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Original Articles

The Role of Human Brain Area hMT+ in the Perception of Global Motion Investigated With Repetitive Transcranial Magnetic Stimulation (rTMS)

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ABSTRACT

Background: Psychophysical evidence suggests that the perception of the motion and color of moving stimuli are determined separately in the human brain. Here we aim to determine the role of visual cortical areas hMT+ and V1/V2 in each task by measuring the effect of rTMS of each area using an off-line continuous theta-burst stimulation (cTBS) protocol.

Methods: In the motion task, the direction of moving dots was identified using a global motion stimulus that avoids tracking, and in the detection task for the same stimulus, the presence of the dots was detected regardless of motion. Performance was measured using forced-choice methods in 8 subjects, both before and at 4 time-intervals in the 1-hour after brain stimulation. All experiments were done using achromatic and isoluminant, red-green chromatic stimuli.

Results: Performance on global motion for both achromatic and chromatic stimuli was significantly impaired following cTBS of visual area hMT+, with a maximum effect occurring 11 min after stimulation. In comparison, there was no effect of cTBS on the motion task for areas V1/V2 or the vertex (control). cTBS did not affect the detection task in either area.

Conclusions: Our experiments validate the use of cTBS as an advantageous off-line rTMS protocol for studying visual areas. The results indicate a causal link between neural activity in area hMT+ and perception of motion of isoluminant chromatic stimuli. We conclude that area hMT+ is part of a common pathway processing the global motion of chromatic and achromatic stimuli, but is not involved in their detection.

Introduction

Psychophysical evidence accumulated over several decades has shown that human color vision is poor in the perception of motion. This is thought to arise from the distinct specializations of the dorsal and ventral streams in primate vision for the attributes motion and color, respectively, with good processing of motion but poor sensitivity to color in the dorsal pathway and good processing of color but little sensitivity to motion in the ventral pathway. An overlap of function between the two streams appears to remain, however, allowing color vision to perform on motion tasks under a range of conditions. Such tasks include direction discrimination of isoluminant chromatic gratings at contrasts above threshold [1,2], motion discrimination on global motion tasks at isoluminance [3], tasks using higher order motion stimuli [4–6] and the perception of motion after-effects generated by isoluminant chromatic stimuli [7,8]. In color vision, a clear dissociation has been found between two different types of visual threshold: stimulus detection (color/form threshold) and the discrimination of its direction of motion (motion threshold) [3,9]. This is based on the surprising observation that luminance noise masks the motion of chromatic stimuli but not their detection: as luminance noise contrast increases, chromatic stimuli show no change in detection threshold (visibility) but loose their perceived motion, eventually appearing static. This supports the idea that motion and detection thresholds are independently determined, with different physiological origins.

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Here we aim to determine the physiological origins of chromatic global motion perception versus color detection. We aim to test two linked hypotheses, that hMT+ is involved in chromatic global motion thresholds but not chromatic detection thresholds, by selectively and temporarily impairing processing in two different areas of the human visual cortex using repetitive Transcranial Magnetic Stimulation (rTMS). We predict that stimulation of area hMT+ will selectively impair performance on discriminating the direction of motion of chromatic stimuli but will not affect performance on the detection of the stimulus. In addition, we measure the effect of rTMS applied to areas V1/V2 on motion and detection thresholds, with the aim of determining their comparative roles in these two tasks. As V1/V2 are not selective areas for global stimulus attributes, such as motion, we do not expect pronounced effects on motion discrimination, but might expect an effect on color detection [10].

On-line [11–16], and off-line [17] TMS have previously been shown to be effective at reducing, or improving [18] motion sensitivity using a range of different stimuli and tasks, stimulation protocols, and brain areas targeted. Here we use a continuous theta-burst stimulation protocol (cTBS) [19], an off-line rTMS protocol, which is relatively novel to vision testing. As part of the study, we aimed to identify the time course for the effects of cTBS, which has not been well established yet for vision. We use global motion stimuli, as these are well suited to reveal the motion selective functions of area hMT+, and can also be used for color detection tasks. We also run all experiments on achromatic stimuli as a control and to verify the effectiveness of cTBS. This is the first attempt to determine the relative selectivity of dorsal area hMT+ (in relation to V1/V2) for color and global motion by direct stimulation of the human brain.

Materials and methods

Participants

Eleven healthy participants (5 female, 6 male) took part in the experiments and all had normal or corrected to normal vision, and normal color vision assessed by the Farnsworth–Munsell 100-hue color test (Munsell Color Company Inc, 1957). Written consent was obtained from all participants and none reported any contra-indications to rTMS. Experiments were approved locally by the Ethics Review Board of the Montreal Neurological Institute and were performed in accordance with the ethical standards of the Declaration of Helsinki (1964), and established TMS safety protocols [20].

Psychophysical apparatus

Stimuli were generated using Cambridge Research Systems ViSaGe video-graphics card with 14-bit contrast resolution, connected to a Sony Trinitron (GDM 500DIS) monitor (Sony Corporation, Tokyo, Japan) with a spatial resolution of 1024 × 768 pixels and 120 Hz frame rate. Calibration of this equipment has been described previously [3]. All stimuli were viewed binocularly in a dimly lit room at a viewing distance of 62 cm.

Visual stimuli

Stimuli (Fig. 1A) were limited lifetime random dot kinematograms (RDKs) with a diameter of 12°, a gray background (mean luminance of 51 cd/m^2). Motion sequences of 50 luminance or chromatic Gaussian blobs (sigma = 0.25° and FWHM of 0.58°) appeared and disappeared with a limited lifetime duration of 240 ms, and each blob moved at 5.4 deg/s. Stimulus presentation was ramped on and off in a Gaussian temporal envelope (sigma = 0.125 s). The centers of the stimuli were 6° away from the fixation mark in the right visual field.

Stimuli were designed to isolate the luminance (achromatic) or the L/M (red/green, RG) cone opponent mechanism and were represented within a three-dimensional cone contrast space [21,22]. The isoluminant point was determined for each participant using a minimum motion method as previously described [3].

Transcranial magnetic stimulation

Apparatus

TMS was delivered using a Magstim Super Rapid2 biphasic stimulator with an air-cooled figure eight 70 mm coil (Magstim, UK). Participants were blindfolded and seated in a chair with a chinrest in order to minimize movement throughout stimulation.

Localization of visual areas V1/V2 and hMT+

All participants received stimulation over the left hemisphere [23–25]. In preliminary experimental sessions, areas hMT+ and V1/V2 were localized using a functional phosphene method in order to designate the correct stimulation site in each individual [24,26]. In this procedure, single TMS pulses with 70–80% maximal stimulator output (MSO), were delivered over the striate cortex, targeting the primary visual cortex by placing the coil at 4 cm above the inion and 2 cm to the left [15,27–29]. The handle of the coil pointed upwards, parallel to the participant's spine, and was moved systematically over this area until the participant reported the perception of a clear stationary phosphene in his/her central visual field. Localization of area hMT+ was found by systematic stimulation of an area approximately 3 cm dorsal and 5 cm lateral from the inion with the TMS coil pointing down at 45° to the spine of the participant [24,28]. The point that elicited the strongest moving phosphene was designated as area hMT+. If a participant was unable to perceive a phosphene, double pulses of stimulation were applied (80% MSO, 50 ms inter-stimulus interval) [29,30]. All participants described moving phosphenes when area hMT+ was stimulated and stationary phosphenes during area V1/V2 stimulation. The coil-position within each target brain area that elicited the most vivid phosphene responses were marked using a stereotaxic image guiding system (Brainsight, Rogue Research Inc, Montreal, Canada), which was used to co-register each participant's head with an MRI scan and ensured the same site was stimulated across testing sessions. The vertex, located at the intersection of the inion, nasion and interaural lines, was used as a control site for stimulation in order to control for non-specific effects of TMS, such as auditory clicking sounds and sensory tapping sensation on the scalp, without targeting specific brain sites related to the tasks [26].

Continuous theta-burst stimulation protocol

cTBS was delivered at 45% MSO as bursts of three 50 Hz pulses every 200 ms (5 Hz) over a 41 s stimulation period, cumulating in a total of 600 pulses given in a continuous train [19,29,31].

Experiment 1: effect of contrast on coherence threshold (psychophysics)

Prior to the rTMS experiments, the effect of stimulus contrast on motion coherence thresholds (direction discrimination) was determined for both achromatic and isoluminant chromatic stimuli. Motion coherence thresholds were acquired using a method of constant stimuli (MCS) with a 1AFC protocol in which the subject indicated in which direction, left or right, the stimulus moved. Coherence threshold was 82% correct. Coherence thresholds were measured as a function of stimulus contrast, scaled in multiples of detection threshold, in three subjects. Contrast detection

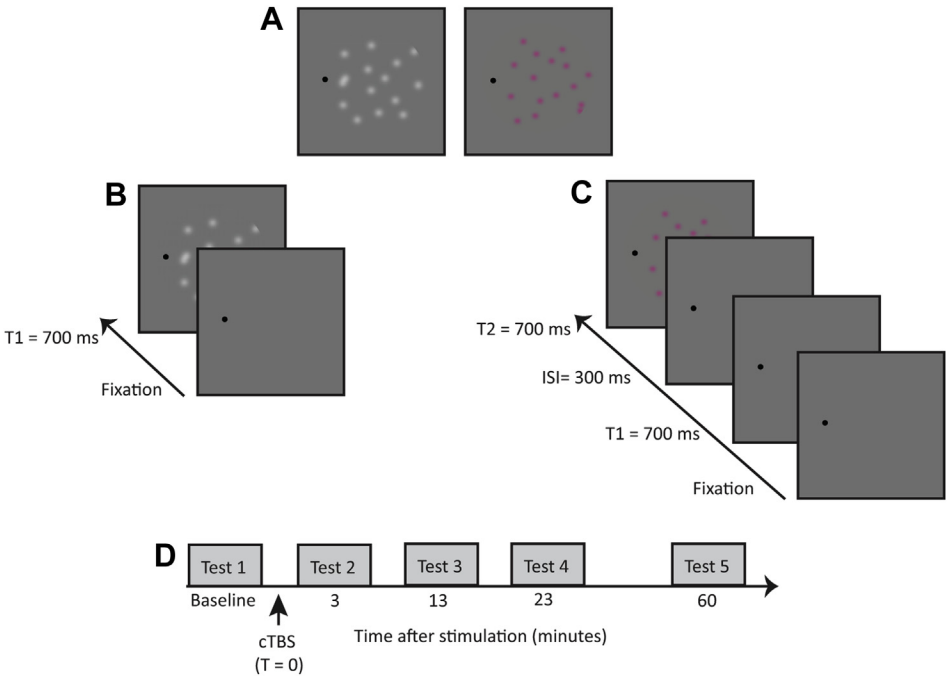

Figure 1. (A) An illustration of a frame of the random dot kinematogram for the achromatic stimuli composed of gray blobs (left) and the chromatic stimuli composed of isoluminant red blobs (right). This example uses 15 instead of 50 blobs. (B) Motion direction discrimination task protocol (1-interval). (C) Contrast detection task protocol (2-interval). (D) Timeline of the TMS testing protocol. Each block represents 100 trials. $T = 0$ represents the time of cTBS application. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

thresholds and motion discrimination thresholds were obtained in all subjects.

Experiment 2: effect of cTBS on motion coherence thresholds

The contrast of the stimuli was fixed at 8× detection threshold to ensure coherence thresholds are independent of stimulus contrast. The motion discrimination task is the same as for experiment 1. The motion coherence levels of the stimuli were set at the 82% correct level for each participant based on their measured coherence thresholds. The effect of cTBS on motion direction discrimination was measured at the pre-set coherence level across time.

The rTMS session (Fig. 1D) comprised 5 blocks, of 100 trials each. Block 1 was run prior to stimulation to set baseline performance. cTBS was then applied to one of the three brain areas of interest (hMT+, V1/V2, or vertex). After stimulation, testing blocks 2–4 were completed with a 5-min break between each block during which the participant sat quietly wearing a blindfold. After removal of the blindfold prior to each block of testing, sufficient time was allowed for the participant to light adapt. Block 5 was run 60 min after stimulation. Sessions for each brain area were pseudo-randomized and run on separate days. Eight participants took part in this experiment.

Experiment 3: effect of cTBS on stimulus detection

A 2AFC protocol was used to acquire detection thresholds, in which participant's task was to indicate in which interval the stimulus appeared. Based on the pilot measurements, three levels of contrast (detection threshold, 1.1 and 1.2 times detection threshold) were presented randomized within each block and were set for each participant to attain approximately an average 82% correct performance level. An additional ten trials at a high contrast (5× detection threshold) were added as catch trials for attentional purposes but were not included in the results. The effect of cTBS on contrast detection was then measured across time using the same protocol and timeline from experiment 2 (Fig. 1). Eight participants took part in this experiment most of whom also participated in experiment 2.

Experiment 4: follow-up psychophysics on threshold stability across time

Based on our results from experiment 3, we measured threshold performance as a function of time without the application of cTBS in a group of six subjects, using the same psychophysical protocols and timelines as the cTBS experiments. Participants did not receive any brain stimulation but sat quietly wearing a blindfold for the duration of the cTBS portion of the session.

Results

Experiment 1: effect of contrast on motion direction thresholds

Figure 2 shows thresholds for motion discrimination (percent coherence) as a function of contrast for both the achromatic (circles) and chromatic (triangles) stimuli for three subjects. Stimulus contrast was scaled in multiples of detection threshold in order to control for the effects of stimulus visibility. Thresholds for discriminating global motion direction follow a similar trend for both stimulus types with coherence thresholds asymptoting to stable levels as the contrast of the stimuli increases and becoming independent of contrast. These results show that integration of global motion at suprathreshold contrasts is possible for both achromatic and chromatic stimuli, as shown previously for achromatic [3,32,33] and chromatic stimuli [3]. Based on these results, all experiments are performed at the 8× threshold condition to acquire coherence thresholds, at which the motion coherence level is contrast-independent. This control ensures that any loss of

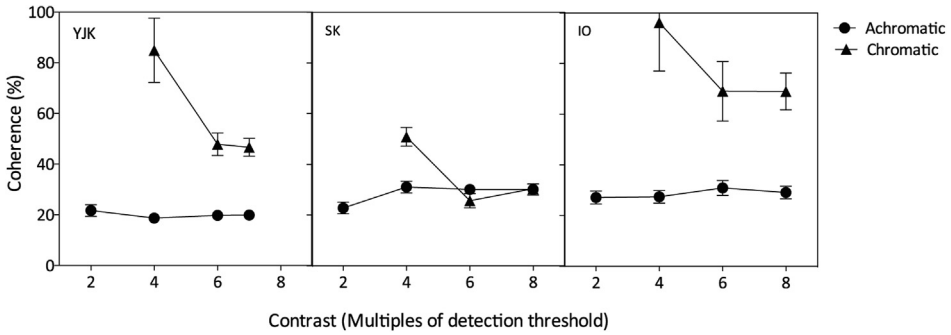

Figure 2. Thresholds for motion discrimination (percent coherence) as a function of contrast, scaled in units of detection threshold for achromatic (black circles) and chromatic (gray triangles) stimuli for three subjects. Error bars were estimated by parametric bootstrap analysis.

performance on the motion discrimination task after stimulation is not simply a secondary consequence of a loss of stimulus visibility.

Experiment 2: effect of cTBS on motion coherence thresholds

Figure 3 shows the results for the effects of cTBS on the achromatic (Fig. 3A) and chromatic (Fig. 3B) motion discrimination task for the three difference brain areas (hMT+, V1/V2 and the vertex) as marked. Performance data following cTBS were collapsed across time ($t = 3$, $t = 13$, $t = 23$ min) for the eight subjects for each brain area (gray bars) and compared with baseline performances before cTBS (black bars). Achromatic and chromatic conditions were analyzed separately. Data were analyzed using the Wilcoxon signed ranks test for paired samples using SPSS version 22 (IBM Corp. Armonk, NY). Results indicate that the median performance after cTBS was significantly lower than median baseline performance levels before cTBS for both achromatic ($Z = -2.103$, $P = 0.035$), and chromatic ($Z = -2.103$, $P = 0.035$) stimuli. Stimulation of either the vertex or primary visual cortex did not yield significant differences in median performance post-stimulation compared to baseline for either stimulus type. These results indicate that stimulation of area hMT+ causes a significant decrease in performance on the global motion discrimination task, with subjects performing worse after stimulation. This effect occurred for both the achromatic and chromatic stimuli.

In Fig. 4 we investigate the time course of these effects. Mean performance data were analyzed using the generalized linear model (GLM, see Appendix A) and a planned contrasts comparison of 6 pairs of interest was used to compare performances after stimulation of hMT+ and V1/V2 with the vertex at each time point ($t = 3$, $t = 13$, $t = 23$ min) (Fig. 4A and B). A Bonferroni corrected P-value of 0.0083 ($P = 0.05/6$) was used. We used this model in order to analyze the use of the vertex as our control and to compare the interactions between brain areas and time. Achromatic (Fig. 4A) and chromatic (Fig. 4B) conditions were analyzed separately. Both the achromatic and chromatic stimuli showed a trend of decreasing performance between 3 and 13 min, and had returned to baseline levels by 60 min after stimulation (Fig. 4A and B). Stimulation of area hMT+ caused a significant decrease in performance at the 13-min time interval for achromatic stimuli compared to baseline performance levels (Fig. 4A). For chromatic stimuli, although the trend was similar, due to individual variability of subjects, results did not reach significance. Stimulation of V1/V2 or the vertex did not show any decrease in performance across time for either type of stimuli.

In order to illustrate trends across time and to determine time points at which the effect of cTBS on motion thresholds is greatest, a Gaussian function was fitted to the results (Fig. 4C and D). The difference scores were calculated by subtracting vertex (control) stimulation from performances during hMT+ or V1/V2 stimulation. Peak effects of cTBS on hMT+ (black triangles) occurred 11 min after stimulation for both types of stimuli.

Collectively, the results obtained for the motion discrimination task suggest that area hMT+ is mediating the motion processing of both the achromatic and isoluminant chromatic visual stimuli.

Experiment 3: effect of cTBS on stimulus detection

Figure 5 shows the results for the effects of cTBS on the chromatic and achromatic detection task. Data were analyzed in the

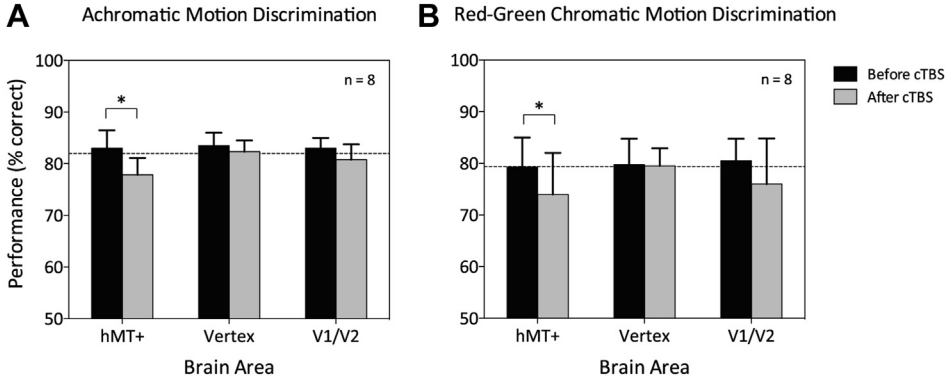

Figure 3. Median values of the data before cTBS and after cTBS collapsed over time for 8 subjects for performance on (A) achromatic and (B) chromatic motion discrimination tasks. Performance is measured as percent correct and as a function of brain area. The dotted lines indicate the average of the baseline conditions (achromatic = 82% correct, chromatic = 80% correct). Asterisks denote significance. Error bars represent the upper (75th) percentile.

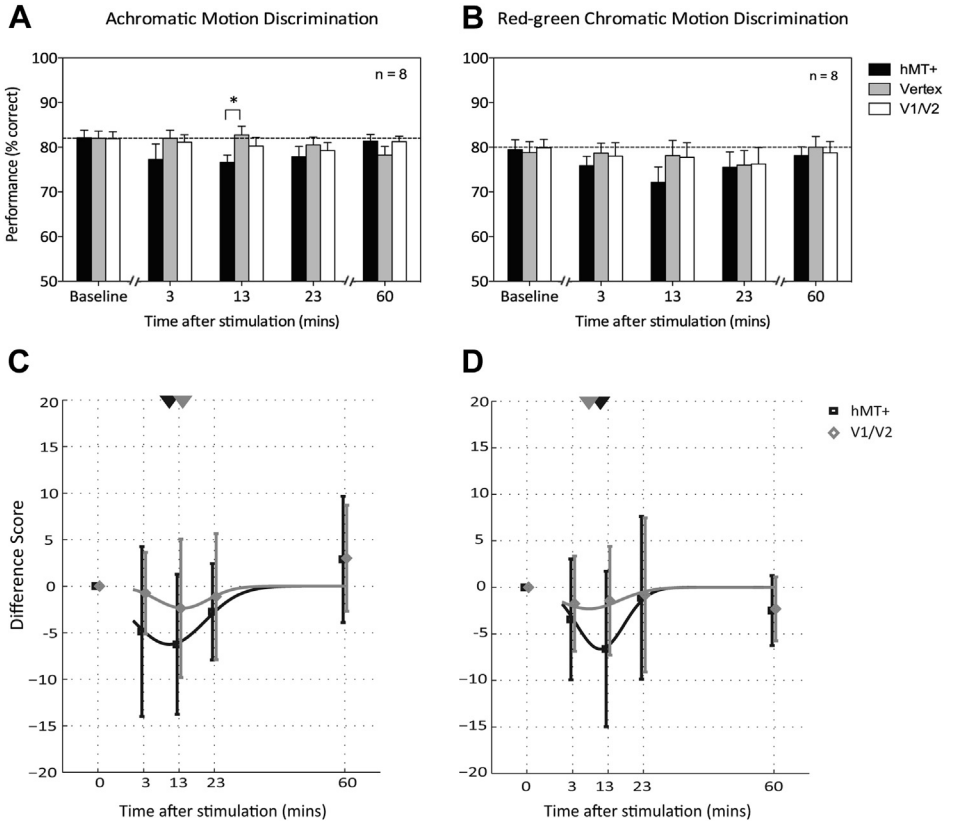

Figure 4. Mean performances averaged across 8 subjects on the motion direction discrimination task measured as percent correct and plotted as a function of time (min) for (A) achromatic and (B) chromatic stimuli. Each bar consists of 800 trials overall (100 trials per subject for 8 subjects). Dotted lines indicate the average of the baseline conditions (achromatic = 82%, RG-chromatic = 80%). Error bars represent the standard error of the mean (SEM). (C) Achromatic and (D) chromatic difference scores fitted with a Gaussian function. Difference scores were calculated by subtracting vertex (control) stimulation from performances during hMT+ or V1/V2 stimulation. The time of the peak effects are denoted by triangles.

same manner as described for Fig. 3. Performance data following cTBS were collapsed across time ($t = 3$, $t = 13$, $t = 23$ min) for the eight subjects for each brain area (gray bars) and compared with baseline performances before cTBS (black bars). Achromatic (Fig. 5A) and chromatic (Fig. 5B) conditions were analyzed separately. For the achromatic detection task (Fig. 5A), all three areas showed a significant decrease in performance after cTBS (hMT+: $Z = -2.103$, $P = 0.035$; V1/V2: $Z = -2.38$, $P = 0.017$; vertex: $Z = -2.38$, $P = 0.017$), including the vertex (control). Therefore, such deficits cannot be attributed to the effect of cTBS but are likely due to another effect independent of the brain area stimulated, such as attention or habituation effects. For the chromatic detection task there were no significant differences (Fig. 5B). Therefore, there is no effect of cTBS on performance of the chromatic detection task, which also seems robust to the attentional or habituation effects we find for the achromatic stimuli. These results indicate that cTBS did not selectively impair performance of contrast detection for both achromatic and chromatic stimuli types.

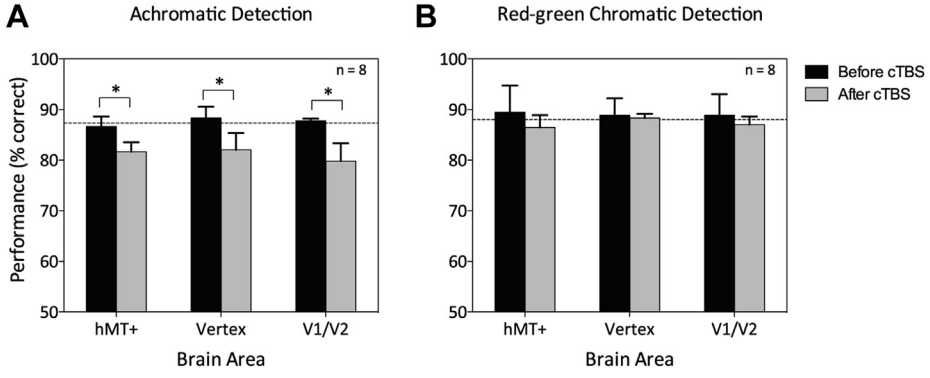

Figure 5. Median values of the data before cTBS and after cTBS collapsed over time for 8 subjects for performance on for performance on (A) achromatic and (B) chromatic contrast detection task. Performance is measured as percent correct and as a function of brain area. The dotted lines indicate the average of the baseline conditions (achromatic = 87% correct, RG-chromatic = 88% correct). Asterisks denote significance. Error bars represent the upper (75th) percentile.

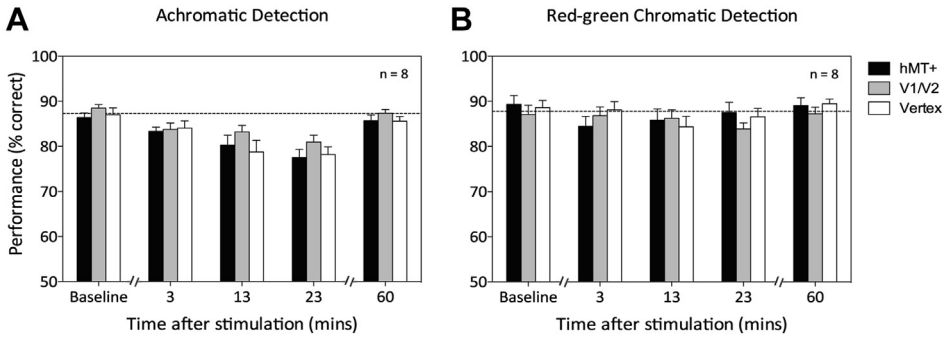

Figure 6. Mean performances averaged across 8 subjects on the contrast detection task measured as percent correct and plotted as a function of time (min) for (A) achromatic and (B) chromatic stimuli. The dotted lines indicate the average of the baseline conditions (achromatic = 87%, RG-chromatic = 88%). Each bar consists of 800 trials overall (100 trials per subject for 8 subjects). Error bars represent the standard error of the mean (SEM).

For completion, time course data for the detection task were analyzed using the same GLM analysis as the motion direction task for achromatic (Fig. 6A) and chromatic conditions (Fig. 6B). No pairs yielded any significant differences, however, a clear decreasing trend for all three brain areas was observed in the achromatic detection condition, which returned to baseline levels by 60 min after stimulation.

A follow-up psychophysical experiment was run to further investigate the decrease in performance over time observed only during the achromatic stimulus detection task. The obtained data confirm that this interesting result was not due to non-specific effects of cTBS, as the same trend can be seen across time when no stimulation was applied (Fig. 7A). No decrease in performance was found for the chromatic stimuli during either the sessions with stimulation (Fig. 6B) or without (Fig. 7B).

Collectively, the results obtained for the stimuli detection task suggest that areas hMT+ and V1/V2 are not mediating detection of our achromatic and chromatic visual stimuli.

Discussion

This study demonstrates that the use of cTBS significantly impairs the function of area hMT+ in a task-specific manner. Participants performed at significantly lower levels in the motion direction discrimination task after application of cTBS over hMT+ in comparison to stimulation of either the vertex or primary visual cortex. This was apparent for both the achromatic and chromatic global motion stimuli, with maximal effects observed 11 min after stimulation. Contrast detection of either stimulus was not affected by cTBS of any of the target areas. The implications of these results are threefold. Firstly, the impairment in performance post-stimulation validates the use of the advantageous cTBS protocol as an off-line rTMS protocol for studying visual brain areas and encourages future usage. Secondly, they provide further supporting evidence that area hMT+ is involved in the analysis of luminance-defined global motion. Finally, the results are novel as they causally demonstrate that activity in area hMT+ contributes to chromatic global motion perception at isoluminance, illustrated by the decreased performance post-stimulation for chromatic stimuli.

Possible mechanisms of color motion perception

hMT+ can be considered as a neural correlate of global motion perception for stimuli defined by either color or achromatic contrast. Michna and Mullen [3] demonstrated in a psychophysical experiment using the same global motion stimuli as the ones used here that direction discrimination of the isoluminant chromatic stimuli was masked by luminance noise but was unaffected by chromatic noise. The cross masking of chromatic motion by luminance noise, combined with the absence of masking by color noise suggested that processing of chromatic motion is mediated by a luminance-based system and is key evidence that the color information in the stimulus is lost and instead treated as an achromatic signal. This type of luminance signal, which has been termed "temporal chromatic aberration" [9], may originate subcortically in the dynamics of magnocellular (M) cell responses to isoluminant

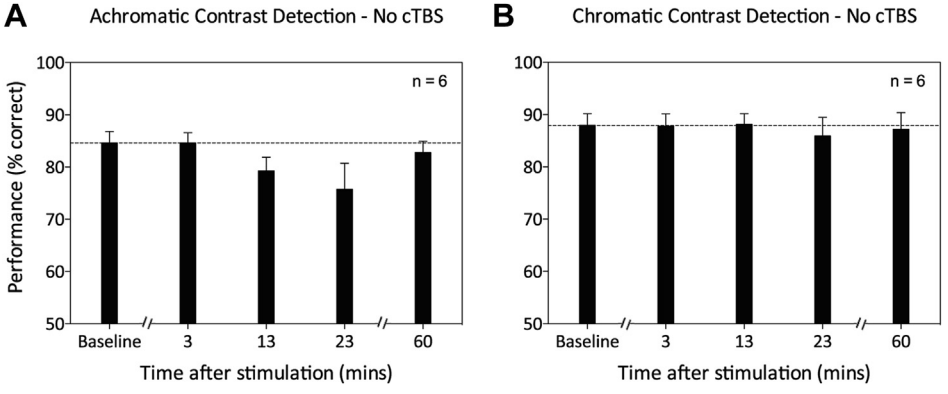

Figure 7. Mean performance averaged across 6 subjects on the contrast detection task without application of cTBS, measured as percent correct and plotted as a function of time (min) for (A) achromatic and (B) chromatic stimuli.

red-green contrast, either in the retina or the LGN [34–37]. In addition, Dobkins and Albright [35] based on single cell primate experiments, suggested that neural signals at the level of MT might arise from "unsigned" chromatic information. Motion processing area hMT+ may be able to use chromatically defined boundary information to encode motion direction without encoding information about the colors themselves. As such, the sign of chromatic contrast is discarded and neurons have no selectivity for specific colors. Thus the perception of chromatic motion may be based on an energy mechanism that is capable of utilizing cues extracted from isoluminant stimuli that are similar in nature to luminance information [9,38]. Our results, demonstrating a loss of motion coherence in global motion stimuli, are complimentary to those showing a perceived slowing of motion for non-global, grating stimuli obtained using different on-line TMS protocols [12,13]. It is not yet understood how these two different aspects of motion are related mechanistically, or exactly how the different types of TMS may impact them. However, the functional impact of cTBS on neuronal activity is generally interpreted as a straightforward excitability loss [19,39].

We found no impairment in motion performance post-stimulation of areas V1/V2. This is probably not surprising as we are investigating a global motion task that requires the spatial integration of signals across the stimulus extent, which is relatively large at 12° in diameter. Area MT, with its very large receptive fields relying on the integration of smaller V1 inputs, is more likely to be susceptible to stimulation than V1 for two reasons; first, MT is specialized for the integrative nature of the global motion task, and second, because the area of cortex stimulated in V1 may not cover the full extent of the stimulus. In support of the latter point, we note that prior TMS studies, although using very different types of stimuli and TMS protocols, have found V1/V2 effects on motion when very small stimuli were used (0.7 degrees square) [40,41], but not when larger ones are (2.5 degrees square) [12,13].

cTBS did not have any effect on stimulus detection thresholds, which may be surprising, specifically with regards to the stimulation of area V1/V2, as it known to be a source of direct input to higher order areas that are concerned with the detection of a stimulus [42–45]. The absence of an effect, either a deficit or improvement, on detection thresholds after cTBS of V1/V2 may potentially be due to the size of the stimulus in relation to the area stimulated, as raised above. Because the receptive fields in V1 are retinotopically organized and are much smaller in the primary visual cortex, it is possible that the stimulation only affects a subset of neurons responding to the stimulus while allowing the unaffected neurons to signal the appropriate information. Also our big stimuli, representing relatively low spatial and high temporal frequencies, were optimized for driving extra-striate areas rather than V1. To our knowledge, no study has previously reported any effect of off-line rTMS on a pure contrast threshold detection task, although previous studies using stimuli optimized for V1 using other on-line [46–48] or off-line [49] TMS protocols have reported improvements in stimulus detection tasks that may in some cases be persistent [49].

Conclusion

This study demonstrates that cTBS can disrupt normal cortical function when area hMT+ is targeted, selectively and reversibly impairing motion direction perception in a task-specific and location-specific manner, with the effect peaking 11 min after stimulation. The effect on isoluminant chromatic stimuli suggests some form of cross-talk between the dorsal and the ventral pathways with color providing some input to the dorsal pathway. Overall, the results indicate a causal link between neural activity in area hMT+ and the perception of chromatic as well as achromatic global motion, suggesting that area hMT+ is mediating the processing of global motion for both chromatic and achromatic contrast.

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Appendix A

The generalized linear model expands the general linear model to allow for the dependent variable (performance, % correct) to have a non-normal distribution, in our case, a binomial distribution. A link function is used in the GLM, which allows the performance (dependent variable) to be related to the factors and covariates in a linear manner. Here, the link function used was a binary logistic function.

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