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A differential role for the posterior cerebellum in the adaptive control of convergence eye movements

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ABSTRACT

Introduction: The vergence oculomotor system possesses two robust adaptive mechanisms; a fast "dynamic" and a slow "tonic" system that are both vital for single, clear and comfortable binocular vision. The neural substrates underlying these vergence adaptive mechanisms in humans is unclear.
Methods: We investigated the role of the posterior cerebellum in convergence adaptation using inhibitory continuous theta-burst repetitive transcranial magnetic stimulation (cTBS) within a double-blind, sham controlled design while eye movements were recorded at 250hz via infrared oculography.
Results: In a preliminary experiment we validated our stimulation protocols by reproducing results from previous work on saccadic adaptation during the classic double-step adaptive shortening paradigm. Following this, across a series of three separate experiments we observed a clear dissociation in the effect of cTBS on convergence adaptation. Dynamic adaptation was substantially reduced while tonic adaptation was unaffected. Baseline dynamic fusional vergence response were also unaffected by stimulation.
Conclusions: These results indicate a differential role for the posterior cerebellum in the adaptive control of convergence eye movements and provide initial evidence that repetitive transcranial magnetic stimulation is a viable tool to investigate the neurophysiology of vergence control. The results are discussed in the context of the current models of implicit motor adaptation of vergence and their application to clinical populations and technology design in virtual and augmented head mounted display architectures.
Significance statement: The cerebellum plays a critical role in the adaptive control of motor systems. Vergence eye movements shift our gaze in depth allowing us to see in 3D and exhibit two distinct adaptive mechanisms that are engaged under a range of conditions including reading, wearing head-mounted displays and using a new spectacle prescription. It is unclear what role the cerebellum plays in these adaptive mechanisms. To answer this, we temporarily disrupted the function of the posterior cerebellum using non-invasive brain stimulation and report impairment of only one adaptive mechanism, providing evidence for neural compartmentalization. The results have implications for vergence control models and applications to comfort and experience studies in head-mounted displays and the rehabilitation of clinical populations exhibiting vergence dysfunctions.

Introduction

Shifting our gaze between objects at different distances involves synkinetic changes in ocular alignment (vergence) and focus (accommodation) in order to maintain the perception of a clear, single image. The human convergence oculomotor system exhibits a remarkable capacity for adaptation. This enables binocular vision and stereopsis across a wide variety of visual environments. Understanding the neural mechanisms responsible for the adaptive elements of convergence has become increasingly important as they play a vital role in providing a comfortable and immersive virtual reality (VR) and augmented reality (AR) experiences [1–3], are highly susceptible to impairment by mild traumatic brain injuries (mTBI) [4] and can be underdeveloped in children as the

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clinical disorder of convergence insufficiency [5], which can affect academic performance and social development [6,7].

The literature has characterized 3 different oculomotor subsystems driving changes in the convergence angle in response to step changes in retinal disparities. The neural circuitry of these control systems is distributed across the parietal cortex, frontal eye fields, midbrain, pons and cerebellum [8]. The fusional system dynamically alters the convergence angle (roughly symmetric between each eye) in order to obtain binocular motor fusion [9–11]. The tonic system represents the underlying physiological vergence bias [9,11,12]. Finally, the saccadic-vergence system is responsible for the dynamic change in vergence observed during horizontal saccades between objects at different depths [13–15]. The encoding of the fusional and tonic systems involves a binocular motor signal [8,16–18], while new evidence suggests that the saccadic-vergence system is encoded as a monocular motor signal at the level of the superior colliculus [18,19].

There are at least two different adaptive elements found in the disparity-driven convergence system; dynamic and tonic [9,20]. The dynamic mechanism recalibrates fusional convergence responses to minimize errors during fixation changes in depth [21–23]. Tonic vergence adaptation is engaged during prolonged fixation, especially in visual environments where blur and disparity cues are incongruent, as would be encountered in fixed-focal stereoscopic displays. Here, a shift in the underlying tonic innervation uncouples the synkinetically-driven accommodative response and allows the accommodative and vergence systems to focus and converge to different distances [24–27]. This adaptive capacity underpins a comfortable user experiences in fixed focal VR and AR display architectures. Discomfort, fatigue and reduced image quality from optical defocus in VR and AR environments result when tonic vergence adaptation is insufficient and accommodation is drawn away from the displays focal plane [1–3]. Tonic adaptation also minimizes steady-state vergence error during prolonged viewing of incongruent blur and disparity scenes [28–30]. Dysfunctional vergence adaptation contributes to the symptoms experienced after mTBI [4] and is negatively associated with academic performance and behavior [6,7]. Despite their importance, the specific locations of the neural circuits underlying these two adaptive mechanisms are currently unknown.

There are multiple neural loci that could support tonic vergence adaptation. First, cells with firing rates that correlate with vergence position, known as 'tonic' cells, have been identified in the midbrain [31,32]. These cells discharge linearly in conjunction with convergence angle and have been isolated in the mesencephalic reticular formation dorsal to the oculomotor nucleus in the supraoculomotor area [16,33]. One electrophysiology study suggested that some, but not all of the tonic vergence adaptation signal occurred in this region [34]. Other studies have identified similar 'tonic' vergence cell types in the dorsal vermis of the cerebellum [35,36]. When these cells were chemically inhibited, a reduction in convergence but not divergence peak velocities to step changes in retinal disparities was observed. A second study assed the effect of surgical ablation of the dorsal vermis and reported impaired tonic vergence adaptation to base out prism in some, but not all primates tested [37]. In human patients with cerebellar lesions, tonic vergence adaptation has been reported to be both impaired [38] and preserved [39–41] in different studies. Thus, it is likely that the neural mechanisms responsible for tonic vergence are distributed across a number of areas.

Significantly less neurophysiological evidence exists regarding the specific location of dynamic vergence adaptation. The oculomotor vermis (OMV) of the posterior cerebellum (PC) plays a significant role in the backward adaptation of pro-saccadic eye movements [42–47]. This type of saccadic adaptation is a close cousin of dynamic fusional vergence adaptation. Preliminary functional MRI data suggests involvement of the dorsal vermis during clinical rehabilitation of vergence control dysfunctions [48], which are hallmarked by poor tonic and dynamic adaptation [49]. After orthoptic vision therapy, these adaptive responses increased to levels matching controls, as did functional activation of the posterior cerebellum [50]. Alvarez et al. also identified correlations between the hemodynamic response of the cerebellar vermis and enhancements of vergence dynamics following orthoptic treatment [51]. Together, current evidence suggests that the posterior cerebellum is a potential location for the neural machinery contributing to dynamic vergence adaptation.

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation that can safely and transiently influence neural activity [52–54]. The effects of single-pulses of TMS are immediate and short-lived [55,56]. When applied in repetitive patterns (rTMS) the effects can persist for hours [57,58]. Previous work has demonstrated that repetitive TMS applied to the posterior cerebellum can transiently alter the adaptive capacity of horizontal saccades in healthy observers [59,60]. Single pulse TMS has been shown to alter saccadic and convergence response latencies when applied to the posterior parietal cortex within a specific temporal window surrounding a stimulus [61,62].

We leveraged non-invasive brain stimulation techniques to test the hypothesis that the OMV also plays a role in the control of human convergence adaptation by applying an inhibitory form of repetitive TMS, known as continuous theta-burst stimulation (cTBS), to the PC and observing the resulting impact on dynamic and tonic convergence adaptation using a range of experimental and clinical metrics.

Results

Experiment #1: effect of cTBS on adaptation of pro-saccadic eye movements

We validated our cTBS protocol by demonstrating that cTBS applied over the PC impaired the adaptation of visually guided pro-saccadic eye movements measured using infrared oculography. Fig. 1 and Fig. 2-A illustrate the effects of the cTBS on saccadic adaptation (left eye only) in a typical observer in our sample. This effect has been previously reported using an inhibitory repetitive TMS (rTMS) protocol [63,64]**.** Using a within subject design ($n = 13$) and a leftward saccadic shortening double-step paradigm [65–67] ($16^\circ + -5^\circ$), relative to sham, active cTBS resulted in significantly less adaptive reduction of primary saccade amplitude (active: 7.9% ± 2.2 vs. sham: 15.9% ± 1.4, $F(2,248) = 39.3$, $p < 0.0001$) and peak velocity (active: 4.9% ± 3.2 vs. sham: 11.7% ± 1.9, $F(2,248) = 25.6$, $p < 0.0001$) as illustrated in Fig. 2-B. In pre-adaptation measures, the mean 'open-loop' pro-saccadic amplitude and peak velocity were smaller after active compared to sham cTBS (amplitude - active: $12.9^\circ \pm 1.7$ vs. sham: $14.0^\circ \pm 1.0$, $t(13) = 2.5$, $p = 0.03$; peak velocity - active: $373^\circ/s \pm 17$ vs. sham: $394^\circ/s \pm 16$, $t(13) = 2.6$, $p = 0.02$). This result is consistent with other rTMS studies, where differences between pre-adapted saccadic peak velocities after active and sham cerebellar stimulation bordered on statistical significance [64]. Supra-threshold single pulse TMS has also been shown to influence the amplitudes and peak velocities of visually guided pro-saccade execution [56]. This dual effect of the cTBS was accounted for by expressing each participant's adaptive changes as a percentage of mean baseline amplitude.

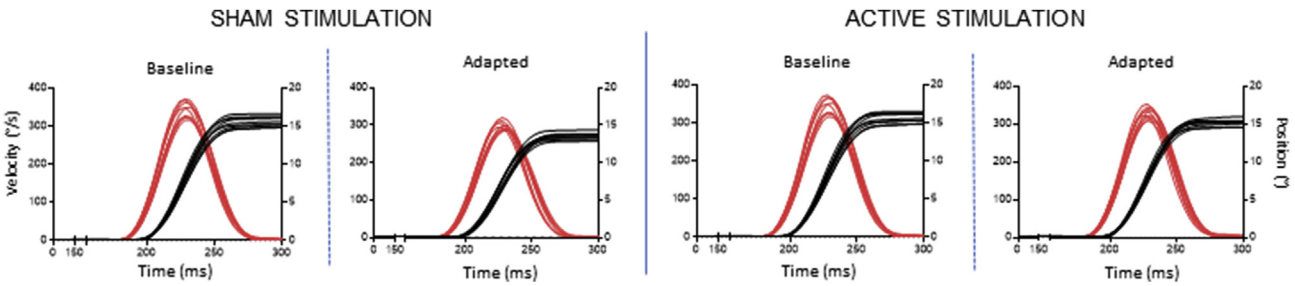

Fig. 1. Baseline and adapted saccadic responses (position: black traces, right ordinate and velocity: red traces, left ordinate) from a single subject for sham (left 2 panes) and active (right 2 panes) simulation conditions in Experiment #1. There is significantly less change (reduction) in the adapted saccadic response amplitudes and peak velocities in active condition (far right), indicating the cTBS inhibited the adaptation of the saccades to the shortening double-step stimulus. Data were smoothed using a 12 ms moving average prior to plotting. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Experiment #2: effect of cTBS on vergence amplitude and velocity

Because cTBS of the PC reduced saccade amplitude prior to adaptation, we tested whether the same effect occurred for fusional convergence responses. We applied a main sequence analysis (within subject design, $n = 10$) to convergence responses initiated by step changes (1°, 2°, 3° and 4°) in retinal disparity. The main sequence describes a relationship between eye movement response amplitude and peak velocity that is quasi-linear within a given range [68]. The slope of the function reflects greater neural recruitment for increasingly larger movements [31]. Relative to sham, active cTBS had no effect on the slope (active: 5.7(°/s)/° ± 0.3 vs. sham: 6.1(°/s)/° ± 0.4, $t(10) = 0.7$, $p = 0.50$) or y-intercept (active: 1.6° ± 1.5 vs. sham: 1.2° ± 1.1, $t(9) = 0.55$, $p = 0.59$) of the main sequence (Fig. 3). These results suggest PC-cTBS does not affect the execution of fusional convergence responses. Fig. 4 further illustrates this observation, whereby the fusional convergence responses at baseline to a 2° disparity step stimulus are virtually identical in sham and active stimulation conditions within a given participant.

Experiment #3: effect of cTBS on the dynamic adaptive element of convergence

Next, we investigated PC-cTBS effects on convergence adaptation. Fusional convergence was adaptively lengthened using double-step

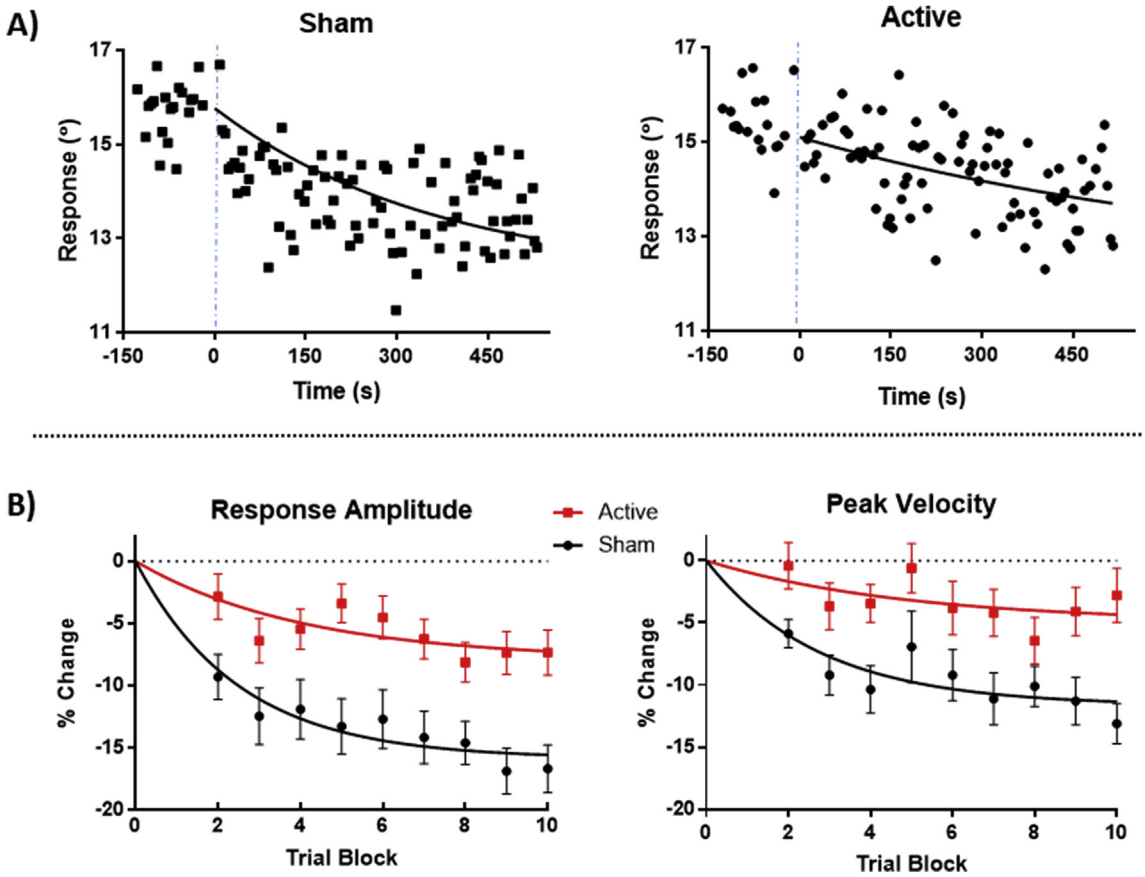

Fig. 2. -A) Leftward saccadic amplitudes for one subject's left eye in the active and sham sessions. Dashed vertical lines denote the start of the adaptation phase. **2-B)** Group mean (SE) of the percent change in primary saccade response amplitude and peak velocity from baseline for each block of 10 stimuli during adaptation.

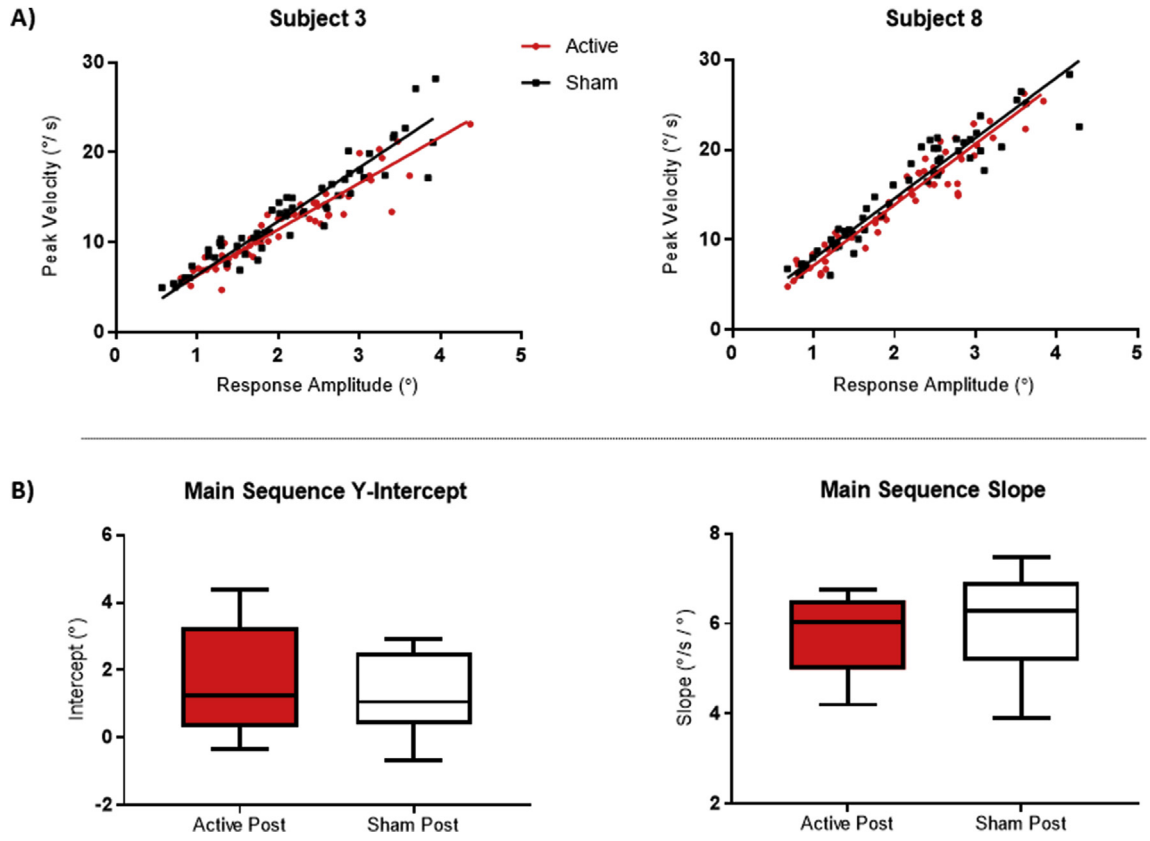

Fig. 3. -A) Main sequence plots with bivariate regressions for two subjects in both active and sham cTBS conditions. **3-B)** Box plots (IQR and 95% CI) of the grouped main sequence slope and y-intercept data for each stimulation condition.

changes in stimulus disparity [69] (2°+ 1.5° crossed disparity) after active or sham cTBS (within subject design, n = 13). This double-step paradigm engages both dynamic and tonic vergence adaptation processes [20]. Fig. 4 illustrates the baseline and post-adaptation convergence responses for both stimulation conditions for five of the thirteen subjects. The baseline responses are similar to those observed to the 2° convergence step stimulus used in Experiment #2. Fig. 5 illustrates the temporal effects during the adaptive paradigm for each condition for a single subject (A) and the grouped effects (B). Relative to sham, active cTBS impaired the dynamic adaptive increase in fusional convergence response amplitude (active: 15.1% ± 8.9 vs sham: 37.6% ± 4.7, md(12) = 16.9, p = 0.02) and peak velocity (active: 11.6% ± 7.8 vs sham: 36.2% ± 6.7, t(12) = 3.2, p = 0.006). Unlike experiment #1, there was no difference in pre-adaptation fusional convergence response amplitudes (active: 1.67° ± 0.07 vs. sham: 1.68° ± 0.09, t(12) = 0.04, p = 0.97) or peak velocities (active: 11.6°/s ± 0.7 vs. sham: 11.8°/s ± 0.9, t(12) = 0.3, p = 0.98) between active and sham conditions, consistent with the observations from experiment #2. A significant convergent increase in tonic vergence via the tonic adaptive mechanism was observed after adaptive lengthening (active: 1.17° ± 0.34 t(12) = 3.6, p = 0.004; sham: 0.96° ± 0.24, t(12) = 3.9, p = 0.002) that did not differ between the two conditions, t(12) = 1.01, p = 0.33. The results of this experiment indicated a significant effect of PC-cTBS on dynamic but not tonic convergence adaptation.

Experiment #4: effect of cTBS on the tonic adaptive element of convergence

We then investigated the effects of PC-cTBS on tonic vergence adaptation in greater detail by characterizing the temporal properties of the adaptive change using well-established clinical techniques. Participants maintained binocular fusion through a 12-prism diopter base-out optical prism placed in front of the right eye for a total of 4.5 min after receiving active or sham PC-cTBS (within subject design, n = 14). Changes in tonic vergence innervation were captured by changes in participant's heterophoria [70] using the Modified Thorington Technique (MTT) [71] initially and then after every 15 s of binocular fusion through the prism [72]. Relative to sham, there was no effect of active cTBS on the amplitude (t(13) = 1.4, p = 0.19), or rate of heterophoria change (md(13) = 1.1, p = 0.46) that were derived from exponential functions fitted to the data (Fig. 6). This result supported the results of Experiment #3, where tonic vergence adaptation was unaffected by PC-cTBS and suggests that the neural control of dynamic but not tonic vergence adaptation involves the PC in the healthy adult visual system.

Individual effects within each experiment

We observed between-subject variability in the response to cTBS, as has previously been reported [73]. Fig. 7 plots the individual participants as a function of the change between active and sham conditions in saccadic response properties from Experiment #3. The figure is representative of the overall effects observed in the 3 experiments. This highlights the point that while there were net mean inhibitory effects of the cTBS in our study, there were some participants who showed minimal if not opposite effects than expected. A generalized trend can be observed in Fig. 7, which was also true in the other experimental results, where the mean net effect was significantly different between conditions, as reported in the text; however, it is important to note that not all participants demonstrated the same effect of cTBS.

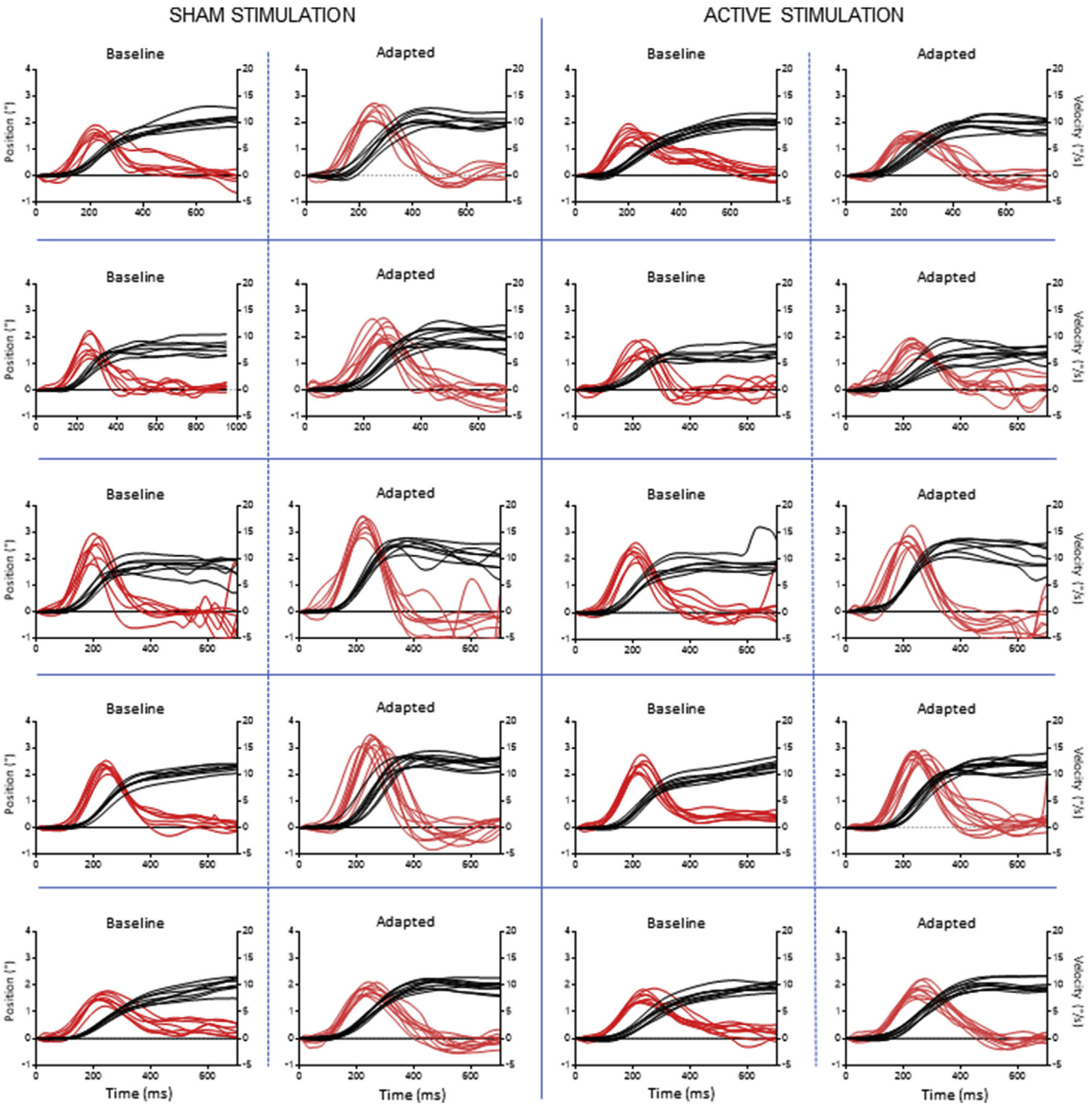

Fig. 4. Baseline and adapted ocular vergence responses (position: black traces – left ordinate, velocity: red traces – right ordinate) plotted for five different subjects (rows) for the sham (left 2columns) and active (right 2 columns) different stimulus conditions in Experiment #3. Note that the baseline responses plotted here reflect the same behavior observed for vergence responses to the 2° stimulus in Experiment #2. The observers in the top four rows exhibit varying degrees of inhibitory cTBS effects, where the adaptive increases in convergence response amplitude and peak velocity to the lengthening double-step stimulus are significantly reduced in the active condition. The bottom row depicts an observer where the cTBS appeared to have no effect, as the adapted convergence responses in both conditions show a similar increase in response amplitude and peak velocity. Absolute values are plotted for divergence. Data were smoothed using a 40 ms (10 sample) moving average for this figure. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

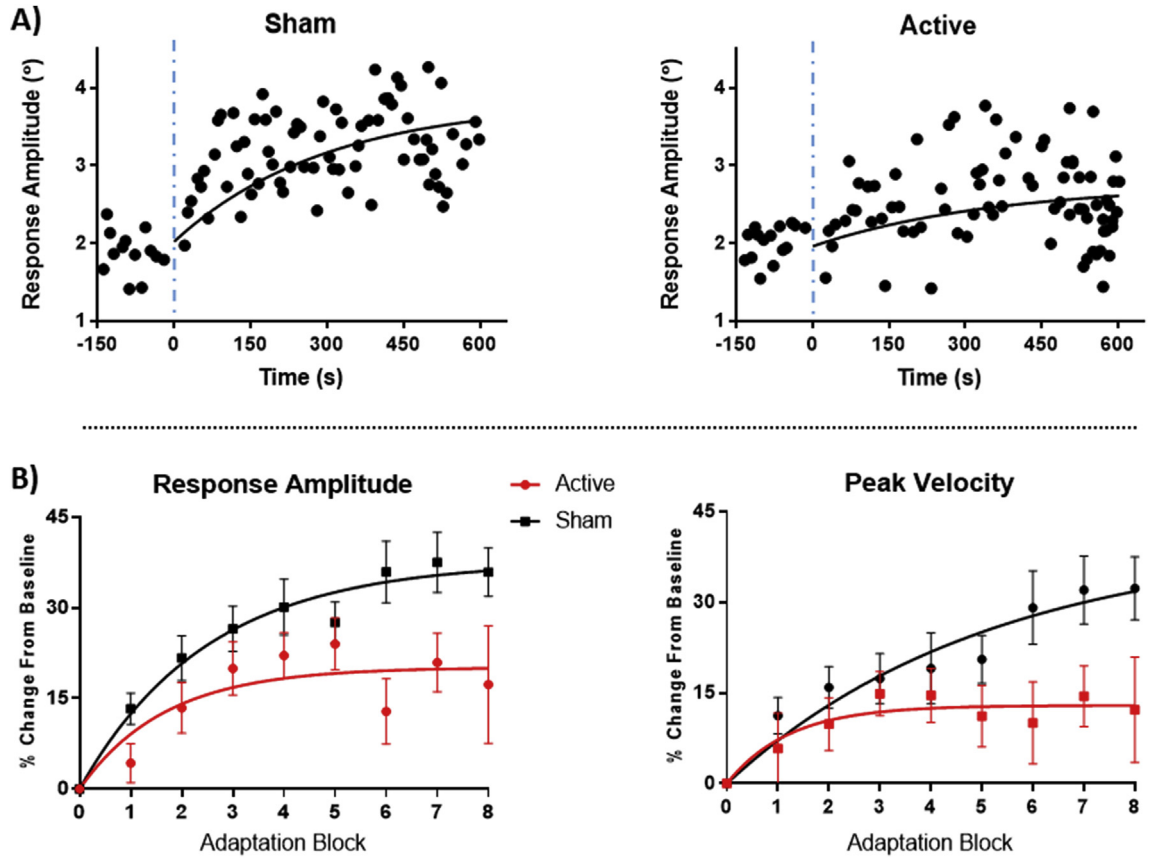

Fig. 5. -A) Convergence response amplitudes for one subject's active and sham visits. Dashed vertical lines denote the start of adaptation phase. Baseline responses are to the left of this line. The adaptive lengthening found in the sham treatment is attenuated in the active cTBS condition. **5-B)** Group mean (SE) of the percent change in convergence response amplitude and peak velocity compared to the baseline mean parameters for each block of 10 stimuli during adaptation.

Genetic influences

The Val-Met66 genetic polymorphism (also known as Rs6265) of brain derived neurotropic factor (BDNF) is a single nucleotide polymorphism that has been associated with reduced experience dependent plasticity [74,75], as well as a reduction in the inhibitory effects of cTBS [76]. We sequenced the BDNF gene in all our participants. In total, 18% (9 out of 49) of our subjects had either the Val-Met or Met-Met BDNF polymorphism (Val-Val is normal). In 10% (5 out of 49) of the samples we were unable to obtain an accurate profile of the gene, while one participant declined genetic testing. The remaining 71% of the participants (35 out of 49) possessed the expected allele, Met-Met. Within each experiment there was no effect of BDNF polymorphism on the degree of adaptation observed in the sham condition or the difference between the active and sham conditions ($p > 0.41$).

Discussion

Our results clearly indicate distinct neural control circuitry for dynamic and tonic vergence adaptation. In particular, the cerebellar regions maximally affected by the cTBS, the OMV [59,63,64]), play a key role in dynamic but not tonic vergence adaptation. In addition, we demonstrate that cTBS is a viable neurophysiological tool for investigating the neural substrates of vergence control.

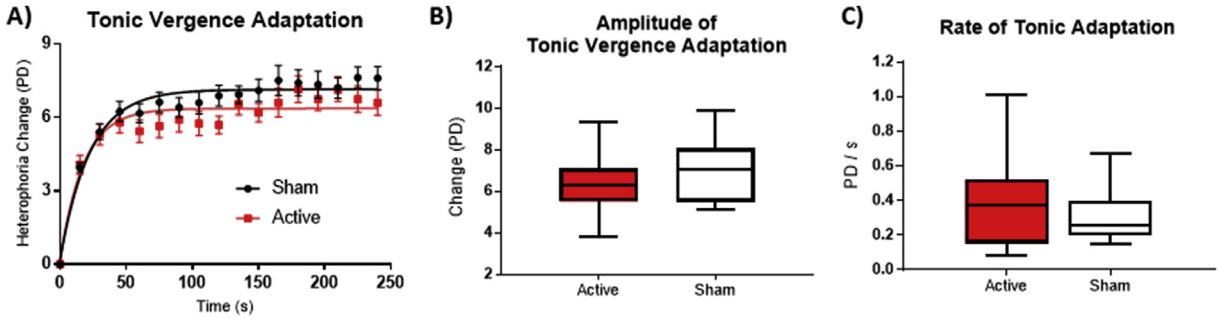

Fig. 6. -A) Group mean (SE) heterophoria values for each time point in both the active and sham cTBS conditions. Exponential functions fit to the group data are shown. **6-B)** Box plots of the mean (IQR and 95% CI) for the amplitude and **6-C)** rate of heterophoria change following active and sham cTBS determined from the exponential functions fit to each individual dataset.

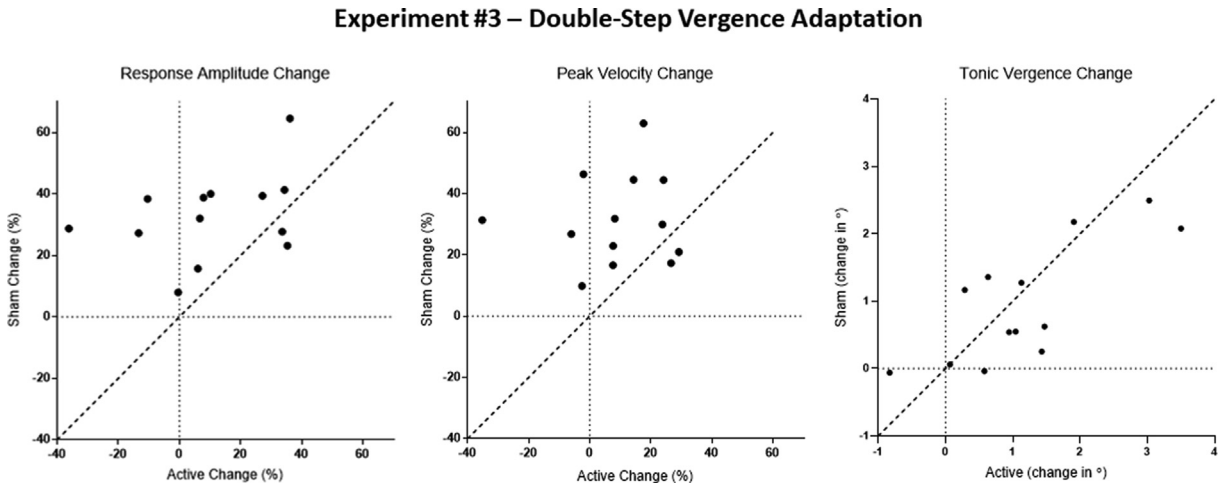

Fig. 7. Percent adaptive change from baseline vergence responses in sham versus active stimulation conditions from Experiment #3. The dotted line indicates the identity line, where the effects would be similar between conditions. Values falling above this line had a greater adaptive change in the sham condition.

The effects of TMS are strongest in superficial brain areas [53]. Therefore, the cTBS-induced inhibition of saccadic adaptation we observed (see also [63,64]), most likely reflects a disruption in the processing of the incoming feedback-driven error signal [77–79] which occurs in the parallel fiber-purkinje cells complex in the superficial layers of the OMV [45,80,81]. The disruption likely occurs via a reduction in the excitability of this neural complex as a result of the inhibitory effects of our cTBS protocol. While our coil position was directed over the midline of the OMV, we do report a subtle reduction in baseline leftward saccadic peak velocity. Thus, it is possible that some of the effect we observed resulted from the lateral spreading of the stimulation waveform, as others have reported a side effect on baseline saccadic gain [60].

Extending this hypothesis, our observations in experiments 2,3 and 4 imply that the neural complex in this particular vermal region is also involved in the dynamic, but not tonic adaptation of vergence. Specifically, cTBS interfered with the processing of the incoming error signal from dynamic fusional vergence responses and not the static steady-state fusion maintaining mechanisms driving adaptation in tonic vergence innervation. And while all TMS studies must accept some limitations on the spatial resolution of the stimulation, our results are congruent with previous human rTMS [63,64] and primate inhibition/ablation [45,81] studies that have demonstrated the importance of the PC, in particular the OMV, in the adaptation of pro-saccades. Evidence from the primate vergence literature also implicates the cerebellar vermis in fusional vergence control [35,36,82]. In terms of an effect of stimulation laterality and vergence adaptation, there is no evidence that convergence and divergence have lateralized vermal distributions and sensitivities to TMS like saccades [56,60]. Further, we do not report an effect on baseline fusional convergence responses as we do in reflexive saccades and thus take this as further evidence that our stimulation site and coil positioning was generally centered around the midline of the OMV (preferentially targeting lobules VIc and VII).

The results do not preclude the involvement of other cerebellar structures in tonic vergence adaptation however, as there are reports of variable impairments of heterophoria adaptation in primates with surgical ablations of the PC, including the OMV [37] and in patients with cerebellar degenerations [38,40] or ischemic damage [39].

The 'dual-rate-state-space model' of motor adaptation posits that separate slow and fast mechanisms underlie implicit forms of sensorimotor adaptation [83] in most systems, including those involved in upper-limb reaching and saccadic eye movements [78,84,85]**.** Disentangling the behavior and effects of these difference mechanisms in skeletal and saccadic motor systems is difficult, in part because observation of each mechanism in isolation, particularly the slow mechanism, is challenging. Tonic adaptation of convergence is analogous to the slow mechanism in the dual-rate-state-space model and can be readily observed and measured in isolation [70]. While it is not currently possible to provide a stimulus that only engages dynamic convergence adaptation, we were able to rapidly and directly observe the changes in the slow-tonic adaptive mechanism and then infer changes isolated to the dynamic mechanism. Our results demonstrate that control of the fast, dynamic mechanism involves the PC whereas the slower, tonic mechanism does not. Given this finding, our data supports the hypothesis that adaptive mechanisms modulating oculomotor control also exist outside the superficial layers of the cerebellar OMV control network.

Dynamic adaptation of reflexive saccadic and convergence responses was observed in both the active and sham PC-cTBS conditions**,** albeit significantly reduced following active cTBS. A potential explanation for the residual adaptation following stimulation is that PC-cTBS attenuates but does not eliminate vergence adaptation. A second, mutually non-exclusive explanation is an interaction with a second neural system responsible for the adaptation of tonic convergence innervation that does not involve the PC-OMV area. Adaptive shifts in tonic vergence innervation are known to enhance reflexive convergence response amplitudes and peak velocities [86,87]; therefore, the attenuated increase in fusional vergence dynamics following active cTBS in Experiment #3 may be attributable to the significant tonic adaptation that occurred. Indeed, the change in tonic innervation was positively correlated with the final change in reflexive vergence response amplitude in Experiment 3 (Pearson $r = 0.56$, $R^2 = 0.31$, $p = 0.048$, two-tailed), while this correlation was not significant when the change in vergence peak velocity was considered (Pearson $r = 0.48$, $R^2 = 0.23$, $p = 0.09$, two-tailed). Overall, these observations suggest that vergence adaptation can occur through an alternate neural mechanism if the cerebellum is compromised; however, such adaptations are slower and less complete. This possibility is consistent with studies of rodents [88] and patients with impaired cerebellar/OMV function [43,46].

Evidence for the compartmentalization of the neural mechanisms responsible for vergence plasticity has diverse implications. Clinically, the results suggest that fusional and tonic vergence plasticity must be assessed independently. Specifically, a single metric of adaptation may not generalize to the overall function of the disparity-driven vergence system, as we [69] and others have suggested [89]. It is unclear if this would apply to clinical populations, where the dysfunction may be the result of more diffuse, non-cerebellar related impairments. Convergence insufficiency is the most common developmental non-strabismic oculomotor disorder [5,90], and the most prevalent visual dysfunction observed in patients diagnosed with a traumatic brain injury [91–93]. Assessing the function of these independent adaptive mechanisms in these two separate populations that share a similar clinical dysfunction may provide insight into neural substrates impacted. In terms of VR/AR optics and display architectures our results similarly suggest that each subsystem of vergence and its corresponding adaptive mechanisms are important to consider when searching for biomarkers of comfort and visual quality impacts of a given device.

Summary

This study demonstrates that cTBS is an effective tool for exploring the neural substrates of vergence oculomotor control. The results indicate that the PC-OMV plays a central role in the dynamic adaptive capacity of fusional convergence but not on the tonic adaptation of tonic convergence. This provides additional evidence supporting the division and compartmentalization of (oculo)-motor adaptation across separate neural substrates.

Detailed methodology

Participants

Recruitment & screening

Participants were recruited from the University of Waterloo undergraduate and graduate student population. Written and verbal informed consent was obtained after verbal and written explanation of the study procedures were given. The study protocol was approved by the University of Waterloo ethics review board and adhered to the tenets of the Declaration of Helsinki. After informed consent was obtained participants filled out a TMS screening questionnaire that served to identify and exclude any who had contraindications for TMS application.

After passing this criterion, a licensed optometrist then assessed each participant's visual and oculomotor function. To be eligible participants were required to have monocular best-corrected visual acuity of at least 6/7.5, local stereoacuity better than 60′ arc seconds (Randot Stereopsis Test; Bernell Corp., USA), with a near point of convergence closer than 6 cm. Participants were excluded if they had a history of ocular injuries, surgeries or visual developmental abnormalities such as amblyopia or strabismus or a self-reported history of post-concussion symptoms. The participants ranged in age from 19 to 35 years (25.6 mean ± 4.9 SD). Participants wore the same habitual refractive correction at each visit. Four participants from experiment #1 also completed experiment #4 and six participants from experiment #2 also completed experiment #3.

Study withdrawals & data exclusions

15 participants were initially recruited for each experiment. Experiment #2 was the only study that recruited only 10 participants. In experiments #1, #2 and #4 one participant withdrew after experiencing TMS stimulation. In these cases, the participant either reported that the stimulation intensity being used during motor thresholding was too uncomfortable, or they were unable to comfortably remain still while cTBS was applied, resulting in an inability to stabilize the coil position and target location. In addition, one participant's data from experiment #1 and #3 were excluded due to a high frequency of blinks throughout each trial, which corrupted the majority of the data.

TMS protocols

TMS equipment

TMS was delivered using the MagVenture® MagPro X100 stimulator (MagVenture Farum, Denmark). TMS coil center position and participant location were monitored through the Brainsight® neuronavigation system (Rogue Research Inc., Montreal, Canada) using infrared optical tracking. The on-board Montreal Neurological Institute (MNI) model brain coordinates were co-registered to each participant's skull at the beginning of every session. The co-registration accuracy was assessed before and after active motor thresholding (AMT) and before cTBS application. If the mean square error was greater than 0.5 mm over the right motor cortex or the cerebellum at any point, the co-registration was repeated until such accuracy was obtained.

Each participant's active motor threshold (AMT) to the TMS stimulation was obtained from the belly-tendon of the first dorsal interosseous (FDI) muscle of the participant's dominant hand using the MCF B-65 figure- 8 butterfly coil (75 mm outer coil diameter, MagVenture Farum, Denmark) and standardized protocols [52,54,94].

cTBS was applied using the Cool-B65 Active/Placebo figure- 8 butterfly coil (MagVenture Farum, Denmark). This coil is visibly symmetric on each side, but is magnetically shielded internally on the placebo side, reducing the intensity of the magnetic field produced by greater than 95%**.** Before cTBS application, the experimenter would input one of two 6-digit codes (denoting active or sham stimulation) into the MagPro system. The A/P coil has an internal gyroscope allowing the MagPro system to identify the correct side of the coil to position against the participants skull based on the input code given. The input code order was randomized for each participant. cTBS was administered with the participant positioned in a face down position with their head supported in a commercially available massage chair. The OMV of the PC was localized in the MNI model of Brainsight™, and targeted using both the coil guidance software and an expected physical coil center positioning along the midline, 1 cm caudal to the inion [56] (Fig. 8). The A/P coil position was constantly monitored during cTBS application, which was applied at 80% of AMT determined at that visit. cTBS stimulation consisted of 3 biphasic pulses delivered at 50 Hz. These “bursts” of 3 pulses were repeated every 200 ms (5 Hz) for 40 s, resulting in a total of 600 pulses being delivered in one session [95]. The time of stimulation was recorded and was delivered at the same time (within 1 h) on the active and sham visit days.

Apparatus

Eye tracker & experimental control

In experiments #1, 2 and 3 the position of each eye was recorded at 250 Hz using infrared oculography via the EyeLink2™ system (SR Research, Canada). The visual stimuli were created and controlled using Experiment Builder™ (SR Research, Canada). At the beginning of each eye-tracking recording session the system was calibrated and then validated for accuracy on each eye using a custom 9-point procedure that spanned 40° horizontally and 20° vertically. If the accuracy at any gaze position differed by more than 0.5° upon validation, the procedure was repeated for that eye.

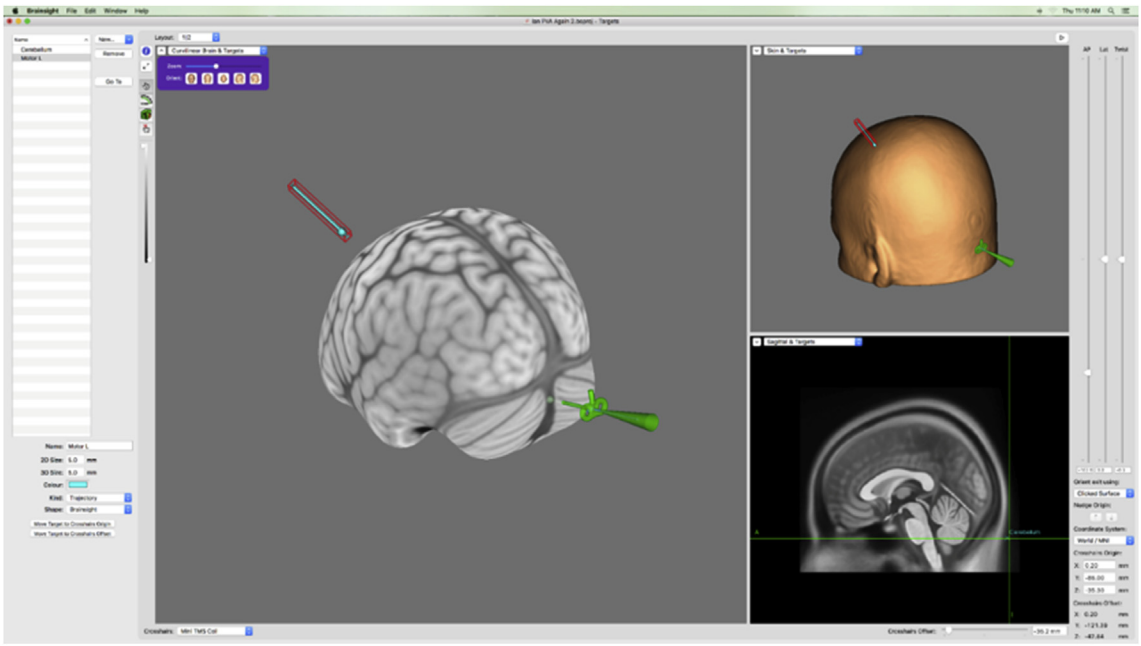

Fig. 8. Screen capture from a TMS application session demonstrating the anatomical MRI and our target TMS coil vector used to orient and guide our coil positioning during stimulation (cerebellar stimulation - green TMS coil, left motor cortex for thresholding – blue pin with highlighting red cube). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Saccadic display (experiment #1)

For experiment #1 participants were seated 50 cm in front of a 27-inch LED display monitor (ASUS VP79Q-P, 1920 × 1080 resolution, 60 Hz refresh rate). Their head was stabilized at this working distance using a custom chin rest. The target was a small white square (0.5° x 0.5°) with a central black dot (0.1° x 0.1°) on black background. Edge to edge the display subtended 62° of the visual field. The fixation target was restricted to the central 56° (3° from either screen edge) to ensure the eye movements recorded fell within the linear range of the eye-tracker (±30°).

Haploscope display (experiments #2 & #3)

Vergence stimuli for experiments #2 & 3 were created in a custom-built haploscope, which has been described in detail in our previous work [96]. In this apparatus the participant was seated (head supported and immobilized with a custom chin rest) 12 cm in front of two infrared passing mirrors placed orthogonally to each eyes line of sight. One 7-inch LCD display (Lilliput 619 GL-70NP/C, 800 × 480 resolution, 66 Hz refresh rate) was placed 28 cm from each mirror, creating a total combined viewing distance of 40 cm. The entire apparatus was placed in large darkened enclosure to eliminate visual distractions in the surrounding environment. Before each trial the participant's interpupillary distance was set between the two infrared mirrors in order to most accurately reproduce real-world viewing conditions. Identical white fixation crosses (0.5° × 0.5°) surrounded by a white box (2.75° × 2.75°) on a black background were presented to each eye. There was one horizontal and one vertical line (2° long) that were attached to adjacent sides of the box for each eye and were unique to that eye's fixation target. These lines provided a subjective visual cue for the participants to monitor for monocular suppression. The step changes in retinal disparity used to evoke vergence responses were created by shifting each eye's image laterally on the screen, in opposite directions, while the accommodative (blur) demand of the targets remained fixed at 40 cm. The starting position for all fusional vergence step stimuli began from 8.5° of convergence (Fig. 9).

Non-dichoptic vergence target (experiment #4)

In experiment #4 participants were seated 40 cm in front of a Bernell Muscle Imbalance Measure™ ('MIM'; Bernell Corp., USA) card. Their heads were stabilized with the same custom chin rest used for the saccadic display apparatus. The scale on the card was centered in front of the participant and placed directly at eye level. A row of seven text letters (0.3 logMAR) was printed directly above this scale.

Experimental procedures

After cTBS was applied participants were allowed to rest in a quiet room for 15-min. In the vergence experiments (#2–4) the room lights were turned off for the last 5 min of the rest period after cTBS was applied (dark adaptation time). During this time the subject was instructed to relax their eyes and gaze into the distance. On average (SD), experimental recordings began 39.3 ± 6.1 min after cTBS stimulation was applied. This is significant, as the behavioral effects of cTBS appear to peak between 30 and 45 min after stimulation and follows an exponential rise and fall on either side of this time, decaying completely after a few hours [57,97].

In experiments #1, 2 and 4 we chose not to use self-initiated trials. Instead, the target stepped randomly with a 2.5–6 s delay between shifts. This was done to help minimize the effects of anticipation and prediction that have been shown to influence fusional vergence response dynamics [51,98]. A side-effect of such design is the increased frequency of blinks encountered just before or after target movement as the participant is not cued to exactly when the target will be shifting, as would be the case in self-initiated trials.

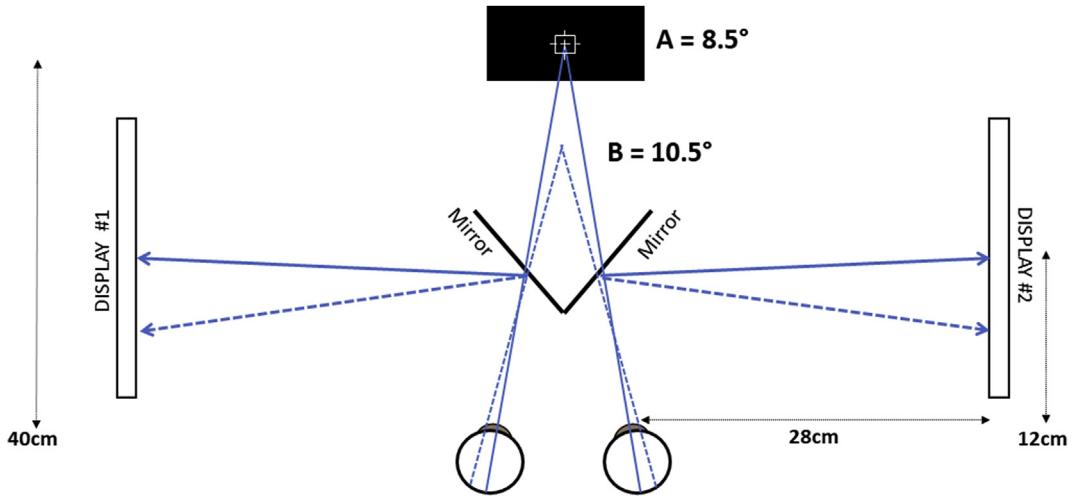

Fig. 9. Schematic of the dichoptic apparatus used and example fusional vergence stimulus used in Experiments #2 and #3. Two mirrors are placed orthogonally to each other, 12 cm from each eye at a 45° angle to each eye's visual axis (solid blue lines). One LCD display is located 28 cm from each mirror for a total viewing distance of 40 cm. The fused binocular percept of the stimulus is shown behind the mirrors with each visual axes intersecting the cyclopean display center at a total convergence angle of 8.5° (labeled 'A'). Step changes in crossed retinal disparities were created by shifting the images laterally on each display. An example of a 2° disparity step is illustrated by the dashed blue lines, now intersecting at 10.5° (labeled 'B'). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Experiment #1 – pro-saccade adaptation

Participants were instructed to follow the fixation target as quickly and accurately as possible throughout the experiment. The fixation target for leftward saccades always began within 8° of screen center but was randomly offset within this range to prevent the subjects from making saccades to remembered targets. The step stimulus had an inter-stimulus gap of one screen refresh rate (16.7 ms) so that only one fixation target was visible at a time. Only leftward saccadic responses from the left eye were analyzed in the entire experiment. Adaptation in pro-saccades was achieved via the classic 'double-step shortening' stimuli, where the initial stimulus is moved in backward, towards the original fixation point, in rapid succession after the motor command has initiated in order to produce repeated, systematic end-point errors in the initial movement outcome. The saccadic 'double-step' paradigm used in this study followed similar procedures to a previous rTMS work [64].

The baseline, pre-adaptation task consisted of twenty 16° leftward pro-saccade trials with a randomized delay (2–4s) between trials. The adaptive task used was almost identical to the pre-adaptation task. It was initiated automatically following a 2-min break, where the participant remained in the chin rest apparatus and were instructed to close their eyes. The difference in this task was that a second shift in the fixation target (5° backward, to the right) was introduced after the initial 16° leftward step [65]. This second step was triggered when the leftward saccadic velocity crossed a 40°/s threshold (velocity was calculated online via the EyeLink2 software). This ensured that the second step occurred during the first initial saccade, where visual suppression would be the greatest. During this phase, the double-step stimulus was shown only in the leftward direction and was repeated for a total of 100 double-step trials. The adaptation phase was subdivided into blocks of 10 stimuli. Adaptation was defined as the difference between the mean response properties of each block within this phase and the mean of the last 10 responses in the pre-adaptation phase. The difference was normalized to a percent of the mean pre-adaptation parameter.

Experiment #2 – fusional convergence main sequence

The main sequence of fusional convergence was created from each subject's vergence responses to step changes in retinal disparity of various amplitudes. Here disparity step stimuli were presented dichoptically within the custom haploscope. Participants were instructed to maintain fixation on the central cross within the target and maintain a single and clear percept at all times. The experiment was broken up into 3 phases, each identical in length with a 2-min break between each (with the same instructions as in experiment #1). In each phase a series of step changes in retinal disparity were presented from an initially congruent vergence and accommodative demand, simulating real-world fixation conditions. These disparity steps elicited dynamic fusional vergence changes. From this initial starting position, the target would step nearer (crossed disparity) or further (uncrossed disparity) after a randomized delay (3–6 s). After this the target would remain here for 3–5 s before returning to the initial starting position and constituted one trial. The disparity step amplitudes were 1°, 2°, 3° and 4° in both crossed and uncrossed directions. The order in which they were presented was also randomized within each trial. Each phase contained 5 trials of the 8 different stimuli amplitudes (40 trials per phase). Only convergence responses were analyzed. Uncrossed disparities were presented to balance the vergence demand around the congruent starting position and prevent excessive adaptation of tonic vergence innervation to a more converged position.

Experiment #3 – objective assessment of tonic and dynamic adaptation of fusional convergence

Adaptation within the fusional convergence system was achieved using a modified disparity version of the saccadic double-step stimuli, outlined in Experiment #1. Here, the disparity stimuli and experimental design used to induce and evaluate the dynamic adaptation of fusional convergence was identical to our previous work [69]. The same dichoptic apparatus in Experiment #2 was used. All convergence responses analyzed were to step changes in disparity from an initially congruent accommodative and vergence demand.

The baseline, pre-adaptation task consisted of twenty 2° step changes in crossed disparity that were initiated after a randomized delay (3–6 s). The adaptive task consisted of the same baseline step stimulus combined with an additional crossed disparity step of 1.5° that occurred 175 ms after the first 2° crossed disparity step. A total

of 80 vergence-double step stimuli were presented within the adaptation phase. As in experiment #1, convergence responses in this phase were subdivided into blocks of 10. The degree of tonic vergence adaptation was defined by the change in the participant's heterophoria amplitude, measured objectively at the beginning and end of this phase. The heterophoria defines the vergence angle in the absence of binocular disparity (one eye occluded) and provides an indirect measure of tonic vergence neural innervation [70,99]. The heterophoria was measured by removing all visual stimuli from the right eyes monitor, simulating occlusion, for 15 s. The change in the mean vergence angle of the 3 s preceding this occlusion period and the last 3 s of the 15 s occlusion period defined the heterophoria [100].

Experiment #4 — clinical evaluation of tonic adaptation of fusional vergence

Tonic adaptation of fusional convergence was achieved using previously defined clinical protocols. Here, participants binocularly fused the 0.3 logMAR text at the center of the Bernell MIM card while viewing through a 12-prism diopter (PD) optical prism placed base-out (BO) in front of the right eye. This prism induces roughly 6.8° of additional convergence from the accommodative demand at 40 cm. Heterophoria was measured subjectively via the Modified Thorington Technique (MTT) at baseline and then after every 15 s of during 4 min of binocular viewing through the prism. The Modified Thorington Technique (MTT) is a standard clinical test used to ascertain heterophoria direction and amplitude. Briefly, the right eye was first manually covered with an ophthalmic occluder and a red Maddox Rod was placed behind it with the lens striations horizontally. A penlight was then turned on and shone through the central fixation hole of the Bernell MIM card. The participant was then instructed to shift their gaze from the text to the light. The right eye was occluded for 12 s and then was manually 'flashed' the red vertical line created by the Maddox Rod 3 times at 1 Hz. The subject was instructed to report where they perceived the red line on the horizontal scale of the MIM card (resolution 1 PD, range 28PD exophoria to 28PD esophoria). The average of the reported positions defined the heterophoria. Immediately following the third flash, the occluder, Maddox Rod and penlight were removed and the subject was instructed to binocularly re-fixate on the text while maintaining a clear and single percept.

Data analysis & statistics

Raw eye-tracker data

All eye-tracking data was analyzed using custom built MatLab™ software (MathWorks®, USA). The Eyelink2 system records the eye position in pixels as a function of screen location. The pixel position data was analyzed offline and converted to degrees, with zero defining the horizontal screen center. Horizontal eye position data was filtered (saccadic data 80 Hz low-pass filter [101], vergence data 40 Hz fourth order Butterworth filter [102]) and velocity calculated using a two-point central difference algorithm [101].

Saccade data analysis

Data reported for the saccadic adaptation experiment are for the left eye only. We truncated the analysis to a single monocular signal, as the purpose of this experiment was to validate our methodology against previous TMS studies that used this same analysis pipeline. The start and end of saccades were defined using a 40°/s velocity threshold. The data from each phase was subset into bins of 10 movements. Within each bin, responses containing blinks or with latencies greater than 400 ms or less than 100 ms were excluded. Remaining responses that then fell 2 standard deviations outside of the mean of the bin were also excluded. Parameters used within the analysis were response amplitude (defined by the start/end criterion), peak velocity, latency and duration.

Vergence data analysis

Vergence was defined as the difference between the left and right eyes position and thus the eye-tracking signal from both eyes was utilized in this analysis. Vergence response start and end points were identified using a 1.5°/s velocity threshold. The data was subset into bins of 10 and filtered for responses containing blinks within the first 500 ms of stimulus onset, significant conjugate components (>0.5°, indicating a saccadic vergence interaction), latencies greater than 500 ms and shorter than 80 ms and responses that were outside 2 standard deviations from the mean. Parameters used within the analysis were open-loop "pulse" vergence response amplitude (see next section), peak velocity, latency and duration.

Phase-plane analysis

Dynamic fusional vergence responses measured experimentally are modelled to be the output of two separate neural controllers; an open-loop, pre-programmed 'pulse' response and a feedback driven 'step' response [10], much the same as pro-saccades [77]. The difference between fusional vergence and saccades however, is that vergence is an order of magnitude slower in terms of velocity and thus have much longer durations and subsequently a greater input from the visually guided step response. The focus of the experiment was to assess changes in the pre-programmed pulse response; therefore, we analyzed vergence responses in the phase-plane in order to mathematically estimate the amplitude of the pulse response. Briefly, an open-loop response is assumed to have a symmetric velocity profile on either side of the peak velocity. In the phase plane, we extrapolate from the rising velocity waveform what the falling waveform would be if the response was entirely free of feedback. The response amplitude is then predicted from the shape of this estimated combined (symmetric) velocity waveform.

Main sequence regressions

The main sequence of convergence was defined using a bivariate regression of the peak velocity versus response amplitude plot. In convergence, the main sequence is generally linear up to 8° in the current experimental apparatus used [103]. Therefore, we applied a bivariate regression to the plotted data from convergence responses to the 1°, 2°, 3° and 4° step stimuli (Fig. 3) where the variation in each parameter for the regression function was defined by the average variance of the 4 conditions combined.

Heterophoria analysis

Heterophoria can be used to closely approximate the level of tonic vergence innervation when measured at 6 m [70]. When measured at nearer distances, the change in heterophoria overtime can be used to approximate changes in tonic vergence innervation. We used the change in heterophoria measured both objectively in experiment #3 and subjectively in experiment #4 to define tonic adaptation. In experiment #4 the average heterophoria value measured with the MTT was then compared to the baseline, pre-adapted heterophoria value and plotted as a function of time (convergent changes in heterophoria were defined as positive). A single-phase exponential growth function was fit to this data using the robust fit function on Prism 7 software (GraphPad Software®, USA). The plateau of this function defined the maximum amplitude of heterophoria change (tonic adaptation) while the time constant was used to derive the maximum velocity of this adaptive change by dividing the plateau of the function by it.

Statistics

The data sets to be compared were assessed for normality using Shapiro–Wilk tests before further statistics were applied. The experiments all used a within-subject design, therefore paired t-tests were performed (t). In cases where the data distributions were skewed, Wilcoxon sign rank tests were applied and the median of the ranked differences (md) was reported. Data sets reported are given as mean ± standard error unless otherwise noted.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Author contributions

IME, BT and WRB conceived and designed the experiment. IE directly supervised the entire project, built the apparatus and designed the analysis. IE, ACM, CMC, HP and NLM collected and analyzed the data. IE wrote the manuscript, while BT and WRB provided edits and revisions to the final manuscript.

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