Continuous Theta Burst Stimulation to the Secondary Visual Cortex Does Not Impair Central Vision in Humans

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Abstract

Background: Continuous theta burst stimulation (cTBS) is a powerful form of repetitive transcranial magnetic stimulation capable of suppressing cortical excitability for up to 50 minutes. A growing number of studies have applied cTBS to the visual cortex in human subjects to investigate the neural dynamics of visual processing, but few studies have specifically examined its effects on central vision, which has crucial implications for safety and inference on downstream cognitive effects.

Objective: Assess the safety of offline, neuronavigated cTBS to V2 by examining its effects on central vision performance on a computerized stimulus detection task.

Methods: In a single-blind, randomized sham-controlled, crossover study, 17 healthy adults received cTBS and sham to V2 two weeks apart. Their central vision (≤ 8°) was tested at 1-minute (T1) and again at 50-minutes (T50) post-stimulation. Effects of condition (cTBS vs. sham) and time (T1 vs. T50) on accuracy and reaction time were examined using Bayes factor.

Results: Bayes factor results suggested that cTBS did not impair stimulus detection over the entire central visual field nor subfields at T1 or T50.

Conclusions: Our results offer the first explicit evidence supporting that cTBS applied to V2 does not create blind spots in the central visual field in humans. Any subtler changes to vision and downstream visual perception should be investigated in future studies.

Keywords: Transcranial magnetic stimulation; theta burst stimulation; vision; safety; V2; visual cortex

Introduction

Transcranial magnetic stimulation (TMS) is a powerful, non-invasive technique for modulating cortical activity. When multiple pulses are delivered in patterned succession, as occurs in repetitive TMS (rTMS), it can excite or inhibit cortical activity within focal regions for sustained periods [1]. In the field of cognitive neuroscience, low-frequency rTMS protocols (e.g. 1 Hz)—capable of eliciting long-term inhibition in the human cortex [2]—have become a popular non-invasive tool for elucidating the neural mechanisms of mental processes through induction of 'virtual lesions.' In 2005, a patterned form of rTMS—continuous theta burst stimulation (cTBS), comprised of three pulses of stimulation at 50 Hz delivered every 200 ms for 40 s, for a total of 600 pulses [3]—has gained attention because this specific pattern is capable of suppressing activity for longer periods (up to 50-minutes) with briefer administration times than more non-patterned stimulation (40 seconds vs. 10-20 minutes) [3–6]. As such, cTBS provides a quick, non-invasive, and well-tolerated [3] means to test the causal roles of specific brain regions in functional abnormalities observed in traumatic brain injuries or neuropsychiatric disorders.

The inhibitory effects of cTBS have been established and well-studied in motor cortices [3]. Recent evidence suggesting that cTBS similarly suppresses cortical excitability when applied to *visual cortex* [7,8] has prompted a growing number of studies to use cTBS to advance our understanding of brain dynamics underlying visual processing. For example, applications of cTBS to late-stage visual areas such as V5 have shown modulation of higher-level (global motion) processing without impairing lower-level (local motion) perception [9]. However, when administering cTBS on early visual areas (i.e. V1-V3) to examine downstream effects, one critical challenge arises. Studies on cats have shown that brief TMS pulse trains (1-8 Hz for 1-4 seconds) to early occipital regions can generate visual field defects or scotoma for up to 10-

minutes [10]. Given cross-species similarities in the organization of these early areas [11], it is possible that cTBS applied to early visual areas in humans can also induce blind spots and impair vision for extended periods. Without confirming the integrity of vision following stimulation, altered performance on visual processing tasks [9,12–15] after cTBS to early visual cortex could be merely due to blind spots (i.e., the subjects could not see), rather than the hypothesized mechanism of reduced feedforward activity from early visual areas to later processing areas in the visual system. Impaired vision not only seriously threatens the internal validity of the findings, but also constitutes a safety issue for human subjects research.

Relatively few studies applying cTBS to early visual areas in humans have examined its effects on vision. Among those that have, many have focused primarily on more peripheral locations in the visual field. From both the safety and scientific integrity perspectives, blind spots to the central visual field would be more problematic and thus warrant more attention for investigation. Additionally, findings from these studies have been inconsistent—reporting impairments [9,12–14], improvements [16,17], and non-significant changes [17–20] to vision. This is likely due to variability in methods across studies, including differences in stimulation intensity, performance measurement, target localization method, and task demands. In many cases, these results were also obtained based on extremely small samples (many had $N < 10$) (e.g. [17–20]), and therefore negative findings could simply reflect a failure to reject the null hypothesis due to the limited statistical power rather than a true absence of stimulation effect on vision. As a result of these issues, it is unclear whether cTBS can be safely applied to early visual areas without inducing transient blind spots in the central visual field.

The Present Study

The present study assessed the effects of cTBS to an early visual cortical area, V2, on central vision. We used a single-blind crossover design, in which all participants received both conditions (randomized to receive either cTBS first or sham first) and underwent central vision testing at 1-minute and 50-minutes post-stimulation in both conditions. V2 was targeted because it is one of the earliest visual processing regions and has strong feedforward connections to higher-level processing areas in both the dorsal and ventral visual streams. We used MRI-guided neuronavigation to ensure accurate localization of V2 for each participant. We tested central (inclusive of foveal and parafoveal) vision (visual angle ≤ 8°), which is critical to performing most visual perception tasks and may be particularly susceptible to cTBS effects due to the size and depth of the cortical surface it occupies [21].

Lesion studies in macaques show that V2 has unique functionality in visual detection dependent on task demands—V2 lesions impair complex but spare basic stimulus detection [22]. Thus, we hypothesized that cTBS to V2 in humans would not impact detection accuracy on a basic visual detection task. Given previous reports of slowed visual detection following cTBS to an early occipital target [23], we also hypothesized that reaction time (RT) would be increased, despite intact accuracy, after cTBS compared with sham.

Material and Methods

Participants

Participants were N = 17 healthy adults (6 females; age 24.8 ± 8.6; education 16.5 ± 2.3 years) with normal vision (20/30 or better on a Snellen chart, and intact central/peripheral vision—test details below), no contraindication to TMS [24] or MRI, and no prior mental illness

according to the Structured Clinical Interview for DSM-IV-TR (SCID-NP [25]). All passed urine drug screenings in each test visit.

Procedure

The study protocol was approved by the Institutional Review Board at the University of Michigan Medical School and conducted in accordance with the Declaration of Helsinki. Prior to data collection, written informed consent was collected from all participants.

Participants completed three sessions: baseline, cTBS, and sham (Figure 1). Order for cTBS and sham sessions was counterbalanced across participants. At baseline, following a diagnostic interview to confirm eligibility, each participant completed a high-resolution T1-weighted (T1w) and T2-weighted (T2w) structural MRI scans, followed by procedure to determine personalized active motor threshold. Vision tests (central, acuity, peripheral) were administered to allow participants to become acclimated with the tasks and to confirm all had normal vision (see Vision Tests below for details). TMS was delivered with a Magventure MagPro X100 70mm Figure-8 TMS coil. In each of the stimulation (cTBS or sham) sessions, central vision was tested ~1 minute after stimulation ('T1' hereafter) and then again at ~50-minutes ('T50' hereafter) after completing a ~40-minute fMRI scan (results not reported here). Beyond monitoring for common adverse events associated with TMS (e.g. headache, syncope), we also tested for additional vision-related adverse events following cTBS (and sham) that would pose a safety concern for participants. These 'vision safety checks' involved a peripheral vision test and a visual acuity test that were administered at the end of each stimulation session, to ensure intact vision and safety before participants leave the laboratory.

[Figure 1]

Transcranial Magnetic Stimulation

Intensity. Stimulation intensity for the cTBS or sham was based on the participant's active motor threshold (AMT), determined as the lowest intensity eliciting motor-evoked potentials of the first dorsal interosseous muscle (right hand; at 20% maximum voluntary contraction) ≥ 100mV on 5/10 trials. Mean raw AMT across participants was 36% (*SD* = 7%) of maximum stimulator output (MSO).

Target localization. Individual structural brain images were used to localize the stimulation target of V2. High-resolution (256x256 FOV, 208 slices, 1mm isotropic voxels) T1w and T2w anatomical images were acquired using a GE (MR750 DV25.0) 3T scanner and prospective motion correction (PROMO) [26]. Images were processed offline in Freesurfer image analysis suite (version 6.0; http://surfer.nmr.mgh.harvard.edu/), which was used for cortical reconstruction and volumetric segmentation, using both T1w and T2w volumes (T2w images improve the quality of the pial surface reconstruction and thus the accuracy of the cortical surface map). Technical details of these procedures are described elsewhere [27–30]. Briefly, we conducted motion correction of volumetric images, removal of non-brain tissue, automated Talairach transformation, segmentation of subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles), intensity normalization, tessellation of gray matter white matter boundary, automated topology correction, and surface deformation. Individual V1 and V2 masks were generated during the surface reconstruction (recon-all) process.

V2 and V1 (to facilitate determination of V2 boundaries) masks in the right hemisphere were superimposed on the native T1w volume in Brainsight software (Version 8; Rogue Research Inc, Montreal, Canada). A target was placed in the center of a gyrus within the V2 cortex. Care was taken to avoid V1 and to allow easy/feasible coil placement that minimizes the

scalp-to-target distance, as E-field strength reduces as a function of distance [31]. Across participants, the average distance from coil to target was 16.9 mm (*SD* = 3.7 mm). Figure 2A depicts this process for a representative subject. Figure 2B shows V2 targets for all subjects.

[Figure 2]

Continuous theta burst stimulation. cTBS was delivered to V2 off-line at 80% of AMT with the coil oriented perpendicular to the gyrus of the target to optimize effects of the E-field [32]. Average stimulation intensity across participants was 29% (SD = 5%) of MSO. cTBS parameters consisted of three 50 Hz pulse trains delivered every 200 ms continuously for 40 seconds, totaling 600 pulses [3]. Brainsight Neuronavigation software with Polaris 3D Tracking (Version 8; Rogue Research Inc, Montreal, Canada) utilizing T1w images enabled precise localization of target-centric subject/coil tracking during stimulation.

During stimulation, participants' forehead was stabilized against a headrest to minimize movements. Given that research on state-dependent effects that TMS to visual areas (V1-V4) maximally affects neuronal populations that are minimally active during stimulation (see [33] for review), cTBS was administered while participants were blindfolded to minimize visual sensory input. For sham, the coil orientation was rotated 90° so that the coil handle was perpendicular to the participant's scalp.

Vision Tests

Central Vision Task. A computerized task was used to examine binocular detection of visual stimuli across the central visual field (≤ 8°). Participants looked at a central fixation (size = 1°) while target stimuli ('1' or '2'; size = 0.75°) flashed briefly for 50 ms at different locations, one at a time, on the screen. Participants pressed the number key "1" or "2" to indicate what they saw. To eliminate the confound of individual differences in processing speed, the next target did

not appear until a response had been given. In other words, slower responders may obtain more incorrect responses due to longer response times (not impaired detection) when a fixed response period is used—an indefinite response period eliminates this possibility. Following a response, a 200 ms interval elapsed before the next trial. Each trial was signaled by a 50 ms tone (2500 Hz) to minimize the effect of attention lapse. Targets were presented at 32 locations across the central visual field modeled on Barendregt et al. [34] as shown in Figure 3. Stimuli covered four visual angle eccentricities extending outward from a central fixation (2°, 4°, 6°, 8°) and eight polarities rotated about a central fixation (22.5°, 67.5°, 112.5°, 157.5°, 202.5°, 247.5°, 292.5°, 337.5°). This formed a circular map of central vision whereby each of the four eccentricities were tested at eight polarities, resulting in 32 stimulus locations. Five presentations occurred at each of the 32 locations in randomized order, resulting in 160 trials and a task duration of ~3-minutes. The task was presented in Psychtoolbox-3 [35–37] in MATLAB (R2019a) using a HP Elitebook laptop (Windows 10, 1920x1080 resolution, 33.5x17.5cm display, 60 Hz refresh rate, 6-bit color depth) placed at an eye-level viewing distance of 55cm. A headrest was used to minimize movements and a keypad was used for response collection. Central vision performance was evaluated by accuracy and RT for each stimulation condition (cTBS, sham) and administration time (T1, T50).

[Figure 3]

Vision Safety Checks. The integrity of peripheral vision was assessed monocularly using an experimenter-administered visual confrontation task (see Supplementary Material Appendix A for description). Normal peripheral vision (requisite for participation) was defined as reliable identification on four trials in all quadrants of both eyes at baseline. Visual acuity was tested binocularly using a Snellen chart. Normal visual acuity (requisite for participation) was defined

as 20/30 or above, with corrective lenses if needed. When re-tested after cTBS and sham stimulation sessions, any reductions in acuity or identification of stimuli in a quadrant were used to test for safety concerns related to stimulation.

Statistical Analyses

The question of whether cTBS applied to an early visual area induces (temporary) blindness can be more meaningfully addressed by evaluating the *comparative* evidence for the null vs. alternative hypothesis. This can be achieved only by Bayesian analysis and not traditional null hypothesis significant testing (NHST). Therefore, we used a Bayesian model comparison approach to evaluate the relative strength of evidence for the null and alternative hypotheses [38]. We compared central vision performance following cTBS vs. sham by calculating the Bayes Factor (BF)—the ratio of Bayesian evidence for the alternative model (cTBS-related vision changes) to that of the null model (no cTBS-related vision changes). A BF < 1 offers evidence for the null model, and a BF > 1 offers evidence for the alternative model. The strength of evidence (the ratio) is interpreted according to the Jeffrey interpretative scale [39]: evidence for denominator = 0.33–1 (anecdotal), 0.10–0.33 (substantial), 0.033–0.10 (strong), 0.01–0.033 (very strong), <0.01 (decisive); evidence for numerator = 1–3 (anecdotal), 3–10 (substantial), 10–30 (strong), 30–100 (very strong), >100 (decisive).

We used the 'anovaBF' function in the 'BayesFactor'[40] R Studio package to compute the BF of each possible alternative model with Stimulation (cTBS, sham) and Time (T1, T50) as possible fixed factors and subjects as a random effect, against the denominator null model (subjects as random effect only) [40]. This was run separately for accuracy and RT as dependent variable. R code and outputs are provided in Supplementary Materials (Appendix D and E).

Results

cTBS applied to V2 was well-tolerated and no participants reported common adverse side effects related to TMS (e.g. headache, syncope). Additionally, our vision safety checks revealed that no participants experienced vision-related adverse side effects (i.e., reductions in visual acuity or impaired peripheral vision) at the end of any cTBS or sham visit.

Accuracy and RT on the central vision task, as well as the BF results, are summarized in Figure 4.

[Figure 4]

Accuracy. Accuracy on the central vision task was very high both after cTBS (T1 = 98.4% ± 5.8%; T50 = 97.2% ± 8.2%) and sham (T1 = 98.3% ± 5.8%; T50 = 97.9% ± 6.7%). Similarly, accuracy at all individual stimulus locations was also high (above 90% for all locations in both conditions). Vision performance for individual subjects are provided in Supplementary Materials (Appendix C).

The null model had stronger evidence than all six models that contained Stimulation (as main effect or interaction with Time). Specifically, the evidence for the null model was 'substantial' relative to three of these alternative models (BF = 0.31 to 0.14) and 'anecdotal' relative to the other three alternative models (BF = 0.92 to 0.61). Together, the results suggest that cTBS to V2 did not impair accuracy of stimulus detection over the central visual field. The only alternative model with superior evidence than the null model was the one with Time as main effect (BF= 1.98, 'anecdotal' evidence), indicating reduced accuracy at T50 relative to T1.

RT. The null model had stronger evidence ('anecdotal' to 'substantial' evidence; BF = 0.46 to 0.16) than three of the models containing Stimulation (as main effect or interaction with Time). Like for accuracy, the "winning" model with the strongest evidence was that containing

Time as a main effect (BF = 24.91, 'strong' evidence), suggesting learning effects for RT, marked by faster response at T50 relative to T1 in both stimulation conditions (Figure 5B). The other three alternative models containing Stimulation (as main effect or interaction with Time) had 'substantial' to 'strong' evidence relative the null (BF = 4.42 to 11.62). However, each of these alternative models also contained Time as a main effect. To confirm that these models won over the null model just because of the Time effect, we performed additional comparisons showing that Stimulation did not affect RT *in addition to* Time. We compared the model with Time as a main effect against each of these three alternative models by dividing the BF of the former by that of the latter. In all cases, results favored the Time model, offering 'anecdotal' to 'substantial' evidence (BF = 2.14 to 5.63), supporting that Stimulation did not affect central vision RT in addition to Time. Together, these results suggest that cTBS to V2 also did not impact RT during stimulus detection over the central visual field either immediately following stimulation or 50 minutes post-stimulation.

Exploratory Analysis. We also explored whether cTBS differentially impacted subareas of the visual field by considering the effects of Hemifield (ipsilateral vs. contralateral) and Vision Type (foveal [2°] vs. parafoveal [4-8°]) on accuracy and RT. Neither Hemifield nor Vision Type was found to have effects on accuracy and RT (see Supplementary Material Appendix F for methods and results).

Discussion

The present study examined the effects of off-line, neuronavigated cTBS to V2 on central vision performance. Detection accuracy and RT over the central visual field (≤ 8°) were tested following cTBS to V2 (at 1-minute and 50-minutes post-stimulation) and compared to that of

sham stimulation. We hypothesized that cTBS to V2 would not disrupt detection accuracy (based on results from lesion studies of the visual cortex [22]) and that cTBS to V2 would lead to slowed RT's (based on previous TMS results [23]).

As expected, cTBS to V2 did not affect the accuracy of vision performance over the central visual field. This held when hemifield (ipsilateral, contralateral to stimulation) and vision type (foveal, parafoveal) were accounted for (see Supplementary Material Appendix F), which helped rule out the possibility that cTBS to V2 differentially affected detection over a particular portion of the visual field. This extends on previous reports of negative findings (obtained using NHST [18,19]) related to discrimination accuracy changes following visual cortex cTBS. Our findings conflicted with a previous report of low-level visual processing impairment following cTBS to early visual areas [12], but this was likely due to the methodological differences. The Rahnev et al. (2013) study, along with the majority of previous studies in this topic [12,16–19,41], used the phosphene threshold (PT) hotspot as their 'early visual' target, whereas we used an anatomical map of the V2 cortex [42]. Phosphene-based methods of localization can yield targets vary widely between V1 through V3 [43]. This can be problematic because, from lesion studies, we know that disruptions to the different functional areas within 'early occipital' regions have drastically different effects on visual processing (e.g. V1 lesions impair basic and complex visual processing, while V2 lesions impair complex processing only [22]). It is, therefore, possible impairments reported in that study were caused by suppression of activity in V1 in some participants, which would be more likely to cause blind spots. In contrast, given our localization method, we were confident that it was V2 that was stimulated in our study and thus our findings were specific to cTBS applied to V2 (see below for discussion of possible influences of intensity).

Contrary to our hypothesis, our analyses showed that cTBS to V2 did not impact RT of stimulus detection over the overall central visual field nor specific subfields (left/right or foveal/parafoveal). The discrepancy between this result and a previous study reporting slower RT following cTBS [23] could be due to several methodological differences, one of which is task difficulty level. The visual task in the current study was relatively easy—a basic detection task with a fixed stimulus presentation duration (50 ms)—while Fiori et al. utilized staircase adaptation procedures to manipulate difficulty level by reducing the viewing time of stimuli for each participant in order to keep performance at 80% accuracy. The tasks also varied in terms of stimulus complexity: we used coarsely discriminable targets ("1" vs. "2") while Fiori used more complex Gabor elements with varied orientations. Together, the procedures and stimulus complexity used in Fiori et al.'s study placed more demands on the participant than those in the present study. This is important because, as discussed previously, lesions to V1 in macaques cause deficits on even basic visual processing tasks, while lesions to V2 leave basic discrimination and contrast sensitivity unaffected [22] but impair complex visual processing. Perhaps task demand (including stimulus complexity) is another reason why some have reported low-level visual processing impairments [12,23] after cTBS to early occipital regions, while our study and those using easier tasks reported no effects [18]. Others have urged the importance of task complexity in TMS research [17]. Here we add that it is also important to carefully consider the specific visual area stimulated, because failure to consider both may have unforeseen interaction effects on vision performance.

Regardless of stimulation condition, time appeared to impact both accuracy and RT, such that responses were less accurate but faster at T50 (relative to T1). It may be that participants

were more comfortable with the task or desired to finish the study visit sooner at the second administration and thus were faster to respond (at a slight expense of accuracy).

Finally, one might raise the question whether the stimulation intensity used in the present study was insufficient to adequately suppress V2 excitation. Although the intensity we used (80% AMT) was lower than many others (i.e., those using resting motor threshold, phosphene threshold, or a fixed percentage of maximum stimulator output), several studies have successfully modulated other types of behavior, perception, and cognition using visual cortex cTBS at intensities similar to ours [44–46]. This suggests that the absence of cTBS effects on simple visual detection accuracy and response time in this study was not likely due to insufficient stimulation power. While visual impairments may, indeed, be possible at much higher intensities of cTBS to V2, our goal was *not* to demonstrate this per se. Rather, we sought to assess whether blind spots would occur under standard intensities (80% AMT) [24] considered safe and commonly adopted in cTBS research. In doing so, we demonstrated that cTBS delivered at standard intensities to V2 does not impair basic visual detection accuracy or processing speed over the central visual field. However, this does not imply that cTBS to V2 at *any* intensities would leave vision intact. There is evidence that higher-intensity cTBS to early visual areas is capable of altering visual processing, but results are heterogeneous [13,15–17], likely due to variations in task demands, number of cTBS sessions, and/or online versus offline stimulation.

The present findings should be considered in light of several limitations. The sample size used here was modest and replications with larger sample sizes are needed. Additionally, the extant literature on TMS (especially in the motor cortex) indicates that peak effects may not occur until ~10-20 minutes after stimulation [3]. Therefore, the testing points used here (1-minutes and 50-minutes post-stimulation) might not have captured possible visual disruptions

associated with peak TMS effects. Future work should conduct similar testing in additional time intervals between 0 and 50 minutes following stimulation to assess for possible vision changes post-cTBS.

Conclusions

In summary, cTBS delivered at 80% AMT to V2 did not impair accuracy or RT of central vision detection. Our findings provide further evidence consistent with previous reports that cTBS can be safely applied to V2 at standard intensities (80% AMT) and does not disrupt basic early visual detection needed to perform tasks tapping higher-level visual processing or cognition. Replications with larger samples are needed to provide more definitive conclusions about the safety of cTBS in early visual cortices and effects on vision and behavior.

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Declaration of Interests

The authors have no conflicts interests to disclose.

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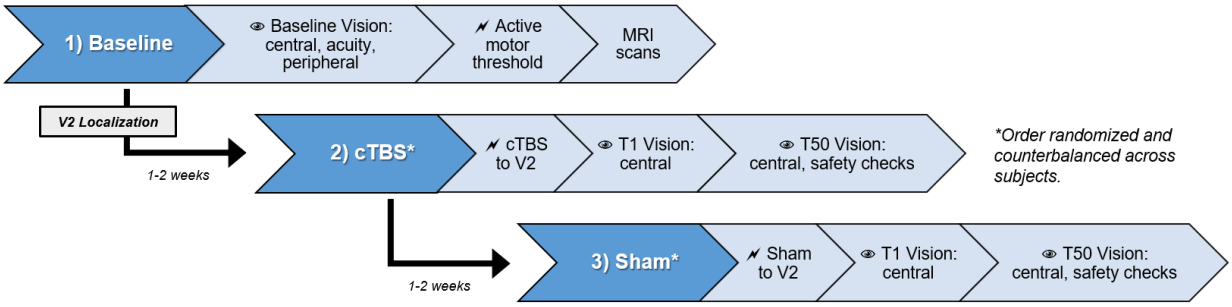

Figure 1. Overview of study procedures. Participants completed 3 sessions: baseline, cTBS, and sham-cTBS. cTBS and sham session order was randomized and counterbalanced across participants. T1 = ~1-minute post-stimulation; T50 = ~50-minutes post-stimulation; cTBS = continuous theta burst stimulation; V2 = secondary visual cortex.

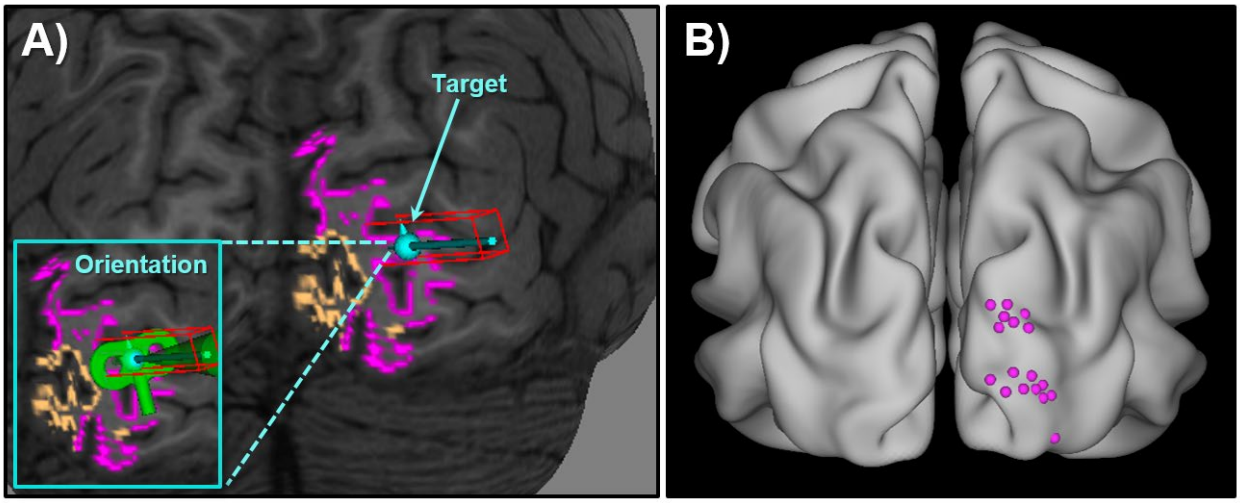

Figure 2. V2 localization overview. A) Target selection and coil orientation for a single representative subject. Individualized V1/V2 overlays were superimposed on the T1 anatomical MRI image (native space)—V1 colored orange, V2 colored pink—and used as guides in the V2 localization process; B) Individual V2 targets for all *N* = 17 participants standardized in MNI space (average location: x = 21±5, y = -95±6, z = 19±12; coordinates for individual subjects provided in Supplementary Material, Appendix B). *Note.* V1 = primary visual cortex; V2 = secondary visual area.

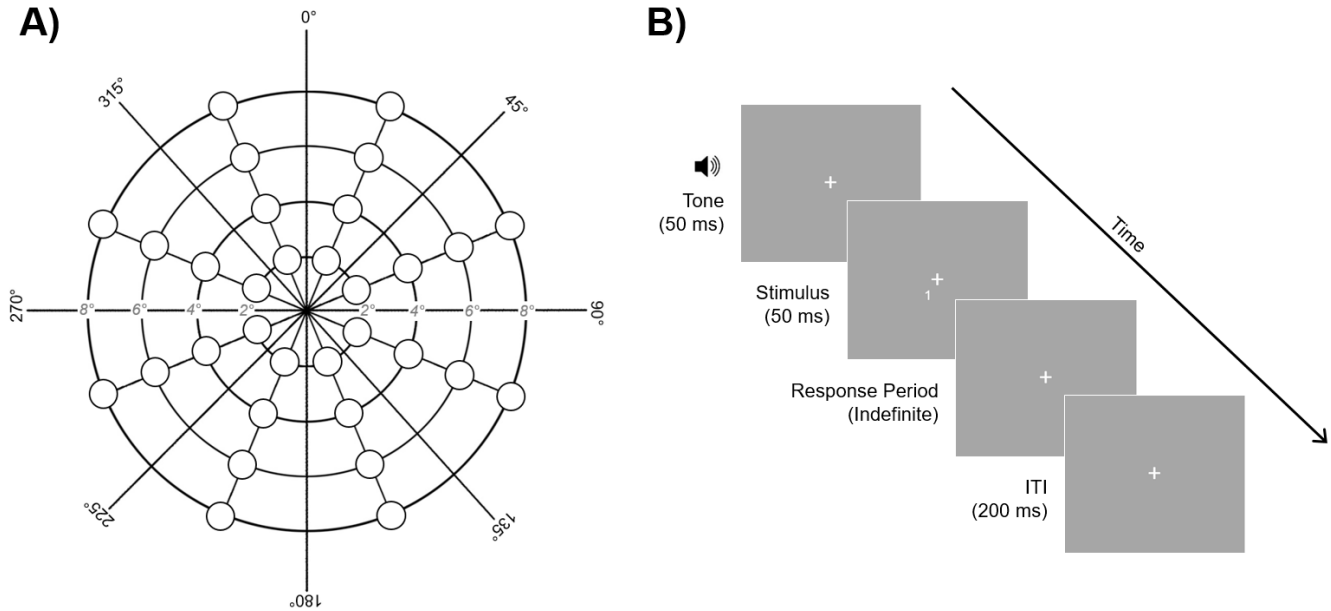

Figure 3. Central vision task. A) Stimulus presentation locations for the computerized central vision task. Stimuli (either "1" or "2") were randomly presented at each of 32 locations over the central visual field. B) Trial structure for the central vision task. Each stimulus was preceded by a 50 ms tone, and then presented briefly for 50 ms. Participants were given an indefinite response period to press a button indicating whether the previous stimulus was a "1" or a "2". Following a response, a 200 ms inter-trial interval (ITI) elapsed before the tone signaling the next stimulus. Five stimulus presentations occurred at each of the 32 locations shown in the left figure, resulting in 160 total trials. The entire task lasted approximately 3-minutes. *Note*: ms = milliseconds.

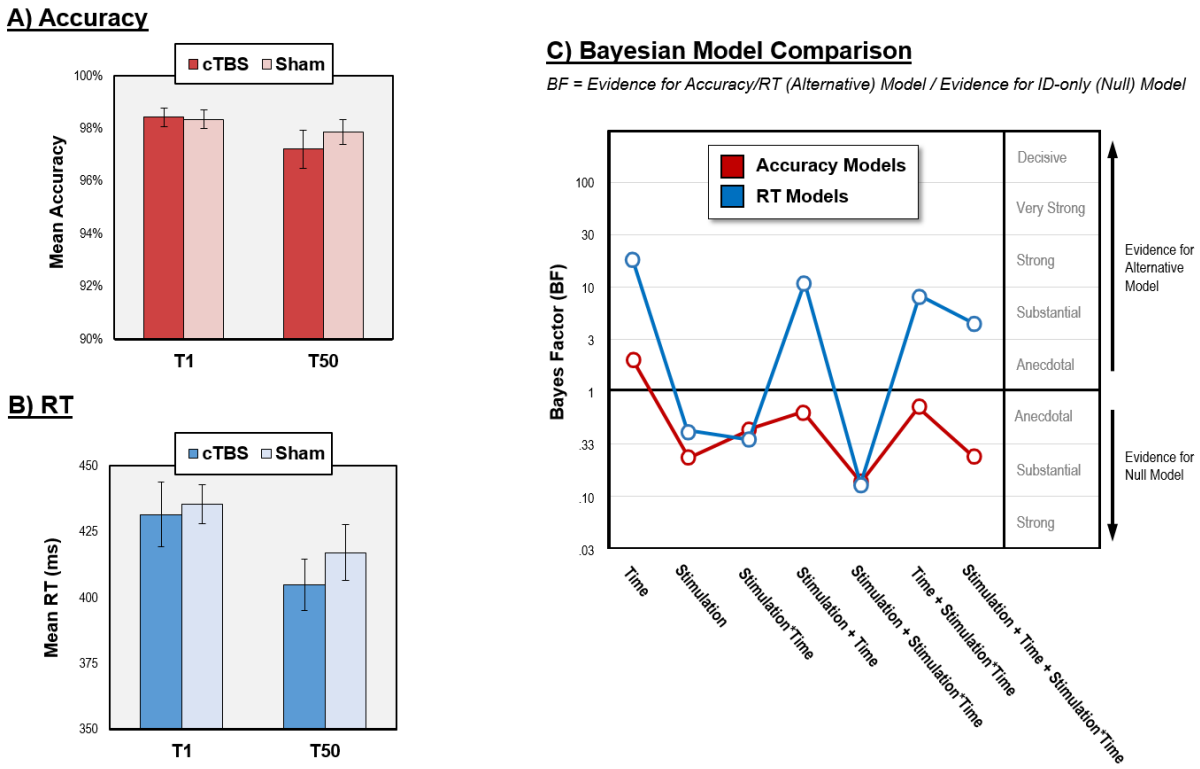

Figure 4. Descriptives and results for central vision performance analysis. A) Mean accuracy for each condition (cTBS, sham) and administration time (T1, T50); B) Mean RT for each condition and administration time; C) Bayesian model comparison results for all accuracy/RT models relative to ID-only model. Values > 1 favor the numerator and suggest change in vision performance. Values < 1 favor the denominator and suggest no change in vision. All other models show anecdotal to substantial evidence for no change in vision performance as a result of cTBS. *Note.* RT = reaction time; cTBS = continuous theta burst stimulation; V2 = secondary visual area; ms = milliseconds; T1 = ~1-minute post-stimulation; T50 = ~50-minutes post-stimulation.