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Applications of neuromodulation to explore vestibular cortical processing; new insights into the effects of direct current cortical modulation upon pursuit, VOR and VOR suppression

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Abstract. Functional imaging, lesion studies and behavioural observations suggest that vestibular processing is lateralised to the non-dominant hemisphere. Moreover, disruption of interhemispheric balance via inhibition of left parietal cortex using transcranial direct current stimulation (tDCS) has been associated with an asymmetric suppression of the vestibulo-ocular reflex (VOR). However, the mechanism by which the VOR was modulated remains unknown. In this paper we review the literature on non-invasive brain stimulation techniques which have been used to probe vestibular function over the last decade. In addition, we investigate the mechanisms whereby tDCS may modulate VOR, e.g. by acting upon pursuit, VOR suppression mechanisms or direct VOR modulation. We applied bi-hemispheric parietal tDCS in 11 healthy subjects and only observed significant effects on VOR gain (tdcs * condition $p = 0.041$) – namely a trend for VOR gain increase with right anodal/left cathodal stimulation, and a decrease with right cathodal/left anodal stimulation. Hence, we suggest that the modulation of the VOR observed both here and in previous reports, is directly caused by top-down cortical control of the VOR as a result of disruption to interhemispheric balance, likely parietal.

Keywords: VOR, pursuit, interhemispheric, brain stimulation, vestibular

1. Introduction

The visual and vestibular systems perform complementary functions in order to stabilise gaze and maintain spatial orientation during head perturbations. In recent years, findings from neuroimaging and lesion studies have highlighted the importance of the cortex in vestibular processing [8,13]. Neuromodulation techniques such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) offer different ways of modulating cortical excitability in order to infer underlying functional properties. These techniques differ fundamentally from galvanic vestibular stimulation as they target cortical processing rather than the peripheral vestibular system directly. In this paper we discuss the findings of recent studies which have employed these techniques to study vestibular

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cortical processing and consider future applications of neuromodulation in vestibular research.

2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) can be used to selectively and focally disrupt different cortical regions or measure underlying cortical excitability [20]. A major advantage of this approach is the spatial and temporal specificity with which it is possible to stimulate the cortex compared to the relatively less focal stimulation achieved with tDCS. An example of this is the work of Seemungal and colleagues who stimulated visual cortex with TMS in order to induce phosphenes [16]. Phosphenes are perceived as brief flashes in the visual field which correspond to excitation of particular areas of visual cortex and are used as a direct, albeit subjective, measure of visual cortex excitability. Since vestibular and visual cortices are thought to be linked via reciprocal inhibitory mechanisms [5], phosphenes offer a direct way of quantifying the influence of the vestibular system upon visual cortex excitability. The authors found that vestibular activation via caloric stimulation differentially modulated early visual cortex (V1) and motion sensitive visual cortex (V5/MT) excitability as measured by TMS-induced phosphenes. It was found that area V5/MT was selectively inhibited, whereas a generalised non-specific enhancement was observed for the early visual cortex (V1) [16]. This work was extended by examining the influence that spatial attention mechanisms might have on these systems [1]. The interaction between vestibular cortical and spatial attention mechanisms has previously been shown to display a bi-directional relationship [2]. This is thought to occur because the cortical areas most frequently implicated in processing vestibular signals (i.e. the multi-sensory fronto-parietal network), located predominantly in the non-dominant hemisphere, are also known to play a critical role in spatial attention [6,8]. In this study TMS was used to probe V1 excitability during caloric stimulation, and then combined with a visuospatial or non-visuospatial task. A specific reduction in the perceived intensity of phosphenes was observed *only* during a right cold caloric (activating primarily left hemisphere) combined with a visuospatial task (remembering a grid of numbers and their allotted locations). However, no changes were observed during left cold caloric or performance of the non-spatial task. These findings suggest that concurrent vestibular and spatial attention processing results in suppression of early visual cortex [1]. The above studies illustrate how TMS can be used to explore visual-vestibular interactions and expand the findings of functional imaging studies by providing causal evidence for the directionality of effects observed in the scanner.

Indeed, other vestibulo-cortical interactions can also be probed using TMS, such as vestibular-induced modifications of the corticospinal tract. This has been investigated by measuring the effect of caloric irrigation on the amplitude of motor evoked potentials (MEP) evoked by applying TMS over the primary motor cortex. It was demonstrated that during caloric activation the activity of the sternocleidomastoid muscle was modulated, suggesting that this neck muscle operates under both corticospinal *and* horizontal semi-circular canal control [9].

TMS can also be used to selectively inhibit and disrupt the function of selected brain areas in order to assess their functional relevance. This approach was recently employed in a study which used TMS to inhibit sub-regions within parietal cortex before measuring subjective judgements of the visual vertical [11]. Prior to participants making a judgement about the verticality of a line, a high frequency inhibitory burst of TMS (continuous theta burst) was applied to the right parietal cortex. By varying the location of the stimulation site, the authors found that the posterior aspect of supramarginal gyrus was associated with significant distortions in the perceived tilt of a line. The application of TMS was combined with neuronavigation techniques in order to accurately localise and identify the targeted brain areas using structural brain scans [11]. The application of inhibitory repetitive TMS has also been used to probe the perception of position in space as the body is rotated. When TMS was applied to posterior parietal cortex during the encoding phase of a rotation it resulted in increased errors when estimating angular displacements, but it did not affect velocity perception. This revealed that posterior parietal cortex may play a critical role in path integration – the process by which angular position in space is determined [15,17,18]. The above studies illustrate how TMS can be used to focally probe and dissociate the specific contribution of different brain regions involved in vestibular cortical processing.

3. Transcranial direct current stimulation

The effects of direct modulation of hemispheric activity have also been investigated using transcranial

direct current stimulation (tDCS). This non-invasive stimulation technique has been used to modulate a range of functions including motor learning, sensory and cognitive systems [14]. Recent work has attempted to assess the impact of tDCS upon vestibular cortical processing. Kyriakareli and colleagues [12] examined the effects on both oculomotor and perceptual components of vestibular processing after bilaterally stimulating the temporo-parietal junction (TPJ) using tDCS. Vestibular-ocular and vestibulo-perceptual thresholds during high frequency rotations were measured before and after 15 minutes of tDCS and resulted in an increase in both VOR and perceptual thresholds following stimulation, regardless of the direction of rotation, with the stronger effect observed on VOR thresholds [12]. In a separate study, Arshad et al. [3] used tDCS to explore what effect stimulation of posterior parietal cortex had upon vestibular processing of a caloric stimulus. In the bilateral stimulation condition with the cathode over left parietal cortex and anode over the right, a significant reduction in the slow phase velocity of the VOR was observed only during the right caloric irrigation. In contrast, no significant modulation of VOR was apparent during the reverse stimulation or 'sham' conditions [3]. These effects were explored further by selectively stimulating either left or right parietal cortex alone, with the reference electrode on the shoulder. This revealed that inhibition of left parietal cortex (cathodal, inhibitory stimulation) was the critical factor in inducing the observed modulation of the VOR [3].

These studies demonstrate that disruption of interhemispheric parietal balance results in modulation of vestibular function [3,12], with the differential effects observed possibly dependent upon the specific nature of the vestibular stimulus employed. One possible explanation for these findings could be related to the impact of brain stimulation upon pursuit or VOR suppression mechanisms. Therefore, we conducted a separate experiment to directly test this hypothesis. Using the same tDCS montage to bilaterally stimulate posterior parietal cortex, we investigated whether similar asymmetries were also induced in pursuit eye movements, VOR and VOR suppression.

4. Methods

We recruited 12 healthy right handed subjects (8 male, mean age = 20) with no history of otological, neurological or ophthalmological disease. One subject was excluded due to technical difficulties associated with one of the brain stimulation conditions. Each subject underwent two sessions at least 24 hours apart to avoid carryover effects, and the order of conditions counterbalanced using a Latin square design. The behavioural eye movement measurements were acquired immediately before and after tDCS in each session. All subjects provided written informed consent as directed by the local ethics research committee. Results were analysed using in-house Analysis software written by Mr D. Buckwell.

5. Vestibular assessment parameters

Horizontal eye movements were recorded using binocular electronystagmography. Eye movements were captured with three small adhesive electrodes (Carefusion, Ag/AgCl) attached to the outer canthi of both eyes and forehead. Testing was performed using a motorised rotatory chair (Neurokinetics Inc., Pittsburgh, USA) in complete darkness. The following parameters; VOR, VOR suppression (VORs) and pursuit were assessed both before and immediately after of tDCS stimulation. The order was randomised according to a Latin square design. The VOR and VORs measurement lasted 1 minute 30 seconds and pursuit data was collected for 40 seconds. Sinusoidal VOR and VOR suppression were measured at a frequency of 0.25 Hz and a peak velocity of 40 degrees/s, and pursuit was assessed at two frequencies, 0.1 Hz and 0.4 Hz.

6. Brain stimulation

Brain stimulation using tDCS was applied using the bilateral montage previously described in Arshad et al. [3], see Fig. 1A. There were two bilateral stimulation conditions, one for each session. In the first condition the anode was placed over the left hemisphere (P3) and the cathode over the right (P4). In the second condition the locations were identical but with the polarity reversed. The electrodes were always placed at least 7–8 inches apart from each other to prevent any local interaction or attenuation of effects. 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 1.5 mA 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.

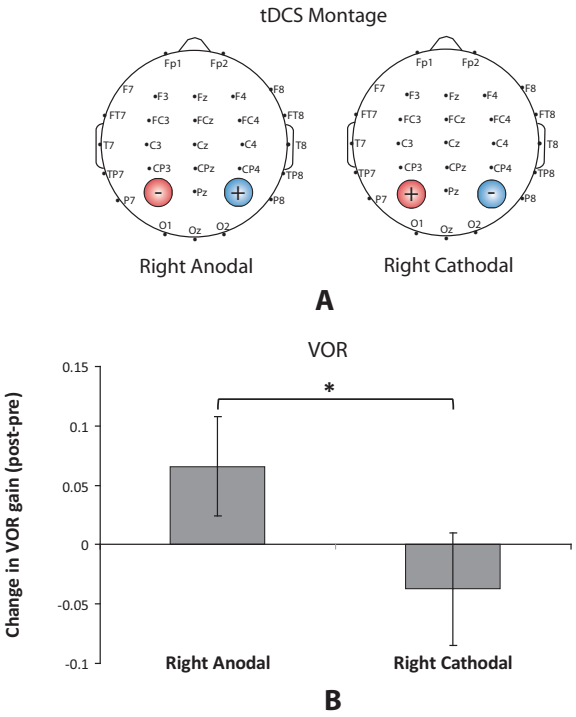

Fig. 1. Brain stimulation montage and results for the VOR modulation following application of tDCS. A) The bilateral stimulation montages are shown for the two conditions employed (i.e. Right Anodal or Right Cathodal) B) Application of either right anodal or right cathodal tDCS has a significant opposing effect on the change in VOR gain (Post-Pre tDCS), Data indicated * are significant at $P < 0.05$ and error bars represent standard error.

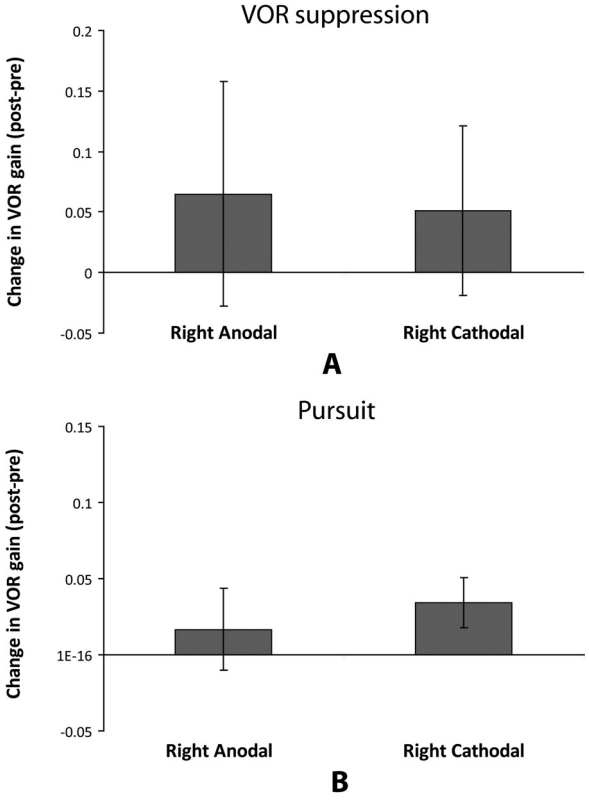

Fig. 2. The change in gain following application of Right Anodal or Right Cathodal tDCS. A) No significant change in gain (post-pre tDCS) was observed for VOR suppression. The graph illustrates the change in gain when both rightward and leftwards rotations were combined. B) No significant change in gain was observed for pursuit, with the graph illustrating combined results for both directions (leftwards and rightwards moving target) and both frequencies (0.1 Hz and 0.4 Hz). Error bars represent standard error.

7. Results

For the VOR during sinusoidal rotation, a 2 × 2 × 2 repeated measures ANOVA was performed with within-subjects factors of tDCS stimulation (Right Anodal or Right Cathodal), condition (pre or post tDCS) and direction of the nystagmus (leftward or rightward). No significant main effects of tDCS stimulation, condition or direction were found but the interaction of tDCS stimulation * condition was significant ($p = 0.041$, $F = 5.47$, $df = 1$). For illustrative purposes the change in VOR gain (Post – Pre tdcs) was calculated with leftward and rightward directions combined together as shown in Fig. 1. Here, the two types of stimulation (right anodal/left cathodal or right cathodal/left anodal) have an opposing effect on the VOR gain; i.e. the change in VOR gain following right anodal/left cathodal stimulation showed a significantly greater increase as compared to left anodal/right cathodal stimulation.

Importantly, for VOR suppression no main effects of tDCS, condition or direction were observed and no significant interactions were found ($p > 0.05$; 2 × 2 × 2 repeated measures ANOVA as above for VOR). For the smooth pursuit, a 2 × 2 × 2 × 2 repeated measures ANOVA was performed with within-subjects factors of tDCS stimulation (Right Anodal or right Cathodal), condition (pre or post tDCS), direction of target (leftward or rightward) and pursuit frequency (0.1 Hz or 0.4 Hz). No significant main effects or interactions were found ($p > 0.05$). Figure 2 illustrates that no significant changes were found for gain in VOR suppression or pursuit following application of either brain stimulation condition.

8. Discussion

The findings we present here suggest that disruption of interhemispheric parietal balance via the ap-

plication of bi–hemispheric tDCS modulates the VOR during high frequency rotation in a non-direction specific manner. Critically, tDCS did not modulate either pursuit or VOR suppression mechanisms, thereby implying that both of the previous reports where modulation of VOR was observed following the application of tDCS were not attributable to either of these mechanisms [3,12]. Neither can the effect observed upon the VOR cannot be explained by non-specific galvanic stimulation effects of tDCS as Kyriakareli and colleagues demonstrated that this protocol does not induce torsional eye movements as measured with 3D-VOG [12]; the dominant eye movement elicited by galvanic stimulation [19].

Indeed, we observe a bilateral modulation of the VOR and not the asymmetrical modulation of the VOR observed by Arshad and colleagues [3]. They argued that the differential effects observed were attributable to the nature of the vestibular stimulus employed. That is, the rotational stimulus employed in this study and by Kyriakereli and colleagues [12] lasts $<$ 1 s (steps) whereas the temperature gradient created by caloric irrigation lasts several minutes [4]. Hence, VOR parameters are measured during the high frequency component of the rotational stimulus – typically within 1–2 s of the high acceleration delivered and when the slow acting velocity storage mechanism is not involved. In the previous study by Arshad and colleagues [3] a caloric stimulus was deployed and the peak velocities reported reached 60–80 seconds after stimulus onset, almost certainly under the influence of the velocity storage mechanism.

Our findings suggest that application of tDCS over the parietal cortical areas is likely to be modulating the VOR not through pursuit or VOR suppression mechanisms, rather via direct top-down cortical modulation of the VOR. Although the stimulation was localised to parietal cortex, there is a possibility that this could also be explained by a generalised effect of disrupting interhemispheric balance between the homologous lobes [1–3]. The lack of any significant effect on pursuit and VOR suppression could also reflect a limitation of the stimulation technique to influence the more complex brain networks involved in these processes.

The last decade has seen significant achievements in understanding vestibular cortical processing using functional imaging techniques. Recent technical advances in non-invasive brain stimulation now present an opportunity to test the causality of the findings from neuroimaging. Future studies could potentially use tDCS to treat aspects of common vestibular disorders in both the acute and chronic stages, as already shown for balance problems of non-vestibular origin [10]. Moreover, probing individual differences in visual cortical excitability with TMS could be used to explore the relationship between health outcomes and behavioural predictors such as visual dependency following vestibular neuritis [7].

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References

[1] Q. Arshad, Y. Nigmatullina, V. Bhrugubanda, P. Asavarut, P. Obrocki, A.M. Bronstein and R.E. Roberts, Separate attentional components modulate early visual cortex excitability, *Cortex* **49** (2013), 2938–2940.

[2] Q. Arshad, Y. Nigmatullina and A.M. Bronstein, Handedness-related cortical modulation of the vestibular-ocular reflex, *J Neurosci* **33** (2013), 3221–3227.

[3] Q. Arshad, Y. Nigmatullina, R.E. Roberts, V. Bhrugubanda, P. Asavarut and A.M. Bronstein, Left cathodal trans-cranial direct current stimulation of the parietal cortex leads to an asymmetrical modulation of the vestibular-ocular reflex, *Brain Stimul* **7** (2014), 85–91.

[4] G. Barnes, Adaptation in the oculomotor response to caloric irrigation and the merits of bithermal stimulation, *Br J Audiol* **29** (1995), 95–106.

[5] T. Brandt, P. Bartenstein, A. Janek and M. Dieterich, Reciprocal inhibitory visual-vestibular interaction. Visual motion stimulation deactivates the parieto-insular vestibular cortex, *Brain* **121** (Pt 9) (1998), 1749–1758.

[6] M. Corbetta and G.L. Shulman, Control of goal-directed and stimulus-driven attention in the brain, *Nat Rev Neurosci* **3** (2002), 201–215.

[7] S. Cousins, D. Kaski, N. Cutfield, B. Seemungal, J.F. Golding, M. Gresty, S. Glasauer and A.M. Bronstein, Vestibular perception following acute unilateral vestibular lesions, *PLoS One* **8** (2013), e61862.

[8] M. Dieterich, S. Bense, S. Lutz, A. Drzezga, T. Stephan, P. Bartenstein and T. Brandt, Dominance for vestibular cortical function in the non-dominant hemisphere, *Cereb Cortex* **13** (2003), 994–1007.

[9] J. Guzman-Lopez, Y. Buisson, P.H. Strutton and A.M. Bronstein, Interaction between vestibulo-spinal and corticospinal systems: a combined caloric and transcranial magnetic stimulation study, *Exp Brain Res* **214** (2011), 37–45.

[10] D. Kaski, R.O. Dominguez, J.H. Allum and A.M. Bronstein, Improving gait and balance in patients with leukoaraiosis using transcranial direct current stimulation and physical train-

ing: an exploratory study, *Neurorehabil Neural Repair* **27** (2013), 864–871.
[11] A. Kheradmand, A. Lasker and D.S. Zee, Transcranial Magnetic Stimulation (TMS) of the Supramarginal Gyrus: A Window to Perception of Upright, *Cereb Cortex* (2013).
[12] A. Kyriakareli, S. Cousins, V.E. Pettorossi and A.M. Bronstein, Effect of transcranial direct current stimulation on vestibular-ocular and vestibulo-perceptual thresholds, *Neuroreport* **24** (2013), 808–812.
[13] C. Lopez, O. Blanke and F.W. Mast, The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis, *Neuroscience* **212** (2012), 159–179.
[14] W. Paulus, Transcranial direct current stimulation (tDCS), *Suppl Clin Neurophysiol* **56** (2003), 249–254.
[15] B.M. Seemungal, S. Glasauer, M.A. Gresty and A.M. Bronstein, Vestibular perception and navigation in the congenitally blind, *J Neurophysiol* **97** (2007), 4341–4356.
[16] B.M. Seemungal, J. Guzman-Lopez, Q. Arshad, S.R. Schultz, V. Walsh and N. Yousif, Vestibular activation differentially modulates human early visual cortex and V5/MT excitability and response entropy, *Cereb Cortex* **23** (2013), 12–19.
[17] B.M. Seemungal, V. Rizzo, M.A. Gresty, J.C. Rothwell and A.M. Bronstein, Cortical processing in vestibular navigation, *Prog Brain Res* **171** (2008), 339–346.
[18] B.M. Seemungal, V. Rizzo, M.A. Gresty, J.C. Rothwell and A.M. Bronstein, Posterior parietal rTMS disrupts human Path Integration during a vestibular navigation task, *Neurosci Lett* **437** (2008), 88–92.
[19] A. Severac Cauquil, M. Faldon, K. Popov, B.L. Day and A.M. Bronstein, Short-latency eye movements evoked by near-threshold galvanic vestibular stimulation, *Exp Brain Res* **148** (2003), 414–418.
[20] V. Walsh and M. Rushworth, A primer of magnetic stimulation as a tool for neuropsychology, *Neuropsychologia* **37** (1999), 125–135.