The effects of a TMS double lesion to a cortical network

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Abstract

Transcranial magnetic stimulation (TMS) has contributed to our understanding of the functions of individual brain regions, but its use to examine distributed functions throughout a network has been more limited. We assess the functional consequences of a TMS pulse to the oculomotor network which was first perturbed by continuous theta-burst stimulation (cTBS), to examine the potential for additive effects from lesions to two network nodes. Twenty-three humans performed pro- (look towards) and anti- (look away) saccades after receiving cTBS to right frontal eye fields (FEF), dorsolateral prefrontal cortex (DLPFC) or somatosensory cortex (S1) (control). On a subset of trials, a TMS pulse was applied to right posterior parietal cortex (PPC). We assessed changes in saccade amplitudes, performance (percentage correct) and reaction times, as these parameters relate to computations in networks involving these nodes. We observed impairments in ipsilateral anti-saccade amplitudes following DLPFC cTBS that were enhanced by a PPC pulse, but that were not enhanced relative to the effect of the PPC pulse alone. There was no evidence for effects from the double lesion to performance or reaction times. This suggests that computations are distributed across the network, such that even a single lesion is consequential.

Keywords: Transcranial magnetic stimulation, Prefrontal cortex, FEF, Frontal Eye Fields, Parietal Cortex, Oculomotor

Introduction

Behavioral consequences of non-invasive neural interventions, such as those evoked with transcranial magnetic stimulation (TMS), have been frequently interpreted as consequences of interference with the cerebral territory being stimulated directly. Yet, it is known that the effects of TMS extend beyond the site of stimulation, revealing an effect of a TMS perturbation that can spread throughout the network (Ilmoniemi et al., 1997; Ko et al., 2008; Morishima et al., 2009; Paus et al., 1997; Ruff et al., 2006). In some instances, such distal effects reflect compensatory responses to the TMS lesion (Hartwigsen et al., 2013; O'Shea, Johansen-Berg, Trief, Göbel, & Rushworth, 2007; Sack, Camprodon, Pascual-Leone, & Goebel, 2005), suggesting "homeostatic metaplasticity" (Müller-Dahlhaus & Ziemann, 2015) at a network nodal level. Here we assess a less described but functionally relevant possibility: namely whether behavioral consequences of a spatially-localized neural interference are driven by the distributed nature of computations throughout a neural circuit (Price & Friston, 2002).

The oculomotor system provides a tractable testing ground for assessing circuit-level consequences of TMS (Leigh & Kennard, 2004; Munoz, Armstrong, & Coe, 2007). Roles of cortical nodes, namely frontal eye fields (FEF), dorsolateral prefrontal cortex (DLPFC), and the posterior parietal cortex (PPC) have been described (Johnston & Everling, 2011; Munoz & Everling, 2004; Paré & Dorris, 2011) in relation to behavioral output in commonly-used paradigms to investigate cortical processes. In particular, the anti-saccade task, where subjects must look away from a peripheral visual stimulus (Hallett, 1978), taps into predictions for the roles of these nodes in voluntary control spanning from planning, to attentional shifts, to motor programming. In brief: DLPFC is thought to be critical to executive function (i.e., preparatory set and inhibition against an automatic response); FEF is thought to be critical to voluntary saccade

programming; and both FEF and PPC are thought to be critical to the spatial attention signals related to developing a saccade "vector" to drive the eyes to a location in space opposite of visual stimulation (Leigh & Kennard, 2004; Munoz & Everling, 2004).

It is known that these cortical nodes share neural variance outside oculomotor tasks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Ptak, 2012; Tschentscher, Mitchell, & Duncan, 2017; Vossel, Geng, & Fink, 2014) and also contribute to larger networks important to attentional processing and top-down control (Miller & Cohen, 2001; Ptak, 2012; Vossel et al., 2014). However, the spatial bias of the oculomotor system for the contralateral visual field in saccade tasks (Munoz & Everling, 2004; Schall, 2009; Silver & Kastner, 2009) is useful for disambiguating the consequences of TMS interferences within the same hemisphere, because it reduces the possibility that homotopic contralateral regions can fully compensate for the perturbation.

We build on this knowledge to interpret saccadic behaviors after a double lesion to the cortical oculomotor circuit in the same (right) hemisphere in a pro- and anti-saccade task. Shortly after applying continuous theta-burst stimulation (cTBS, known to evoke sustained neuronal inhibition, (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005)) to either right FEF or right DLPFC, we measure the saccadic consequences of a second time-resolved perturbation to the oculomotor circuit, in the form of a single TMS pulse to the right PPC. This PPC pulse was applied at a variable time during the saccade generation.

This approach arbitrates between five main hypotheses regarding the consequences of the double lesion. First, the double lesion could produce an additive effect (over a single lesion) by concurrently impairing spatially distinct nodes that provide critical, yet computationally degenerate functions, resulting in behavioral perturbations that are greater than the effect of

either perturbation alone (Figure 1A). Alternatively, if computations are performed by a distributed system at the network-level, a single lesion to either node should perturb behavior as much as the double lesion (Price, Hope, & Seghier, 2017) (Figure 1B). Another possibility is that distal nodes could compensate for the perturbation, which would predict greater effects from the double lesion compared to the cTBS lesion alone (Figure 1C), because the second lesion impairs a region that has now become more important functionally because of the first (cTBS) lesion. Fourth, the effects from cTBS could spread trans-synaptically to other portions of the network (Ko et al., 2008), predicting greater effects from the double lesion than to the single pulse lesion alone (Figure 1D). Finally, additional regions in the network could provide compensation, which would manifest as a perplexing boost to performance following cTBS, and which would also reduce the impairment from further TMS perturbations to the network (Figure 1E).

Figure 1: Hypotheses for the effects of TMS "lesions" to two oculomotor network nodes in the same hemisphere. A) Additive impairment from a double lesion compared to a single lesion to either node. B) No additive effects (a single lesion to the network is disruptive). C) Compensatory effect from second node that became more important. D) Enhanced effect due to cTBS spreading through the network to influence the second node. E) Additional network regions provides source of compensation for cTBS.

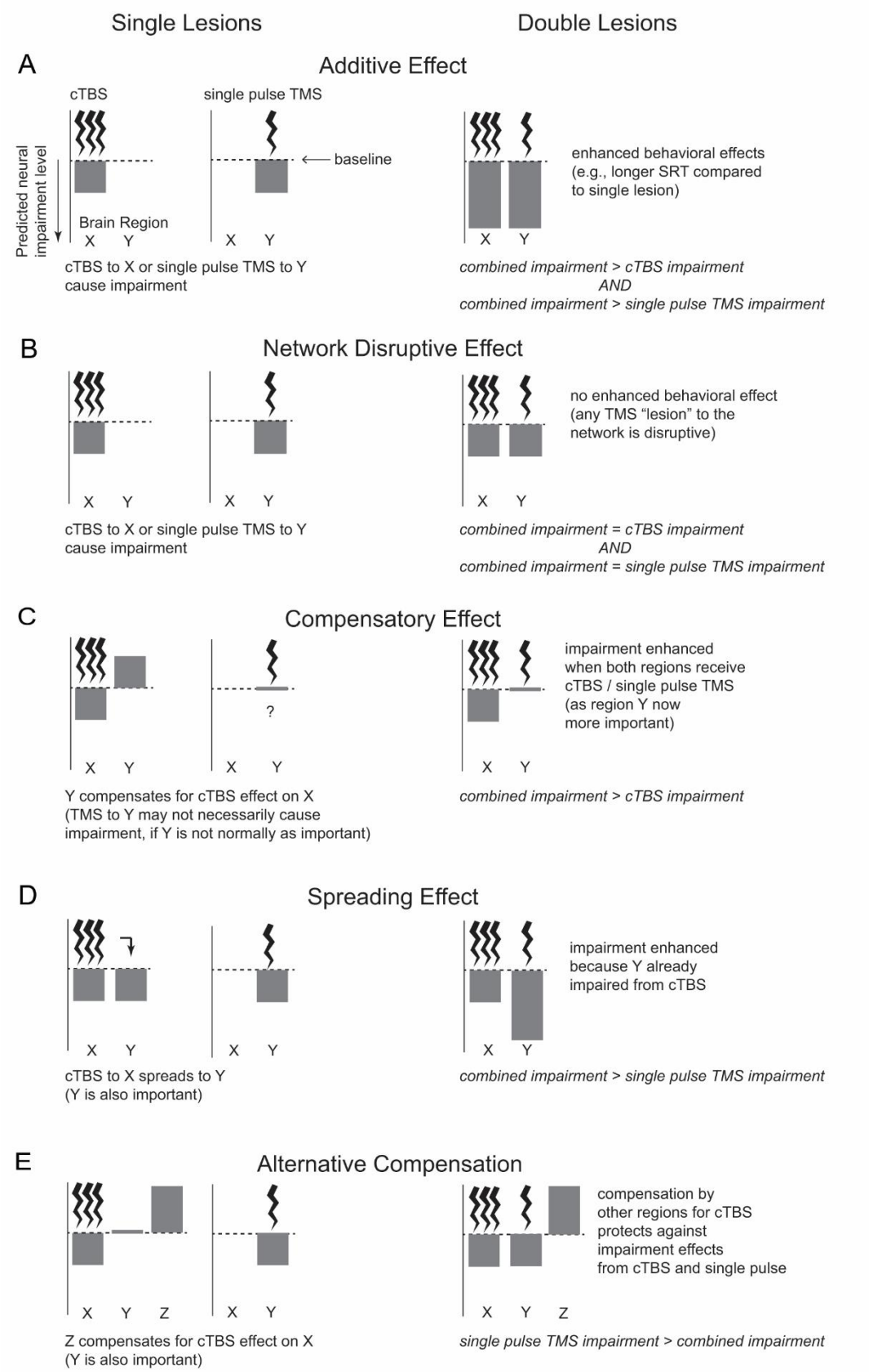
Single Lesions
Double Lesions
A
Additive Effect
cTBS
single pulse TMS
Predicted neural impairment level
baseline
Brain Region
X Y
X Y
X Y
enhanced behavioral effects (e.g., longer SRT compared to single lesion)
cTBS to X or single pulse TMS to Y cause impairment
combined impairment > cTBS impairment
AND
combined impairment > single pulse TMS impairment
B
Network Disruptive Effect
X Y
X Y
X Y
no enhanced behavioral effect (any TMS "lesion" to the network is disruptive)
cTBS to X or single pulse TMS to Y cause impairment
combined impairment = cTBS impairment
AND
combined impairment = single pulse TMS impairment
C
Compensatory Effect
?
X Y
X Y
X Y
impairment enhanced when both regions receive cTBS / single pulse TMS (as region Y now more important)
Y compensates for cTBS effect on X (TMS to Y may not necessarily cause impairment, if Y is not normally as important)
combined impairment > cTBS impairment
D
Spreading Effect
X Y
X Y
X Y
impairment enhanced because Y already impaired from cTBS
cTBS to X spreads to Y (Y is also important)
combined impairment > single pulse TMS impairment
E
Alternative Compensation
X Y Z
X Y
X Y Z
compensation by other regions for cTBS protects against impairment effects from cTBS and single pulse
Z compensates for cTBS effect on X (Y is also important)
single pulse TMS impairment > combined impairment

Figure 1

These hypotheses are important to resolve because they impinge on the local versus distributed organization of a prototypical brain control network. TMS to either DLPFC, FEF (or supplementary eye fields) during saccade programming prolongs reaction times, suggesting that each region has a critical role in "preparatory set" (Nagel et al., 2008). However, preparatory set might also be distributed between these nodes, as it is not clear why each lesion independently would prolong reaction times (Nagel et al. 2008). Similarly, magnetoencephalography (MEG) and fMRI show that FEF and PPC are both involved in the attentional aspects of programming the anti-saccade "vector" to a location opposite a visual stimulus (Medendorp, Goltz, & Vilis, 2005; Moon et al., 2007), and TMS or lesions to either FEF or PPC can produce deficits in terms of reaction times or amplitudes (Cameron, Riddle, & D'Esposito, 2015; Gaymard, Ploner, Rivaud-Péchoux, & Pierrot-Deseilligny, 1999; Jaun-Frutiger, Cazzoli, Müri, Bassetti, & Nyffeler, 2013; Nyffeler, Hartmann, Hess, & Müri, 2008). However, it is not possible to distinguish a difference in timing (even with high temporal resolution MEG) between when an anti-saccade program is developed in the posterior parietal cortex compared to FEF (Moon et al., 2007), implying that attentional processing may be generated as a distributed process in this network. Along similar lines, the study of oscillations within the "dorsal attention network" (Thiebaut de Schotten et al., 2011; Vossel et al., 2014) suggests a mechanism for how bottom-up (gamma band) and top-down (beta band) processing can occur simultaneously across this network (Siegel, Donner, & Engel, 2012).

To discriminate between those five hypotheses, we first used functional magnetic resonance imagining (fMRI) to localize right DLPFC, FEF and PPC in human subjects performing an anti-saccade localizer task. These regions were then used for targeting subject-specific TMS interventions while participants performed pro- and anti-saccades to the left or

right of fixation. Performance (percentage correct direction), reaction times, and saccade amplitude metrics were assessed using Bayesian t-tests, to provide statistical evidence in favour or against additive effects from the double- compared to single- TMS lesions following cTBS to DLPFC and FEF. By evaluating the effects to pro- and anti-saccade behaviors after both DLPFC- and FEF-cTBS, we could assess the generalizability of the effects across network nodes known to be directly connected, but hypothesized to have different roles. We were particularly interested in the effects on saccade amplitude after FEF cTBS, given the well-described hypotheses for the joint roles of FEF and PPC in supporting the spatial attention components of anti-saccade programming (i.e., the vector inversion process).

Material and methods

Participants

The study was approved by the local ethics committee (Commissie Mensgebonden Onderzoek, Arnhem-Nijmegen) and written informed consent was obtained from the participants in accordance with the Declaration of Helsinki. A total of 27 healthy right-handed, young-adult, human subjects were recruited for this study, which included 4 sessions, approximately 1 week apart. Session 1 involved assessment of the motor thresholds and performance of the oculomotor task in the fMRI scanner; sessions 2-4 comprised of performance of the task under different cTBS conditions (described in “TMS Sessions”). 3 subjects were excluded for failure to provide useable eye-tracking data on all TMS sessions, resulting in a sample size of 24 participants (mean ± SE, age 23 ± 2 years, 11 male). Additionally, one subject had error rates on anti-saccade trials exceeding 90% (greater than 3 times the standard deviation), so was excluded.

General experimental design

Participants performed pro- (look towards) and anti- (look away from) saccades to peripheral stimuli that appeared briefly to two different eccentricities in the left and right direction. cTBS was applied to right DLPFC (r-DLPFC), right FEF (r-FEF) or right somatosensory cortex (r-S1) as a control site prior to performing the task on three separate sessions, counterbalanced for order. 40 s of cTBS (at 80% of active motor threshold) has effects lasting approximately 50 minutes (Wischnewski & Schutter, 2015), providing enough time to test the influence of the subsequent right PPC (r-PPC) pulse, which appeared at a variable time during saccade programming to test for an influence on predominantly the visual processing or motor programming components.

Detailed procedure

fMRI session

Participants were screened for contraindications related to fMRI, and to single-pulse TMS and cTBS according to the common safety guidelines for TMS studies (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011; Rossi, Hallett, Rossini, & Pascual-Leone, 2009). On the first (fMRI) session, the resting and active motor thresholds were established for the first dorsal interosseus (FDI) muscle of the subject's right-hand using electromyography (EMG) to display the motor evoked potential (MEP). TMS was applied using a hand-held bi-phasic figure-eight coil with a 75 mm outer winding diameter (MagVenture, Denmark), connected to a MagProX100 system (MagVenture). Coil orientation was chosen to induce a posterior-anterior electrical field in the brain (45º from the mid-sagittal axis). In this way, the motor thresholds were assed independently of all experimental TMS sessions which were counterbalanced in order across subjects (described below).

Functional MRI scans during performance of a pro-/anti-saccade localizer were obtained with a 3 Tesla MRI scanner (Skyra, Siemens Medical Systems Erlangen, Germany) using a 32-channel head coil. The functional images were acquired with multiband sequence (acceleration factor = 3, repetition time (TR) = 1000 ms, echo time (TE) = 30 ms, flip angle= 60º). Each volume consisted of 33 slices, with a distance of 17% and a thickness of 3 mm. The voxel resolution was 3.5 x 3.5 x 3.0 mm, FoV in the read direction of 224 mm and FoV in the phase direction of 100%. Two volumes were discarded from each functional run, to account for scanner steady state equilibrium, leading to a total of 339 volumes per run. The anatomical images were acquired with a MPRAGE sequence (repetition time (TR) = 2.3ms, echo time (TE) = 3.9 ms, voxel size = 1 x 1 x1 mm). In total, 192 images were obtained for each participant. During the scan, participants lay in a supine position and their head was stabilized using soft cushions.

Subjects were asked to perform 5 runs of a pro-/anti-saccade localizer to determine the cortical regions of interest. The task was viewed through a mirror mounted on the head coil. The position of the right eye was monitored in order to be assured that the participants performed the task appropriately. The task was presented using Psychophysics Toolbox extensions running in MATLAB version 2010 (MathWorks, Natick, USA) on a PC. In this task, participants fixated on a blue cross projected on a black screen for 1.5 s. In both pro-saccade and anti-saccade trials the cross changed to green or red for 1.3s. After this the screen turned black for 200 ms and then a blue dot (target stimulus, 1º) appeared at approximately 13º or 9º for 100 ms to the right or to the left, randomized across trials. Participants were instructed to look towards the location of the dot after the cross had turned green and away from the dot (approximately the same distance to the opposite side) when the cross had turned red. They were instructed to stay at this position until the central fixation point reappeared, and they had 1.4 s to respond. Each run consisted of 28 pro-

saccade trials and 28 anti-saccade trials, employing a jittered design such that additional pseudorandom fixation trials (as inter trial intervals) were presented with durations of 1.5 s (12 trials), 3 s (eight trials) or 4.5 s (six trials).

Imaging data were analyzed with SPM8 (Wellcome Trust Centre for Cognitive Neuroimaging, London, UK). At the single-subject level, the data were realigned to the first volume of each run using six rigid body transformations (3 translations and 3 rotations). The images were then coregistered to the individual structural T1 and spatial smoothing was performed by means of an 8-mm full-width half-maximum (FWHM) Gaussian kernel. A first-level analysis was performed by specifying a general linear model with regressors for each condition (fixation trials were not modeled however). Motion parameters (3 translations, 3 rotations) were included as nuisance regressors.

A contrast of anti-saccade trials against baseline was computed to define 5 mm ROIs centered on locations of peak activation on each subject anatomical scan, using a t-contrast at $P < 0.001$ (uncorrected). In this way, right PPC, right FEF and right DLPFC were defined based on the spatial and cognitive processes of voluntary anti-saccades (Brown, Vilis, & Everling, 2007; Cameron et al., 2012; Ford, Goltz, Brown, & Everling, 2005). Table 1 provides the mean MNI coordinates of these ROIs, and Figure 2A illustrates these coordinates on a canonical T1 scan. Right DLPFC was defined as peak activity at the middle frontal gyrus, anterior to the ventricles (Figure 2A). Right FEF was defined as peak activity in the precentral sulcus (if more than one peak was present, the more medial peak near the junction of the superior frontal sulcus was chosen rather than more lateral peaks, as this has been shown to relate more to anti-saccade aspects (Neggers et al., 2012). Right PPC was defined as peak activity in the intraparietal sulcus, selecting the peak in the more medial cluster if more than one was present. Finally, right S1 was

localized anatomically for each participant, by being the most superior extent of the postcentral gyrus, located on average 9 ± 2 mm lateral to the longitudinal fissure. This medial position was chosen to avoid stimulating a proprioceptive eye representation of orbital position, which has recently been identified in the lateral depths of the central sulcus in monkeys (Zhang, Wang, & Goldberg, 2008) and humans (Balslev, Albert, & Miall, 2011).

Table 1: Average (mm) ± standard deviations of MNI coordinates for Regions of Interest

	X	Y	Z
r-DLPFC	36±7	45±10	31±7
r-FEF	30±5	-5±4	57±6
r-PPC	20±7	-66±8	59±5
r-S1	9±2	-37±5	79±2

Figure 2: A) MRI images: illustration of coil placement over right dorsolateral prefrontal cortex (r-DLPFC), right frontal eye fields (r-FEF), right primary sensory cortex (r-S1), and right posterior parietal cortex (r-PPC) on a standard SPM anatomical template. Mean coordinates are shown as bright dots, and individual subject coordinates are shown as faint dots. Right: scalp "entry" points for TMS stimulation for a representative subject, showing also a representation of the coil orientation over right PEF (handle of coil = base of 'T' shape). B) Paradigm and stimulus timings shown for representative anti-saccade and pro-saccade trials, where the target stimulus was on the left side. C) Illustrations of raw eye-traces from a representative subject in one run (subject 22841) with respect to stimuli on the left side. For 13° stimuli, red illustrates anti-saccades and green illustrates pro-saccades; for 9° stimuli, magenta illustrates anti-saccades, and turquoise illustrates pro-saccades. This subject made a high proportion of direction errors on anti-saccade trials in this run, indicated by the reversals of direction. Blinks are shown as gaps in the traces.

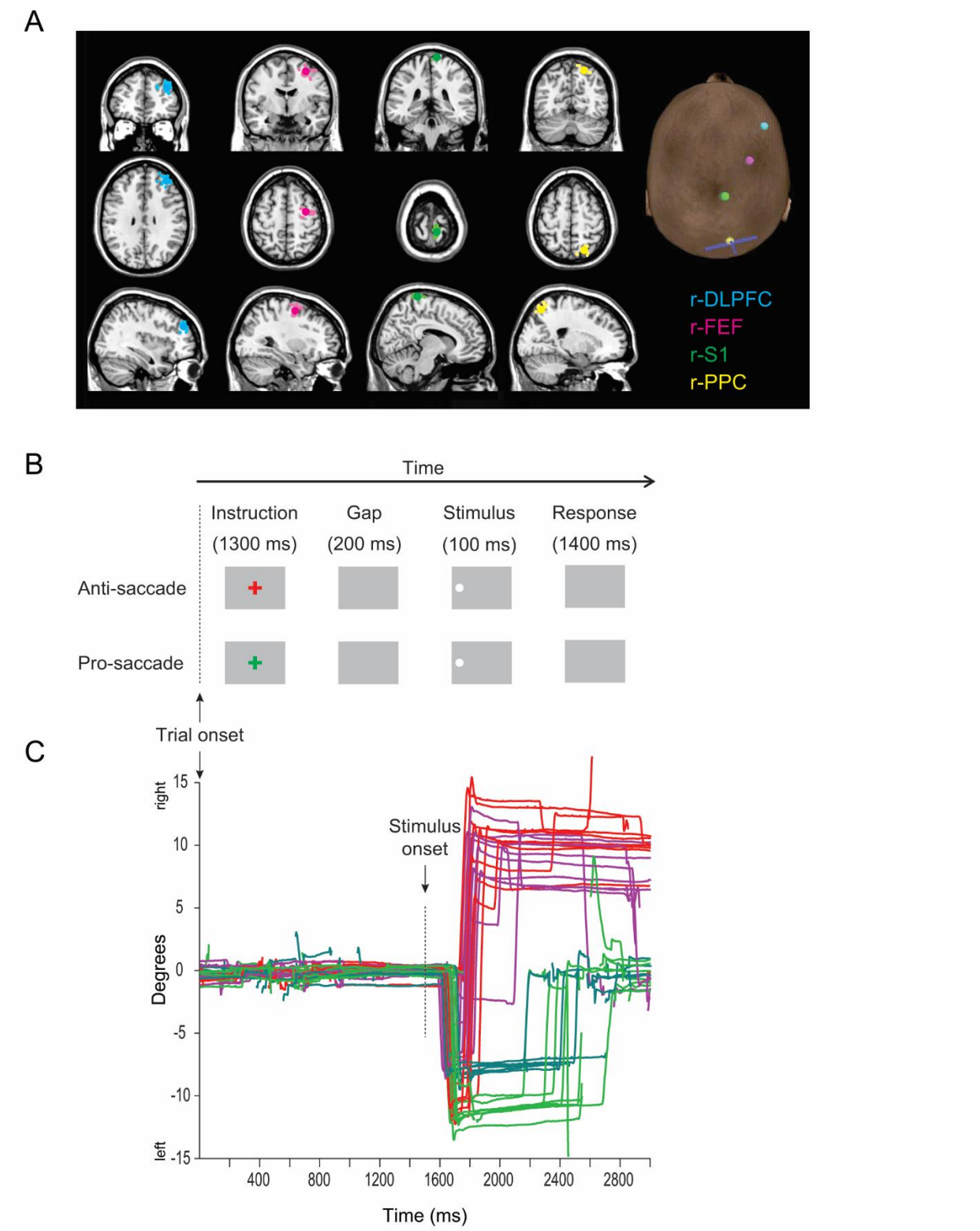
A
r-DLPFC
r-FEF
r-S1
r-PPC
B
Time
Instruction
(1300 ms)
Gap
(200 ms)
Stimulus
(100 ms)
Response
(1400 ms)
Anti-saccade
Pro-saccade
Trial onset
C
Stimulus
onset
right
left
Degrees
15
10
5
0
-5
-10
-15
400
800
1200
1600
2000
2400
2800
Time (ms)

Figure 2

TMS sessions

TMS coil alignment was achieved using Localite TMS Navigation software 2.2 (Localite, Germany), and a T1 anatomical scan acquired for each subject. ROI targets from the fMRI sessions were overlaid on the anatomical scan, and projected to the surface for coil alignment (Figure 2A). cTBS was delivered over r-DLPFC, r-FEF or r-S1 with a posterior-anterior direction of the electric field induced in the brain, such that the TMS coil handle pointed backwards and was held at approximately 30˚ relative to the sagittal plane. In this way the outer windings of the TMS coil did not overlap the other ROIs (e.g., the outer edge of the coil did not overlap r-FEF when centered on r-DLPFC). The parameters for cTBS were identical to those described by Huang and colleagues (2005) consisting of 50 Hz triplets (i.e., three single pulses separated by 20 ms) repeated at 5 Hz over a period of 40 s (600 pulses total) (Huang et al., 2005). Stimulation intensity for cTBS was defined as 80% of the active motor threshold (AMT), defined as peak-to-peak MEP amplitudes exceeding 200 μV on 5 out of 10 trials, while subjects maintained voluntary contraction of approximately 10%. Stimulation intensity for single pulse TMS to PPC was set at 110% of the resting motor threshold (RMT), defined as peak-to-peak MEP amplitudes of 50 μV on 5 of 10 trials.

Eye Tracking and Task

The position of the right eye was recorded using an Eyelink 1000 eye tracker (SR Research, Mississauga, Ontario, Canada) with a 1000 Hz sampling rate. A 9- point eye tracker calibration was carried out for each participant prior to data collection. A drift correction point was used as the inter-trial fixation point, and re-calibration throughout the behavioural session was performed as necessary. Saccades were identified by a horizontal deflection (3 x standard deviation of the baseline velocity) and duration between 15 and 150 ms. The camera was positioned under the stimulus screen, approximately 60 cm away from the eyes of the participant,

who sat precisely at 70 cm from a wide angle LCD screen (with central presentation zone set at 4:3, 1024 X 768 resolution) on each session. An infrared illuminator positioned next to the camera illuminated the subject's right eye.

As with the fMRI version, each trial began with a pro- or anti-saccade instruction cross cue (1.3 seconds), 1.5 º of visual angle, followed by a 200 ms gap in fixation, after which the target stimulus (blue dot, 1 º) appeared at 13 º (wide) or 9 º (short) degrees for 100 ms horizontally to the right or left side of the screen's center (Figure 2B). Subjects were given 1.4 s to respond, and were instructed to make a saccade to the location where the stimulus appeared on a pro-saccade trial, or to make a saccade to the mirror location of the stimulus on an anti-saccade (not simply "look away"). We used the transient 100 ms stimulus so that both pro- and anti-saccades were to spatial positions void of stimulation, and we used two different eccentricities to enforce attention to position. In each run, there were 72 trials, of which 48 contained a single TMS presented at a random interval between 30 and 300 ms after onset of the peripheral stimulus. The first run commenced each session at 10 minutes after cTBS, and we analyzed data up to 50 minutes after cTBS to capture the same cTBS effects on each session. Subjects were asked to perform 5 runs, each taking approximately 8 minutes including drift corrections and breaks, meaning there for each condition (task, direction, and stimulus eccentricity) there were 15 trials without a single TMS pulse (*pulse absent* trials), and 30 trials containing a single pulse (*pulse present* trials).

Data analysis

Data was analyzed with custom MATLAB v11 programs (The MathWorks Inc., Natick, MA). Valid trials consisting of correct and incorrect directions were separated from invalid trials, consisting of saccade reaction times (SRTs) < 90 ms (anticipatory errors), slower than 1000 ms,

and trials where the TMS pulse to PPC occurred after saccade onset. Three behavioral parameters of interest were analyzed: percentage correct direction (based on pro- or anti-saccade instruction), saccade reaction time (SRT), and amplitude of the primary saccade.

We first determined a division between an ‘Early’ pulse time bin, and a ‘Late’ pulse time bin for each cTBS session, to test interactions with pulse time, as follows: using the pulse absent trials, we collected the SRTs across subjects for correctly performed anti-saccades, and for direction errors on anti-saccades for each cTBS session separately, and plotted these data in 10 ms bin histograms (Figure 3). A binomial test revealed the first bin (black arrows, Figure 3) where the two trial types were no longer significantly different than chance (50 %); these bins occurred at 150 ms for the S1 cTBS and DLPFC cTBS sessions, and at 160 ms for the FEF-cTBS session. This method approximates the division between visually triggered ‘express’ saccades, and voluntary saccades (Munoz & Everling, 2004), and as such is a reasonable time approximation to dissociating when the PPC pulse would have greater influences during the visual processing rather than motor programming component (which we hypothesized might produce differences in an anti-saccade trials, depending on saccade direction).

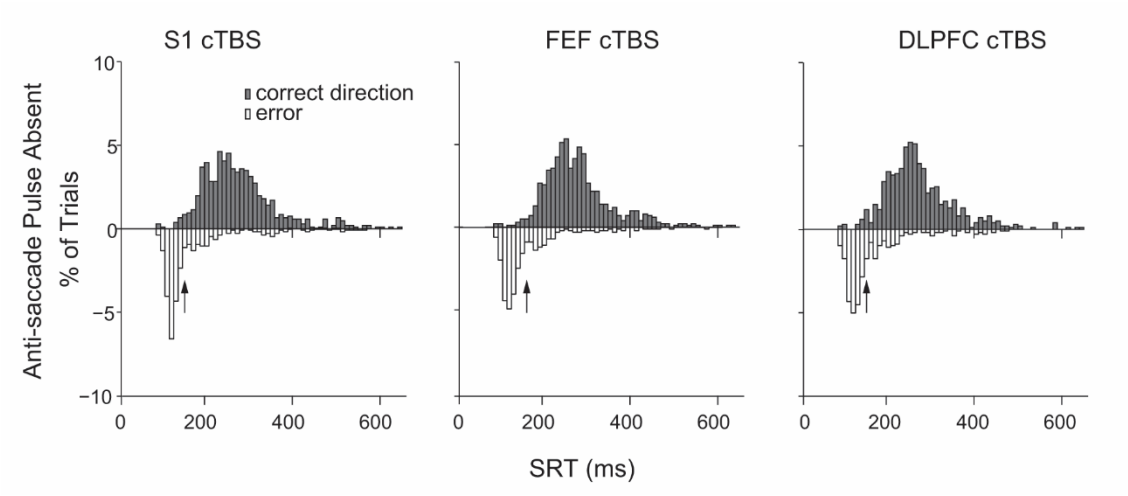

Figure 3: Derivation of the Early and Late PEF pulse bins based on anti-saccade reaction times. Reaction time distributions were calculated for correct and direction error anti-saccades in PEF Pulse Absent trials on each cTBS session. A binomial sign test was performed compared the distributions, and arrows indicate the first reaction time bin where the two distributions were no longer significantly different. This value was taken as the boundary for Early and Late PEF pulses.

Next, we performed a repeated measures ANOVA using pulse absent trials to determine if there were significant interactions between the site of cTBS and stimulus eccentricity for amplitudes. For a cTBS Site (DLPFC, FEF, S1) X Task (Pro, Anti) X Saccade Direction (Left, Right) X Eccentricity (Wide, Short) ANOVA, there was a main effect of eccentricity, $F(1,22) = 407.9$, $P < 0.001$, and a significant Task X Eccentricity interaction, $F(1,22) = 247.1$, $P < 0.001$, (mean Pro-Wide = 11.1°, Pro-Short = 7.5 °, Anti-Wide = 10.3 °, Anti-Short = 9.4 °). However, no interactions with cTBS Site and Eccentricity were significant, $F(2,44) < 1.75$, $P > 0.19$, so we collapsed across eccentricity for the remaining analyses to reduce the number of factors to those important to our hypotheses.

We were interested in investigating the combined effects (i.e., from the PPC pulse *plus* cTBS to FEF or DLPFC), compared to the effects of cTBS to FEF or to DLPFC alone, or to the effects of the PPC pulse alone. Therefore, to directly assess our five network hypotheses

regarding the combined effects from cTBS and the PPC pulse (Figure 1), we performed Bayesian paired-sample t-tests in JASP (JASP Team, 2017). A Bayes Factor (BF_{10}) indicates the evidence for the alternative hypothesis relative to the null hypothesis given the data. Thus, the Bayes Factor (BF_{10}) here indicates whether the *combined effects* (i.e., effects of cTBS to DLPFC or FEF, plus PPC TMS) were greater than the individual effects from cTBS to DLPFC or FEF alone, or from the PPC TMS pulse alone. We used Bayesian statistics specifically because they allowed us to test such hypotheses. We classified "impairments" therefore as lower values for percent correct and amplitude, but greater values for reaction times. The BF_{10} values for these paired sample t-tests are indicated between the corresponding brackets in Figures 4-6. A BF_{10} between 10 and 30 indicates *strong* evidence for the alternative hypothesis (effects < 0), and a BF_{10} between 0.1 and 0.03 indicates *strong* evidence for the null hypothesis (effects not less than zero). Similarly, Bayes factors > 30 and < 0.03 indicate progressively stronger evidence for the alternative, or for the null hypotheses, respectively (Jeffreys, 1961). We report evidence that meets or exceeds "*moderate*" ($BF_{10} =$ 3 to 10, or 0.3 to 0.1) (Jeffreys, 1961).

Tests for each individual trial type (Figures 4-6) compared to the control condition (S1 cTBS PPC Pulse Absent) were also conducted using Bayesian one-sample t-tests in JASP to confirm if the individual lesions did in fact cause an impairment. For these analyses, the BF_{10} indicates the relative likelihood that cTBS or TMS to the oculomotor network impaired behavior compared to the null hypothesis that the effects were equal to the S1 cTBS control condition (effects = baseline). The values for these tests are listed in Tables 2-4, and illustrated as asterisks in Figure 4-6 if strong in evidence. (Note that for the Compensatory Effect hypothesis to be valid (Figure 1C), there should be strong evidence for an impairment from the combined PPC pulse following cTBS to FEF or to DLPFC that is greater than from cTBS to FEF or DLPFC alone,

but, correspondingly, there cannot be strong evidence for an impaired effect from PPC pulses against the control condition (italicized in Tables 2-4): otherwise this shows only that the PPC pulse induced a behavioral impairment).

Results

Saccade amplitude

Here we analyze the differences in saccade amplitudes relative to the control conditions depending on TMS conditions (cTBS or PPC pulse), for leftwards or rightwards anti- or pro-saccades. The relevant statistical comparisons are thus those related to saccade amplitude differences depending on TMS condition, where reduced amplitudes are indicative of an impairment.

FEF cTBS vs control cTBS

As shown in Figure 4 (brackets), neither strong nor moderate evidence was found for additive impairments from the combined effect of the cTBS and PPC TMS pulse (all $BF_{10} \leq 2.91$) meaning that the effects were not greater for the "double lesion" compared to each of the single lesions. Likewise, there was neither strong nor moderate evidence to support the "double lesion" effect being greater than either single lesion, nor was their evidence for any of the PPC TMS lesions producing greater impairments than when following FEF cTBS.

Comparing each trial type relative to the control condition, there was however moderate evidence ($3 < BF_{10} < 10$) that FEF cTBS caused impairments in anti-saccade amplitudes for trial types involving PPC pulses for leftward anti-saccades, and for trial types involving the late PPC pulse for rightward anti-saccades (Table 2).

DLPFC vs control

Strong evidence was found for the enhanced impairment from the combined PPC TMS effect for rightward anti-saccades after the late pulse time relative to the DLPFC cTBS pulse absent condition ($BF_{10} = 325.22$), but not compared to the effects of the late PPC pulse alone ($BF_{10} = 0.75$) (Figure 4). As with FEF cTBS, there was moderate evidence for impairments to anti-saccades after DLPFC cTBS involving late PPC pulses or absent PPC pulses for leftward anti-saccades (Table 2).

Summary

After DLPFC but not FEF cTBS, strong evidence was found for an enhanced impairment from the combined TMS effect for rightward anti-saccades after the late PPC pulse. There was no strong, nor even moderate evidence however that the PPC pulse alone produced an impairment (Table 2). However, after both FEF and DLPFC cTBS, there was moderate evidence that cTBS to either of these regions caused impairments in anti-saccade amplitudes.

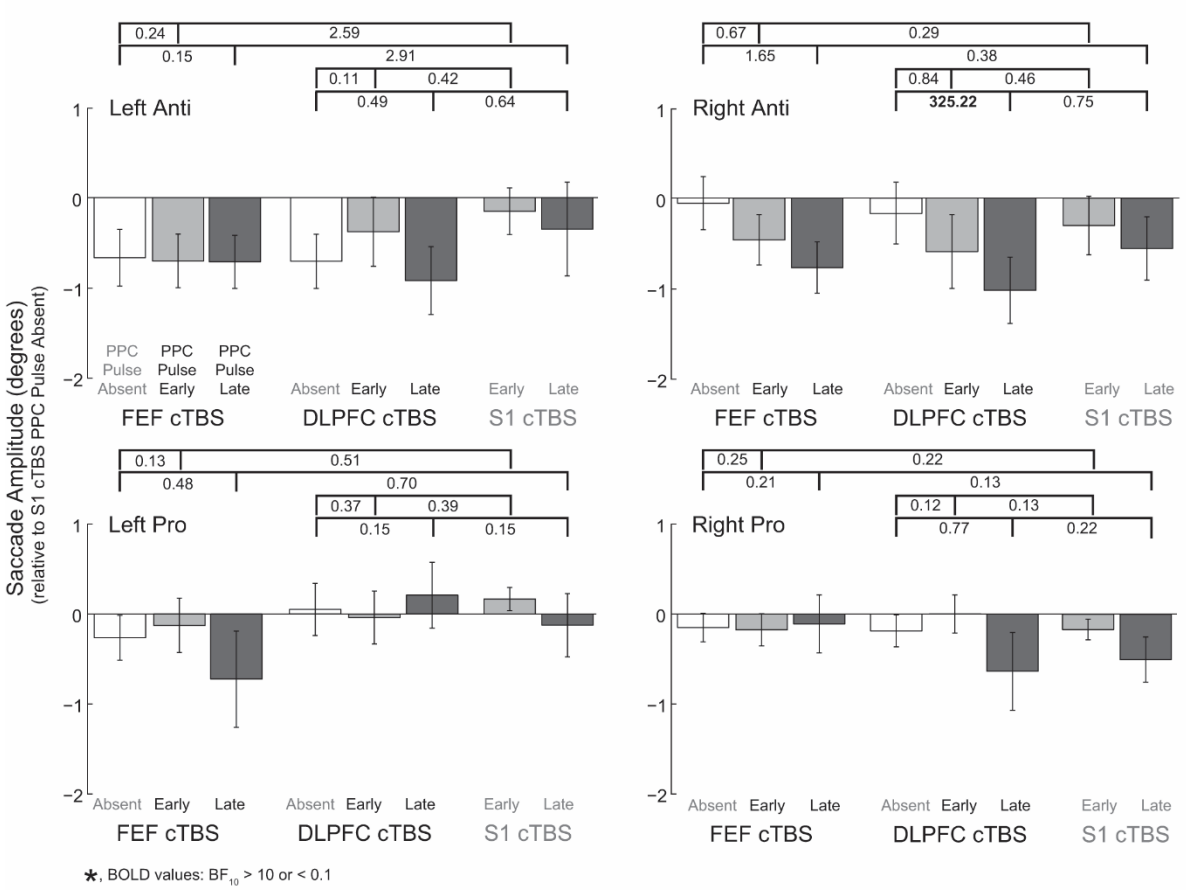

Figure 4: Amplitudes of primary saccades separated into left and right anti- and pro-saccade trials. All data is normalized to the S1 cTBS PEF Pulse Absent baseline. Error bars represent standard error of the mean across subjects (N=23), and black text represent the double lesion conditions. Values between brackets indicate the Bayes Factor evidence for the alternative hypothesis that the combined effects (e.g., FEF cTBS plus PPF Pulse Late) resulted in a greater impairment (more negative values) compared to the effects of cTBS alone (e.g., FEF cTBS Pulse Absent) or the effects of the PEF pulse alone (e.g., S1 cTBS PEF Pulse Late). Values > 10 provide strong evidence for the alternative hypothesis, and values < 0.1 provide strong evidence for the null hypothesis (that the combined effects did not result in a greater impairment). Asterisks show the results from post-hoc Bayesian one-sample t-tests for evidence (BF10) regarding the alternative hypothesis that the values are < 0 where BF10 >10 or < 0.1.

Table 2: Bayes Factors for the alternative (impairment)* vs. null (no impairment) hypothesis (BF_{10}) for each trial type normalized to control cTBS to S1 (see Fig. 4)

Amplitude

Task	cTBS	PPC pulse	BF_{10}	Task	cTBS	PPC pulse	BF_{10}
Left Anti	FEF	Absent	2.69	Right Anti	FEF	Absent	0.26
		Early	4.09			Early	1.31
		Late	4.58			Late	7.60
	DLPFC	Absent	4.21		DLPFC	Absent	0.33
		Early	0.55			Early	0.98
		Late	4.84			Late	8.84
	S1	*Early*	*0.35*		*S1*	*Early*	*0.52*
		Late	*0.39*			*Late*	*1.21*
Left Pro	FEF	Absent	0.61	Right Pro	FEF	Absent	0.54
		Early	0.31			Early	0.56
		Late	0.87			Late	0.30
	DLPFC	Absent	0.19		DLPFC	Absent	0.62
		Early	0.24			Early	0.22
		Late	0.15			Late	1.03
	S1	*Early*	*0.11*		*S1*	*Early*	*1.07*
		Late	*0.30*			*Late*	*2.32*

Bold values: $BF_{10} > 10$ or < 0.1; *impairment means < 0

Percentage correct direction

FEF vs control

There was strong evidence from Bayesian t-tests supporting the null hypothesis that there were no enhanced impairments from cTBS to FEF and the PPC pulse, compared to cTBS only for anti-saccade responses (Figure 5). Likewise, there was strong evidence that anti-saccades were *not* impaired by the PPC pulse from Bayesian t-tests (shown as asterisks in Figure 5, and in Bold in Table 3). (We did not test *a priori* for *benefits* following stimulation, but Bayesian t-tests for anti-saccade benefits to correct directions (i.e., performance after the combined lesion > than after the single lesion, or after control cTBS) revealed strong evidence ($BF_{10} > 10$), for all responses involving FEF cTBS and PPC pulses).

DLPFC vs control

There was also no evidence for enhanced impairment from cTBS to DLPFC and the PPC pulse, compared to cTBS only. As with FEF cTBS, there was no evidence that anti-saccades were impaired by the PPC pulse. (Bayesian t-tests revealed strong evidence ($BF_{10} > 10$) for anti-saccade benefits to performance following late PPC pulses).

Summary

Evidence from Bayesian t-tests did not support hypotheses for differences between the combined effects of cTBS to FEF or to DLPFC plus the PPC pulse compared to the effects of the PPC pulse alone. There was strong evidence *against* a hypothesis that right PPC TMS caused anti-saccade performance impairments (as there was strong evidence for benefits of the PPC pulse relative to control cTBS, as well as to cTBS to FEF or to DLPFC).

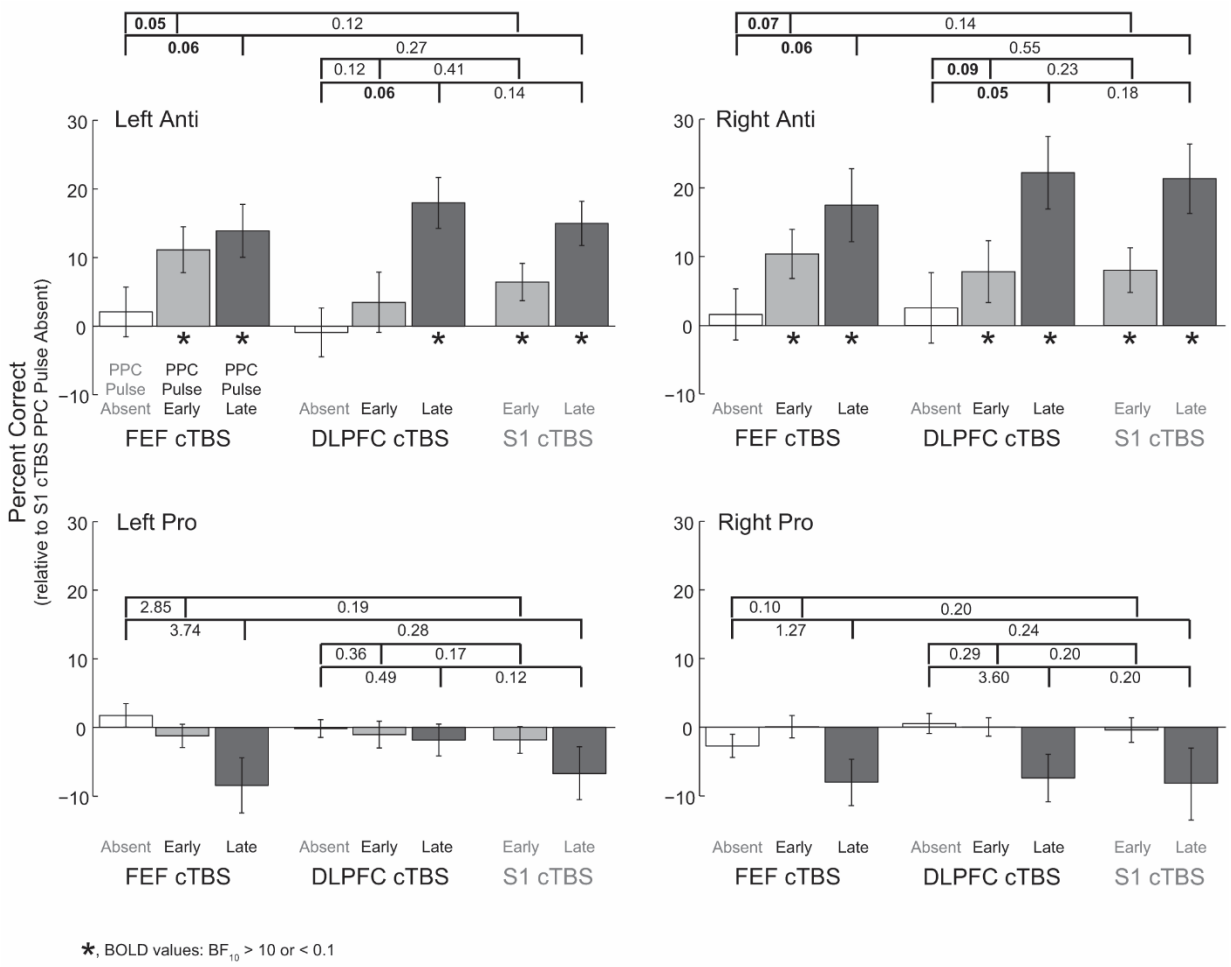

Figure 5: Performance (% correct directions). Conventions as in Figure 4.

Table 3: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for each trial type normalized to control cTBS to S1 (see Fig. 5)

Percent Correct

Task	cTBS	PPC pulse	BF_{10}	Task	cTBS	PPC pulse	BF_{10}
Left Anti	FEF	Absent	0.15	Right Anti	FEF	Absent	0.16
		Early	**0.06**			Early	**0.07**
		Late	**0.06**			Late	**0.06**
	DLPFC	Absent	0.27		DLPFC	Absent	0.16
		Early	0.14			Early	**0.09**
		Late	**0.05**			Late	**0.05**
	S1	*Early*	***0.08***		*S1*	*Early*	***0.07***
		Late	***0.05***			*Late*	***0.06***
Left Pro	FEF	Absent	0.12	Right Pro	FEF	Absent	1.16
		Early	0.41			Early	0.22
		Late	2.63			Late	4.53
	DLPFC	Absent	0.22		DLPFC	Absent	0.17
		Early	0.32			Early	0.21
		Late	0.42			Late	2.84
	S1	*Early*	*0.48*		*S1*	*Early*	*0.24*
		Late	*1.44*			*Late*	*1.19*

Bold values: $BF_{10} > 10$ or < 0.1; *impairment means < 0

Saccade Reaction Times (SRT)

FEF vs control

For both anti- and pro-saccades, there was strong evidence that the combined effects of FEF cTBS and a late PPC pulse resulted in enhanced impairments relative to FEF cTBS alone, and this effect was also present for pro-saccades with the early PPC pulse (Figure 6). However, there was no evidence for an *enhanced* impairment for the combined cTBS to FEF and PPC pulse effects over the PPC pulse effects alone. In fact, strong evidence showed that impairments for leftwards anti-saccades were not greater when the late PPC pulse followed FEF cTBS compared to when it was alone (BF = 0.08, Figure 6. (In fact, there was moderate evidence that the impairment after the late PPC pulse alone was greater than after FEF cTBS, $BF_{10} = 4.12$). Decisive evidence for pro-saccade reaction time impairments was observed during all late PPC pulse times (Figure 6, Table 4) (and during the late PPC pulse time for anti-saccades in the control condition (Table 4)).

DLPFC vs control

Like with the results after FEF cTBS, there was strong evidence that the combined effects of DLPFC cTBS and a late PPC pulse resulted in enhanced impairments relative to DLPFC cTBS alone, and this effect was present with the early pulses for pro-saccades, but no evidence for greater impairment in comparison to the PPC pulse. There was decisive evidence for pro-saccade reaction time impairments at the late PPC pulse time, as well as strong evidence for impaired anti-saccade reaction times at the late pulse time for right anti-saccades (Table 4).

Summary

There was no evidence for impairments from cTBS alone or from enhanced impairments from the combination compared to the PPC pulses alone.

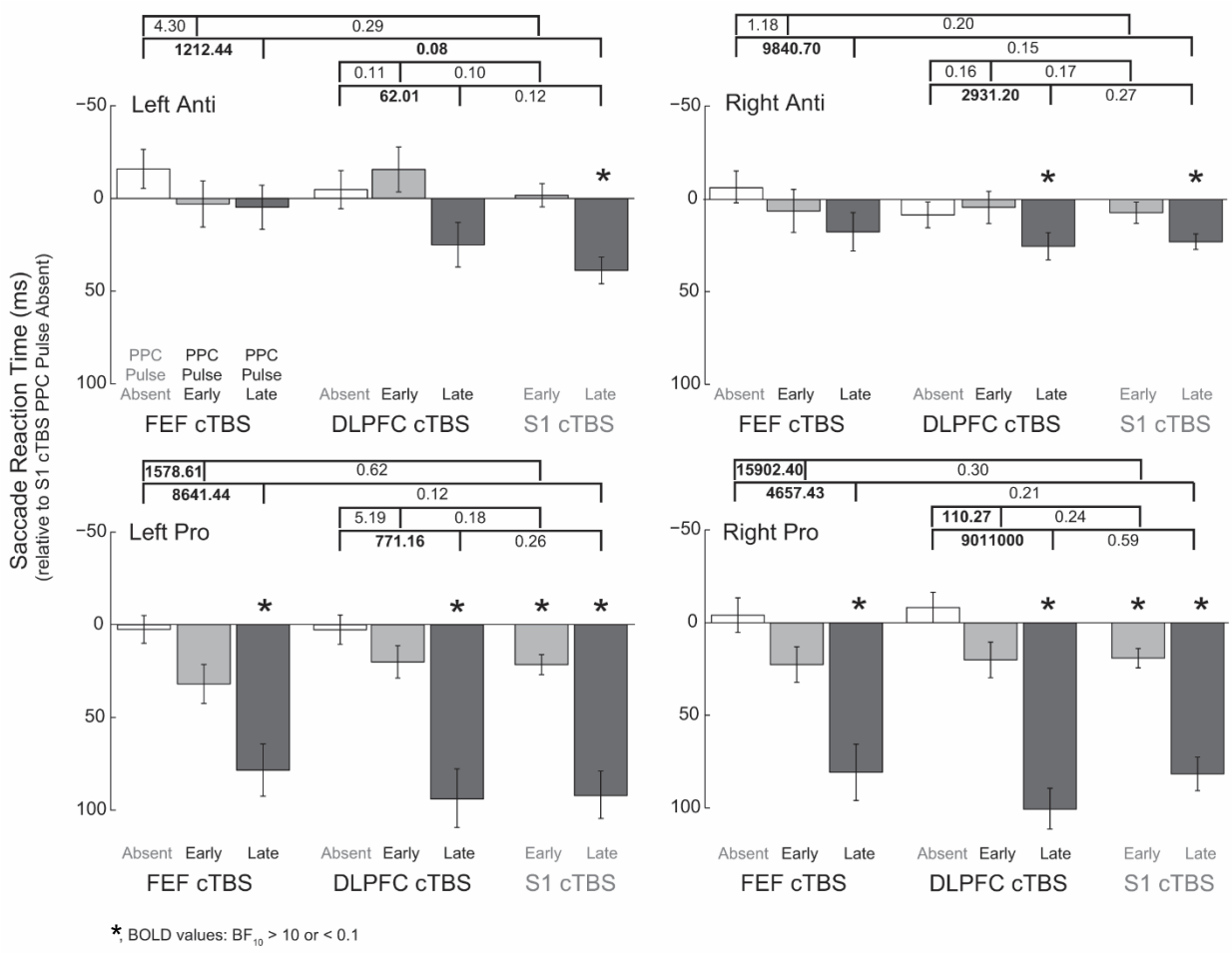

Figure 6: Saccade reaction times. Conventions as in Figure 4. (Note here that positive Y-axis values are plotted downwards).

Table 4: Bayes Factors for the alternative (impairment)* vs. null (no impairment) hypothesis (BF_{10}) for each trial type normalized to control cTBS to S1 (see Fig. 6)

Saccade Reaction Time

Task	cTBS	PPC pulse	BF_{10}	Task	cTBS	PPC pulse	BF_{10}
Left Anti	FEF	Absent	0.59	Right Anti	FEF	Absent	0.29
		Early	0.23			Early	0.25
		Late	0.24			Late	0.74
	DLPFC	Absent	0.24		DLPFC	Absent	0.40
		Early	0.46			Early	0.24
		Late	1.30			Late	**16.96**
	S1	*Early*	*0.22*		*S1*	*Early*	*0.45*
		Late	***1149.80***			*Late*	***1309.96***
Left Pro	FEF	Absent	0.23	Right Pro	FEF	Absent	0.24
		Early	7.47			Early	2.08
		Late	**1657.49**			Late	**730.84**
	DLPFC	Absent	0.23		DLPFC	Absent	0.34
		Early	1.86			Early	1.29
		Late	**2544.68**			Late	**1172000**
	S1	*Early*	***55.31***		*S1*	*Early*	***25.74***
		Late	***26318.61***			*Late*	***1082000***

Bold values: $BF_{10} > 10$ or < 0.1; *impairment means > 0, note Y-axis is reversed

Table 5: Summary of effects of TMS double lesion

Bayesian results from TMS	Supporting Hypotheses (Fig. 1)
Amplitude - moderate evidence for impairments from late PPC pulses for anti-saccades when following FEF or DLPFC cTBS (Table 2) - other evidence (moderate) for impairments to leftward anti-saccades following FEF cTBS or DLPFC cTBS (Table 2)	Network Level Effects from cTBS (Figure 1B)
- strong evidence for ***enhanced*** impairment from late PPC pulse following DLPFC cTBS for ipsilateral anti-saccades (Figure 4)	Compensatory Effect for cTBS (Figure 1C)
Performance (% correct) - strong evidence PPC pulse facilitated anti-saccade performance	(NA)
Reaction Time - decisive evidence late PPC pulses impaired pro-saccade reaction times - moderate evidence late PPC pulse alone impaired contralateral (left) anti-saccade reaction time more than when following FEF cTBS	Alternative source of Compensation (Figure 1E)

Discussion

We tested hypotheses regarding how two TMS "lesions" to the oculomotor network influence behavior, by applying a TMS pulse to right PPC after applying cTBS to right FEF or right DLPFC. Doing so allowed us to assess whether perturbations to two network nodes would result in additive double lesion effects, where impairments are enhanced relative to those induced by a TMS lesion to each node individually. The absence of such effects could suggest that the behaviors were generated by distributed network processes, whereby a single TMS lesion might be sufficient to perturb behavior (Price & Friston, 2002; Price et al., 2017). Additionally, we also evaluated whether there could be compensation by right PPC for the cTBS effects to DLPFC or FEF, suggesting network-level adaptation, or if the cTBS to the frontal nodes could directly affect right PPC nodal function. Table 5 summarizes the effects and their relationship to our hypotheses in Figure 1.

We did not find evidence for additive effects (Figure 1A); instead we found moderate evidence that FEF or DLPFC cTBS alone was sufficient to disrupt anti-saccade amplitudes (Figure 1B). These findings suggest that cTBS to FEF or DLPFC was consequential to behavior such that a second network lesion does not produce additive effects over the effects of the two lesions separately. We did not find evidence for enhanced impairments from spreading lesion effects from cTBS (Figure 1D), which could have been produced if the effects of cTBS to FEF or DLPFC were carried to PPC, such that the TMS pulse to PPC added to the cTBS effects on that node.

We did observe that the PPC pulse after DLPFC cTBS resulted in increased amplitude impairments for rightward anti-saccades compared to cTBS alone (Figure 4), suggesting that there could have been a compensatory contribution involving PPC after DLPFC cTBS for this

behavioral impairment (Figure 1C). Interestingly, there was not strong nor moderate evidence that the PPC pulses alone produced an impairment in this condition. This is consistent with a hypothesis regarding compensation, such that a double lesion reveals a compensatory process in the network by impairing a node which has as a consequence a greater contribution (Hartwigsen et al., 2016). We note that these effects were lateralized, fitting with a hypothesis for compensation by PPC following DLPFC cTBS for ipsilateral anti-saccades only. Because this was not observed for contralateral saccades for either cTBS condition, this suggests that the FEF or DLPFC lesions were more consequential to contra-lateral anti-saccades. We also note that for leftward (contralateral) anti-saccade reaction times, the impairment effects of the late PPC pulse *alone* were stronger than the effects of the late PPC pulse following FEF cTBS. This could suggest that following FEF cTBS, remaining network sources provided compensation, such as those involving the superior colliculus, which facilitated anti-saccade generation and diminished the effect of the PPC pulse (i.e., Figure 1E).

Taken together, the evidence suggests that network interactions are important, over and above summated contributions of individual nodes. Indeed, FEF and DLPFC may be critical nodes in terms of network-level processes, behaving as “connector hubs” for long-range information flow (Bullmore & Sporns, 2009; Sporns, Honey, & Kötter, 2007). Sporns and colleagues (2007) found in monkeys that the lateral intraparietal area (the macaque homologue of PPC) is a hub node with a lower degree (number of connections) than FEF or DLPFC, as well as being a node with relatively greater local connections than FEF or DLPFC. A cTBS lesion to FEF, or DLPFC, may therefore be more consequential for the communication of information in a cortical network critical to mapping the spatial positions for an anti-saccade. The present study suggests DLPFC may be part of this network previously emphasized to involve FEF and PPC

(Medendorp et al., 2005; Moon et al., 2007; Munoz & Everling, 2004). Importantly, these three nodes have been shown in functional neuroimaging as well as anatomical connectivity studies to form interconnected fronto-parietal networks, which are proposed to be recruited when top-down attentional control is needed (Dosenbach et al., 2008; Ptak, 2012; Thiebaut de Schotten et al., 2011; Vossel et al., 2014).

Interpretational issues

Effect on performance and reaction times

We observed a *benefit* of the PPC pulse on anti-saccades relative to pro-saccade performance which can be explained as follows. First, because we rejected trials when reaction time was less than the PPC pulse time, the effects to reaction time by the PPC pulse are biased by longer reaction time trials. Nevertheless, this had particularly greater detrimental effects on pro-trials than on anti-trials. Pro- and anti-trials were pseudorandomly interleaved, and because of this, there was competition from anti- and pro-saccades programs on each trial (note that subjects executed anti-saccades incorrectly on approximately 9% of pro- trials, suggesting that pro-saccades were not performed completely automatically). It is likely that as time increases, any direct influence from the stimulus on triggering a pro-saccade had dissipated (the typical window of such “express saccades” in humans is approximately 90 to 140 ms) (Munoz & Everling, 2004), so trials with longer reaction times are likely under greater voluntary control. A PPC pulse may benefit an *anti*-saccade by removing influences from parietal cortex on generating a stimulus-driven *pro*-saccade. Indeed, human EEG evidence suggests that the posterior parietal/occipital cortex is involved in triggering express saccades (Hamm, Dyckman, Ethridge, McDowell, & Clementz, 2010), possibly by a cortical-collicular mechanism (Chen, Liu, Wei, & Zhang, 2013; Watanabe, Hirai, Marino, & Cameron, 2010).

We also acknowledge that we could not control for the 'non-neural' effects from the PPC pulse clicks or somatosensory sensations (Duecker, de Graaf, Jacobs, & Sack, 2013; Duecker & Sack, 2013), which have been shown to reduce reaction times, if applied pre-stimulus. In the present study the pulse was applied post-stimulus and we found a slowing of reaction times. The pulse could engage a startle-like reflex that inhibits ongoing motor commands, by acting on the superior colliculus or brain stem saccade generator circuits (Xu-Wilson, Tian, Shadmehr, & Zee, 2011), thus having a relatively greater detriment to *pro*-saccade compared to anti-saccade performance and reaction times, because anti-saccades engage a larger network important to voluntary control.

The effects of the PPC pulses on performance and reaction times should be interpreted with caution due to these confounds. However, it was our goal to examine the *interactions* of cTBS to DLPFC and FEF with these PPC pulses, and we did not find any evidence for additive or compensatory effects. (The anti-saccade benefit described above, and any alerting effects, are independent of the influence of cTBS administered prior to these PPC pulses).

Lateralized effects

Previous studies, including our own, found impairments to ipsilateral anti-saccade amplitudes following right FEF cTBS (Cameron et al., 2015; Jaun-Frutiger et al., 2013), which were not observed here. However, there were differences in task design such that these studies did not employ a gap in fixation, and the visual target was not extinguished before saccade generation. We also did not find a clear directional effect as predicted by the vector inversion processes (i.e., that early PPC pulses would impair ipsilateral anti-saccade amplitudes, but late PPC pulses would affect contralateral anti-saccade amplitudes) as found by Nyffeler and colleagues, 2008. However, their study used a memory guided task in six subjects, such that

subjects were still maintaining fixation when the PPC pulses were presented (hence during the time that the vector inversion process could be accomplished, but not directly related to saccade execution). In our study, we cannot prove that a right PPC pulse would only affect contralateral processes, as the pulse effect could have been carried to left PPC (Ilmoniemi et al., 1997), possibly explaining we did not observe significant directional effects for saccades generated in the same time frame. Further work is therefore needed to dissociate the discrepancies that may depend on stimulation location and task timings. We also note that despite the current understanding of the neuronal processes important to vector inversion in saccade generation (Munoz & Everling, 2004; Schall, 2009), right hemispheric dominance has been described in studies of fronto-parietal attentional networks (Vossel et al., 2014).

Effects from TMS

It could be argued that a TMS pulse or cTBS could have an excitatory rather than inhibitory influence, given the excitatory effects that suprathrehold TMS has on the motor system (i.e., triggering an EMG response), or to variability in response across subjects (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013). It has also been suggested that homeostatic responses following one form of brain stimulation could reverse the effects of others (Müller-Dahlhaus & Ziemann, 2015). It has been shown that inhibitory 1Hz repetitive TMS can have excitatory effects when following inhibitory (cathodal) transcranial direct current stimulation (Siebner et al., 2004). However, previous studies in the oculomotor system have found that cTBS to right FEF or right DLPFC impaired behavior (Cameron et al., 2015; Jaun-Frutiger et al., 2013; Liu et al., 2011), and that a TMS pulse to the right PPC region (or to right FEF or right DLPFC) at similar thresholds (110 -130 % resting motor threshold) perturbed saccade programming (Müri, Hess, & Meienberg, 1991; Nagel et al., 2008; Nyffeler et al., 2007; Nyffeler, Cazzoli, et

al., 2008; Nyffeler, Hartmann, et al., 2008; Olk, Chang, Kingstone, & Ro, 2006; Terao et al., 1998). Further, it has not been demonstrated that TMS can directly trigger saccades, though it can facilitate triggering by disrupting a process that might otherwise delay triggering (Müri & Nyffeler, 2011). Thus there is strong evidence that both the cTBS and single pulse TMS can be taken as being disruptive to saccade behaviors in the present study.

Finally, it is possible that any inhibitory cTBS effects on reaction times or performance (correct directions), as expected from other studies, could have been altered or washed out in the present study because of the fact that PPC pulses were also applied to the network. Nevertheless, cTBS to right FEF and to right DLPFC was effective at impairing behavior in terms of the spatial components for anti-saccades compared to pro-saccades, or for leftwards saccades compared to rightwards saccades. It is also possible that the task was not sensitive to the influence of cTBS in terms of reaction times or performance (correct directions), as our previous study found directional impairments in a more complicated task (albeit with cTBS over left DLPFC (Cameron et al., 2015)). Of course, TMS lesions may not be universally disruptive to all task components (Hartwigsen et al., 2016), as shown here by the differential impairments to anti-saccade and pro-saccade behaviors or to the contralateral versus ipsilateral direction, and how we found that a TMS pulse can facilitate performance on some tasks (i.e., anti-saccades) but disrupting a competing process.

Conclusions

Our findings for a lack of additive effects from two TMS lesions to critical cortical oculomotor network nodes in anti-saccade programming, as well as some evidence for compensation for ipsilateral anti-saccades after DLPFC cTBS, suggest that saccade behaviors are governed by distributed computations, rather than by individual nodal contributions. This has

wide implications for our understanding of the computations performed in fronto-parietal networks important to top-down attentional control. Finally, these findings open the way to evaluate distributed processing in other networks, whereby individual lesions may be sufficient to produce impairments, or, alternatively, where compensatory nodal contributions may be present.

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