathways. This is known since in the laboratory setting, rotation at constant velocity in darkness results in a longer time course for the exponential decay of the oculomotor response: a time constant of between 16-20 seconds. This is significantly longer than the time course derived from the direct pathway (i.e. cupular dynamics alone). Prolongation of this response occurs due to the indirect pathways of the neural integrator (i.e. the velocity storage mechanism VSM) (Buttner & Waespe, 1981, Raphan, Matsuo & Cohen, 1979b).

Moreover, one can modulate the function of the velocity storage function in normal healthy subjects. For example, following a velocity step rotation the velocity storage mechanism function is “dumped” if a subject is to visually fixate a light source, hence attenuating the resultant oculomotor response and this ability in accounted for in the velocity storage model (Waespe, Cohen & Raphan, 1985, Cohen et al., 1981).

Accordingly, a revised model should be produced, that is able to incorporate the finding that the output of the velocity storage mechanism can additionally be directly modulated asymmetrically, specifically by parietal cortex top-down signals (as proposed in the supplemental section of chapter 3; supplemental experiment 6). This is a clear implication for future work as well as those to be discussed below

6.8 Future implications

It is apparently clear that the exact mechanisms of the modulations we report in this thesis remain obscure and future work is required to clarify this issue. However, by using behavioural/physiological manipulations it is possible to alter parietal function in an asymmetrical manner; answering the overarching question postulated at the start of this thesis.

In a similar vein, the parietal lobe does much more than modulating low level brain mechanisms. Hence future studies utilising this technique should directly probe the ability of this technique to probe parietal mediated cognitive function such as numerical cognition and decision making and indeed some pilot data we have collected is promising in this regard. Moreover, it is imperative to establish, in parallel, the neural correlates using functional imaging of the effects of the combined dual-stimulation paradigm that results in

these modulations reported herein. Also with respect to this, we have started to conduct pilot studies using caloric and binocular rivalry in the scanner.

6.9 Concluding overview

To surmise, taken together, the findings presented in this thesis demonstrate that the application of concurrent vestibular activation and redirection of spatial attention is able to disrupt parietal function. In doing so I present demonstrable changes in

- (i) the brainstem mediated vestibular ocular reflex (Chapter 3 and 4) (Arshad, Nigmatullina & Bronstein, 2013a)

and

- (ii) perceptual measures of early visual cortical excitability (Chapter 5) (Arshad et al., 2013,)

, with both demonstrations equally subject to the disruption of parietal function (Chapters: 3,4 and 5) (Arshad et al., 2013).

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Appendix: Publications

The Journal of Neuroscience, February 13, 2013 • 33(7):3221–3227 • 3221

Brief Communications

Handedness-Related Cortical Modulation of the Vestibular-Ocular Reflex

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Multisensory visuo-vestibular cortical areas are important for spatial orientation and facilitate the control of the brainstem-mediated vestibular ocular reflex (VOR). Despite reports of visual input and cognitive tasks modulating the VOR through cortical control, it is unknown whether higher-order visual stimuli such as bistable perception and attention tasks involving visual imagery have an effect on the VOR. This is a possibility since such stimuli recruit cortical areas overlapping with those engaged during vestibular activation. Here we used a novel paradigm in which human subjects view bistable perceptual stimuli or perform complex attention tasks during concurrent vestibular stimulation. Bistable perceptual phenomena and attention tasks asymmetrically modulated the VOR but only if they involved a visuospatial component (e.g., binocular motion rivalry but not color rivalry). Strikingly, the lateralization effect was dependent upon the subjects' handedness, making this report the first behavioral demonstration that vestibular cortical processing is strongly lateralized to the non-dominant hemisphere. Furthermore, we show that perceptual transitions can modulate the dynamics of the vestibular system contingent upon the presence of a spatial component in the perceptual transition stimuli. Both perceptual transitions and attentional tasks are thought to invoke a redirection of spatial attention. We infer that such redirection of spatial attention engages multisensory vestibular cortical areas that modulate low-level vestibular function which, in turn, may contribute to spatial orientation.

Introduction

Visual and vestibular functions are complementary for gaze stabilization and maintenance of spatial orientation during head perturbations. Gaze stabilization is partly mediated by retinal slip velocity signals and the vestibular ocular reflex (VOR). Additional higher-order integration of visual and vestibular velocity signals is critical for conscious perception of body position in space and to modulate lower-brainstem vestibular reflexes such as the VOR (Suzuki et al., 2001).

In healthy adults, VOR responses are symmetrical for right and leftward rotations. The responses can be voluntarily modified bidirectionally by visual targets and non-visual tasks (e.g., VOR suppression occurs if subjects are asked to focus on real or imaginary targets rotating with them; Barr et al., 1976). Moreover, simple cognitive tasks such as mental arithmetic increase subjects' attentiveness and, as a result, the gain of the VOR response is enhanced (Jones et al., 1984). However, the effects of higher-order visual stimuli such as bistable perception or attention tasks requiring visualized spatial manipulation are unknown.

Bistable perception implies higher-order visual phenomena in which salient stimuli spontaneously disappear from visual awareness. Such perceptual phenomena include binocular rivalry and motion-induced blindness (MIB) (Bonneh et al., 2001; Knapen et al., 2011). The processing of such stimuli involves frontoparietal areas that have additionally been implicated in processing complex cognitive attentional tasks (that require visual imagery) and vestibular signals (Corbetta et al., 1998; Lumer et al., 1998; Bonneh et al., 2001; Corbetta and Shulman, 2002; Dieterich et al., 2003; Kanai et al., 2011). Lesions in these cortical areas cause spatial neglect by disrupting visuospatial attention, alter (bistable) perceptual transition dynamics, and induce VOR asymmetry (Ventre-Dominey et al., 2003; Bonneh et al., 2004). Reciprocally, vestibular activation can alter perceptual dynamics of bistable perception by modulating perceptual predominance of the rivaling images (Miller et al., 2000) and temporarily alleviate hemispatial neglect (Rubens, 1985).

Thus, it appears that processing of vestibular signals, visuospatial attention, and bistable perception are intertwined. As this has not yet been directly investigated, here we attempt to modulate the VOR by exposing subjects to visuospatial attention tasks and perceptual transitions such as binocular rivalry.

Received April 26, 2012; revised Dec. 16, 2012; accepted Dec. 20, 2012.
Author contributions: Q.A., Y.N., and A.M.B. designed research; Q.A. and Y.N. performed research; A.M.B. contributed unpublished reagents/analytic tools; Y.N. analyzed data; Q.A., Y.N., and A.M.B. wrote the paper.
This work was supported by the Medical Research Council of the U.K. We thank David Buckwell for his technical assistance, Dr. Saiful Islam for statistical advice, Dr. Paroshkov Nachev and Professor Michael Gresty for scientific discussion, and Dr. David Soto for his most helpful critique.
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DOI:10.1523/JNEUROSCI.2054-12.2013
 0270-6474/13/333221-07$15.00/0

Materials and Methods

The experimental strategy consisted of assessing the effects of viewing bistable perceptual visual stimuli or performing visuospatial attention tasks during velocity step rotations upon the post-rotational VOR (stopping) responses.

Experimental apparatus

A motorized rotating chair (Contraves) was used to deliver constant velocity rotations in yaw (90°/s). The chair was surrounded by a 1.44-m-diameter black and white striped (0.1 cycles/°) drum (Fig. 1*a*).

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Brain Stimulation xxx (2013) 1–7

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Research

Left Cathodal Trans-Cranial Direct Current Stimulation of the Parietal Cortex Leads to an Asymmetrical Modulation of the Vestibular-Ocular Reflex☆

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ARTICLE INFO

Article history:
Received 27 February 2013
Received in revised form
6 June 2013
Accepted 4 July 2013
Available online xxx

Keywords:
Vestibular cortical processing
tDCS
Parietal balance
Vestibular-ocular reflex

ABSTRACT

Multi-sensory visuo-vestibular cortical areas within the parietal lobe are important for spatial orientation and possibly for descending modulation of the vestibular-ocular reflex (VOR). Functional imaging and lesion studies suggest that vestibular cortical processing is localized primarily in the non-dominant parietal lobe. However, the role of inter-hemispheric parietal balance in vestibular processing is poorly understood. Therefore, we tested whether experimentally induced asymmetries in right versus left parietal excitability would modulate vestibular function. VOR function was assessed in right-handed normal subjects during caloric ear irrigation (30 °C), before and after trans-cranial direct current stimulation (tDCS) was applied bilaterally over the parietal cortex. Bilateral tDCS with the anode over the right and the cathode over the left parietal region resulted in significant asymmetrical modulation of the VOR, with highly suppressed responses during the right caloric irrigation (i.e. rightward slow phase nystagmus). In contrast, we observed no VOR modulation during either cathodal stimulation of the right parietal cortex or SHAM tDCS conditions. Application of unilateral tDCS revealed that the left cathodal stimulation was critical in inducing the observed modulation of the VOR. We show that disruption of parietal inter-hemispheric balance can induce asymmetries in vestibular function. This is the first report using neuromodulation to show right hemisphere dominance for vestibular cortical processing.

Introduction

The insular-parietal cortical region is known to be involved in vestibular cortical processing based on data from functional imaging and lesion studies [1,2], however the effect of disrupting inter-hemispheric parietal balance [3] upon vestibular processing remains unknown. Trans-cranial direct current stimulation (tDCS) has previously been shown to modulate cortical excitability through the induction of transient changes in local field polarity [3,4]. Moreover, concurrent application of opposite polarity stimulation over parietal regions has been reported to alter the parietal balance between the two hemispheres [4,5].

Normal vestibular responses, as assessed by the vestibular-ocular reflex (VOR), elicited by vestibular activation are approximately symmetrical, irrespective of whether the right or left labyrinth is stimulated. However, the VOR is plastic in that it can be bi-directionally modified by both visual and non-visual input (i.e. VOR suppression is observed if subjects focus on a real or imagined target) [6].

Functionally, the VOR is critical for gaze stabilization during head perturbations, and is mediated by a combination of vestibular and retinal velocity signals. Despite the significant involvement of brainstem centers in the VOR, higher order integration of visuo-vestibular signals may be critical for the conscious perception of body position in space and potentially to regulate reflexes such as the VOR [7]. Moreover, in a recent study an asymmetrical handedness-related down-regulation of the VOR was demonstrated as a result of viewing bistable perceptual visual stimuli (i.e. binocular rivalry) or performing a visualized spatial attentional task during concurrent vestibular stimulation. It was proposed that the effect occurred as a result of engaging overlapping cortical parietal networks in the non-dominant hemisphere resulting in disruption of parietal hemispheric balance [8]. Hence, we sought to modulate relative excitability levels in the parietal lobes of left and right hemispheres with tDCS, thereby inducing parietal lobe imbalance, in order to assess the effect upon the VOR.

This study was funded by the Medical Research Council (UK).

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1935-861X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2013.07.002

CORTEX 49 (2013) 2938–2940

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Letter to the Editor

Separate attentional components modulate early visual cortex excitability

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Disruption of the right lateralised fronto-parietal attentional network using neuro-modulation techniques has been shown to induce both functional and perceptual modulation of early visual cortex (Silvanto, Muggleton, Lavie, & Walsh, 2009). Such modulation is suggested to be mediated by interhemispheric competition (Silvanto et al., 2009). To date in neurologically normal subjects no behavioural demonstration of such modulation exists. In this study, we stimulated the vestibular system during performance of an attentional task. A previous study has demonstrated that passive rotation combined with performance of a visual attentional task results in asymmetric modulation of the brainstem mediated vestibulo-ocular reflex (VOR) (Arshad, Nigmatullina, & Bronstein, 2013). The modulation of the VOR is suggested to occur as a result of activating overlapping cortical networks responsible for processing both vestibular information and the attentional task in the right parietal lobe (Corbetta & Shulman, 2002; Dieterich et al., 2003; Miller et al., 2000; Van Elk & Blanke, 2012), resulting in inhibition of the left hemisphere via interhemispheric competition (Arshad et al., 2013; Miller et al., 2000). This hypothesis was directly tested in a recent study where transcranial direct current stimulation of the parietal cortex was employed to assess the effect upon the VOR (Arshad, Nigmatullina, Roberts et al., 2013), with the largest modulation of the VOR observed during cathodal stimulation of left parietal cortex. Thus in this study, we combined caloric stimulation with a visual attention task to disrupt parietal interhemispheric balance in normal subjects, and measured the possible effect on V1/V2 excitability.

Moreover, for the first time we delineate the specific contributions of spatial versus non-spatial attentional networks in modulating early visual cortex.

We assessed V1 excitability using phosphenes, elicited by briefly stimulating the visual cortex using single pulse transcranial magnetic stimulation (TMS), with the intensity required to elicit a phosphene reflecting the underlying cortical excitability (Marg & Rudiak, 1994). Eighteen right-handed participants (male 14, mean age = 24; range 20–33) gave written informed consent as approved by the local research ethics committee. Subjects were blindfolded and were seated on a chair fitted with a fixed magnetic coil and head restraint system. The head was inclined 30° from the horizontal plane for maximal horizontal canal caloric stimulation. Firstly, V1 stimulation site was localised using a functional method by placing the coil centrally over the inion then moving it dorsally until the brightest stationary phosphene percept is observed in the centre of the visual field (Walsh, Pascual-Leone, & Kosslyn, 2003). Secondly, the threshold was established according to a modified binary staircase algorithm (Tyrrell & Owens, 1988) previously described (Seemungal et al., 2013). Subjects were trained to rate the intensity of the perceived phosphene on a scale from 0 (no phosphene, below threshold) to 5 (maximum brightness, 100% maximum stimulator output). We then used the established clinical approach for cold water (30 °C) caloric irrigation (left or right ear, randomised order) for 40 sec to activate the vestibular system. The irrigations were separated by a period of 5 minutes to allow for any after effects to subside.

Following each irrigation we immediately measured visual cortical excitability using 20 single TMS pulses (Guzman-Lopez, Silvanto, & Seemungal, 2011) applied at 20% above phosphene threshold for each individual, with each pulse separated by 3 sec. Subjects responded verbally and rated

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0010-9452/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cortex.2013.08.016