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The effects of a TMS double perturbation to a cortical network

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Abstract

Transcranial magnetic stimulation (TMS) is often used to understand the function of individual brain regions, but this ignores the fact that TMS may affect network-level rather than nodal-level processes. We examine the effects of a double perturbation to two frontoparietal network nodes, as compared to the effects of single lesions to either node. We hypothesized that Bayesian evidence for the absence of effects that build upon one another indicates that a single perturbation is consequential to network-level processes. Twenty-three humans performed pro- (look towards) and anti- (look away) saccades after receiving continuous theta-burst stimulation (cTBS) to right frontal eye fields (FEF), dorsolateral prefrontal cortex (DLPFC) or somatosensory cortex (S1) (the control region). On a subset of trials, a TMS pulse was applied to right posterior parietal cortex (PPC). FEF, DLPFC and PPC are important frontoparietal network nodes for generating anti-saccades. Bayesian T-tests were used to test hypotheses for enhanced double perturbation effects (cTBS plus TMS pulse) on saccade behaviors, against the alternative hypothesis that double perturbation effects to a network are not greater than single perturbation effects. In one case, we observed strong evidence (BF_{10} = 325) that PPC TMS following DLPFC cTBS enhanced impairments in ipsilateral anti-saccade amplitudes over DLPFC cTBS alone, and not over the effect of the PPC pulse alone (BF_{10} = 0.75), suggesting double perturbation effects do not augment one another. Rather, this suggests that computations are distributed across the network, and in some cases there can be compensation for cTBS perturbations.

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

Significance Statement

We explore whether a frontoparietal network important to executive control, attentional processing, and saccadic gaze behaviors operates in a distributed fashion, as compared to what would be predicted from combining contributions from individual brain regions. This is important as lesions or perturbations to these regions individually can produce behavioral deficits. We apply inhibitory Transcranial Magnetic Stimulation (TMS) to a frontal cortical region, followed by a second TMS perturbation to a parietal region. The point is that this second perturbation could, in principle, build upon the effects of the first perturbation. We tested different hypotheses regarding the effects of such double perturbations, and conclude that the effects do not build upon one another, suggesting a single perturbation affects a network-level process.

Introduction

It is well known that effects of transcranial magnetic stimulation (TMS) extend beyond the site of stimulation (Ilmoniemi et al., 1997; Paus et al., 1997; Ruff et al., 2006; Ko et al., 2008; Morishima et al., 2009). In some instances, distal effects may reflect compensatory responses to the TMS perturbation (Sack et al., 2005; O'Shea et al., 2007; Hartwigsen et al., 2013), suggesting "homeostatic metaplasticity" (Müller-Dahlhaus and Ziemann, 2015) at the level of network nodes. Here we assess another functionally relevant possibility: whether behavioral consequences of a spatially-localized perturbation from TMS are driven by the distributed nature of computations throughout a circuit (Price and Friston, 2002). This would have consequences as to whether nodal effects build-upon one another.

The saccadic eye-movement system provides a tractable testing ground for assessing circuit-level consequences of TMS (Leigh and Kennard, 2004; Munoz et al., 2007). Roles of three cortical nodes, frontal eye fields (FEF), dorsolateral prefrontal cortex (DLPFC), and posterior parietal cortex (PPC) have been well-described (Munoz and Everling, 2004; Johnston and Everling, 2011; Paré and Dorris, 2011). In the anti-saccade task (where subjects must look away from a peripheral visual stimulus (Hallett, 1978)) DLPFC is thought to be critical to establishing the appropriate task set and preventing an automatic saccade to the stimulus; FEF is thought to be critical to voluntary saccade programming, and to "preparatory set"; and FEF, along with PPC are thought to be critical to the visuo-motor transformations to develop a saccade "vector" (Connolly et al., 2002; Leigh and Kennard, 2004; Munoz and Everling, 2004).

Evidence shows how DLPFC, FEF and PPC interact as part of a distributed system: TMS to *either* DLPFC, FEF (or supplementary eye fields) during saccade programming prolonged reaction times, suggesting "preparatory set" is distributed between all three nodes (Nagel et al.,

100 2008). Magnetoencephalography (MEG) and fMRI showed that FEF and PPC are both involved
101 in the attentional aspects of the anti-saccade "vector" (Medendorp et al., 2005; Moon et al.,
102 2007), and TMS to FEF or PPC produces hypometric anti-saccades (Nyffeler et al., 2008b; Jaun-
103 Frutiger et al., 2013; Cameron et al., 2015). However, it is not possible to distinguish a difference
104 in timing (even with MEG) between when an anti-saccade program is developed in the PPC
105 compared to FEF (Moon et al., 2007), implying a distributed process.

106 We build on this knowledge to study the effects on behavior after a "double perturbation"
107 to this network in the right hemisphere. Shortly after applying cTBS (Huang et al., 2005) to
108 either right FEF or DLPFC, we measure the consequences of a second time-resolved perturbation
109 to the circuit, in the form of a single TMS pulse to right PPC. This approach arbitrates between
110 five hypotheses regarding consequences of the double perturbation. In hypothesis A –
111 "*Augmented*", the double perturbation could produce an augmented effect by concurrently
112 impairing spatially separate nodes that provide critical, but computationally distinct functions,
113 resulting in behavioral perturbations that are greater than the effect of either perturbation alone
114 (Figure 1A). Alternatively, hypothesis B – "*Distributed"* pertains to the case where computations
115 are performed by a distributed system at the network-level, so a single perturbation to either node
116 should perturb behavior as much as the double perturbation (Price et al., 2017) (Figure 1B). In
117 hypothesis C – "*Compensatory*" - distal nodes could compensate for the perturbation, which
118 would predict greater effects from the double perturbation compared to the cTBS perturbation
119 alone (Figure 1C), because the second perturbation impairs a region that has become more
120 important functionally, *because* of the first (cTBS) perturbation. In hypothesis D – "*Spreading*"
121 the effects from cTBS spread trans-synaptically to other portions of the network (Ko et al.,
122 2008), predicting greater effects from the double perturbation than to the single pulse

perturbation alone (Figure 1D). Finally, in "*Boosting",* additional regions throughout the network could provide homeostatic compensation, which would manifest as a perplexing boost to performance following cTBS (alone), and which could reduce or prevent the impairment from additional TMS perturbations (Figure 1E). (The difference between this and the Compensatory hypothesis, is that there is the perplexing boost to performance after cTBS).

To discriminate between those hypotheses, we used functional magnetic resonance imagining (fMRI) to localize right DLPFC, FEF and PPC in individual subjects performing an anti-saccade task. These regions were then used for targeting subject-specific TMS interventions while participants performed the same task outside the scanner. Performance (percentage correct direction), reaction times, and saccade amplitudes were assessed using Bayesian t-tests to provide statistical evidence in favor or against greater effects from double- compared to single-TMS perturbations.

Materials 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 4 sessions approximately 1 week apart. 3 subjects were excluded for failure to provide useable eye-tracking data on all TMS sessions, and one subject had error rates on anti-saccade trials exceeding 90% (greater than 3 times the standard deviation), so was excluded resulting in a sample size of 24 participants (mean ± SE, age 23 ± 2 years, 11 male).

Detailed procedure

Session 1

Participants were screened for contraindications related to fMRI, and to single-pulse TMS and cTBS according to common safety guidelines (Rossi et al., 2009; Oberman et al., 2011). Resting and active motor thresholds were established for the first dorsal interosseous (FDI) muscle of the subject's right-hand using electromyography (EMG). 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).

Subjects performed 5 runs of an interleaved pro-(look towards)/anti-(look away) saccade task to identify the cortical regions of interest (Figure 2B). An interleaved task was utilized as evidence suggests an important role for DLPFC (Everling and DeSouza, 2005; Johnston et al.,

2014) as well as for FEF (DeSouza and Everling, 2010) in task or "preparatory set" and thus could not simply default to an anti-saccade task set on each trial. Two target positions (13º or 9º) in the left and right direction were included so that subjects would have to rely on spatial information to calculate the saccade vector. In this way, we could be sure that the paradigm required DLPFC, FEF and PPC processes.

Detailed fMRI procedure

Functional MRI scans 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) = 2300 ms, 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.

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). Table 1 provides the Montreal Neurological Institute (MNI) coordinates of these ROIs, and their distances to the scalp as derived from Localite TMS Navigation software 2.2 (Localite, Germany). Figure 2A illustrates the coordinates on a canonical T1 scan. Right DLPFC (r-DLPFC) was defined as peak fMRI anti-saccade activity surrounding the middle frontal gyrus, anterior to the ventricles. Right FEF was defined as peak activity in the precentral sulcus (selecting medial peaks if lateral peaks were also present, to relate more to anti-saccade processes (Neggers et al., 2012)). Right PPC was defined as peak activity in the intraparietal sulcus, selecting peaks in more medial clusters if more than one was present. Finally, right S1 (the control region) was localized anatomically for each participant, as the most superior extent of the postcentral gyrus, located on average 9 ± 2 mm lateral to the longitudinal fissure to avoid lateral proprioceptive eye-position signals (Zhang et al., 2008; Balslev et al., 2011) (Table 1, Figure 2A).

Session 2-4

cTBS was applied to r-DLPFC, r-FEF or r-S1 prior to performing the task on three separate sessions, counterbalanced for order. cTBS was applied to FEF or to DLPFC because we wished to assess double perturbation effects across two nodes which are both linked to PPC, but where one (FEF) is thought to have a more direct link in visuo-motor processes (Leigh and Kennard, 2004; Munoz and Everling, 2004) and in network interactions described in the resting

state (Corbetta et al., 2005; He et al., 2007; Vossel et al., 2014). cTBS was delivered with a posterior-anterior direction of the electric field induced in the brain, with the handle pointed backwards at approximately 30˚ to the sagittal plane. In this way the outer windings of the TMS coil did not overlap the other ROIs. TMS coil alignment was achieved using Localite and a subject-specific anatomical scan.

The parameters for cTBS were identical to those described by Huang and colleagues (2005) consisting of 50 Hz triplets repeated at 5 Hz over a period of 40 s (Huang et al., 2005). Stimulation intensity for cTBS was defined as 80% of the active motor threshold (AMT: mean = 41% ± 9 % maximum stimulator output), 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: mean = 43% ± 8 % maximum stimulator output), defined as peak-to-peak MEP amplitudes of 50 μV on 5 of 10 trials. 40 s of cTBS (at 80% of active motor threshold) has effects lasting approximately 50 minutes (Wischnewski and Schutter, 2015), providing sufficient time to test the influence of the PPC pulse.

Eye Tracking and Task

The position of the right eye was recorded using an infrared Eyelink 1000 eye tracker (SR Research, Ottawa, Canada) with a 1000 Hz sampling rate. A 9- point calibration was carried out and a drift correction point was used as the inter-trial fixation point. Saccades were identified by a horizontal deflection (3 X standard deviations 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).

228 Subjects performed the same task (Figure 2B) as in the fMRI. Representative eye-traces
229 from a single subject is shown in Figure 2C. In each run, there were 72 trials, of which 48
230 contained a TMS pulse presented to PPC at a random interval between 30 and 300 ms after onset
231 of the peripheral stimulus (described in Data Analysis). The first run commenced 10 minutes
232 after cTBS, and was analyzed up to 50 minutes after cTBS to capture the same cTBS effects on
233 each session. Subjects were asked to perform 5 runs, each taking approximately 8 minutes
234 including drift corrections and breaks, meaning that for each condition of interest (task,
235 direction) there were 30 trials without the single pulse ("*pulse absent*"), and 60 trials containing
236 the single pulse.

237 ***Data analysis***

238 Data was analyzed in MATLAB v11 (The MathWorks Inc., Natick, MA). Valid trials
239 consisting of correct and incorrect directions were separated from invalid trials, consisting of
240 saccade reaction times (SRTs) < 90 ms (anticipatory errors), slower than 1000 ms, and trials
241 where the TMS pulse to PPC occurred after saccade onset. Three behavioral parameters of
242 interest were analyzed: amplitude of the primary saccade, percentage correct direction, and
243 saccade reaction time (SRT).

244 We first set a division between an "Early" and "Late" pulse time bin as follows: using the
245 pulse absent trials, we collected the SRTs across subjects for correctly performed anti-saccades,
246 and for direction errors on anti-saccades for each cTBS session separately, and plotted these data
247 in 10 ms bin histograms (Figure 3). A binomial test revealed the first bin (black arrows, Figure 3)
248 where the two trial types were no longer significantly different than chance (50 %); these bins
249 occurred at 150 ms for the S1 cTBS and DLPFC cTBS sessions, and at 160 ms for the FEF-
250 cTBS session. This method approximates the division between visually triggered "express" pro-

saccades, and voluntary saccades (Munoz and Everling, 2004), and is important to approximate when the PPC pulse would have greater influences during visual processing rather than motor programming components of an anti-saccade, which are in different directions.

We performed a repeated measures ANOVA in SPSS (IBM Corporation) using pulse absent trials to determine if there were significant interactions between the site of cTBS and stimulus eccentricity for amplitudes. However, no interactions with cTBS Site and Eccentricity were significant, $F(2,44) < 1.75$, $P > 0.19$, so we collapsed across eccentricity. Next, we performed a multivariate repeated measures ANOVA using pulse absent trials, split into the first and second half of testing time, to examine if there were any significant interactions involving Half and cTBS Site across the 3 parameters of interest (a potential concern being that cTBS effects wore off): however no interactions with cTBS Site and Half reached significance, *Pillai's Trace values* < 0.19, $F(6,86) < 1.54$, $P > 0.18$.

Statistics

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) (Figures 4-7, brackets). A Bayes Factor (BF_{10}) indicates the evidence for the alternative hypothesis relative to the null hypothesis given the data. Our tests were focused first on situations where the "double perturbation" produces impairments that were greater than the single perturbations; thus, the Bayes Factor (BF_{10}) here indicates whether the *combined effects* were greater than the individual effects from cTBS alone, or from PPC TMS alone). For amplitude and percent correct, lower values are indicative of greater impairments: therefore, the alternative hypothesis for BF_{10} is that the difference of the combined effect minus the single perturbation effect was less than 0, and the null hypothesis would be that this difference is not

less than zero. For reaction times, higher values are indicative of an impairment (slower latency), so the alternative hypothesis is that the combined effect minus the single perturbation effect is greater than zero (and the null hypothesis is that it is not greater than zero). Note, however, that strong evidence from these tests for the null hypothesis (not less than zero) could be driven by a difference in the opposite direction. When such "strong" evidence was found ($BF_{10} < 0.1$) (Jeffreys, 1961; Wetzels et al., 2011), we subsequently performed tests in the opposite direction to determine if the effect of the single perturbation was greater than that of the double perturbation.

We report evidence for behavioral impairments that meet or exceed "*substantial*" ($BF_{10} > 3$) (Jeffreys, 1961; Wetzels et al., 2011). Between 0.33 and 3, the evidence is considered only "*anecdotal*", and in relation to P-values, it was shown that approximately 70% of "positive" results from 855 tests falling in the interval between $P < 0.01$ to $P < 0.05$ corresponded to only "anecdotal" evidence (Wetzels et al., 2011). Therefore, our boundary criteria of "substantial" is conservative in relation to typical P-values.

Tests for each individual trial type 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 perturbations themselves caused impairments. Here, the BF_{10} indicates the relative likelihood that cTBS or single pulse TMS impaired behavior compared to the null hypothesis that the behaviors were not impaired relative to the control condition. The values for these tests are listed in Tables 3-6, and are illustrated as asterisks in Figure 4-7 when substantial.

Table 2 (Statistics Table) lists all BF values from the Bayesian t-tests along with their corresponding effect sizes as the medians of the posterior distributions, with 95% confidence intervals.

Results

FEF vs control cTBS conditions: anti-saccades

Saccade amplitude

There was substantial evidence that FEF cTBS caused impairments in leftward anti-saccade amplitudes for conditions also involving PPC pulses, and for rightwards anti-saccades for conditions involving the late PPC pulse (Table 3A, $BF_{10} > 3$). There was not substantial evidence that the PPC pulse *on its own* produced an impairment, and there was also *not* substantial evidence (Figure 4A, brackets, all $BF_{10} \leq 2.91$) to indicate greater impairments from the double perturbation condition compared to either single perturbation condition.

Percentage correct direction

There was not substantial evidence that anti-saccades were impaired by either form of TMS; in fact, *strong* evidence towards the null hypothesis was found for conditions with the PPC pulse (Table 3B, $BF_{10} < 0.1$). (Bayesian t-tests performed in the opposite direction revealed substantial or greater evidence ($BF_{10} > 3$) for a performance *benefit* from the PPC pulses). Similarly, there was strong evidence that there were *not* greater impairments from the double perturbation compared to either single perturbation (Figure 4B).

Saccade Reaction Times (SRT)

For SRT, "*decisive"* (Wetzels et al., 2011) evidence for impairments were observed for conditions with the late PPC pulse alone, but not for those following FEF cTBS (Table 3C). Strong evidence was found that FEF cTBS plus a late PPC pulse did result in greater impairments relative to FEF cTBS alone (and substantial evidence was found for a greater impairment for the early PPC pulse for leftwards anti-saccades) (Figure 4C). However, strong

evidence was found that impairments for leftwards anti-saccades were *not* greater when the late PPC pulse followed FEF cTBS compared to when it was alone (Figure 4C, BF = 0.08, italicized): when tested in the reverse direction, there was substantial evidence that the impairment after the late PPC pulse *alone* was greater than after FEF cTBS, $BF_{10} = 4.12$.

DLPFC vs control cTBS conditions: anti-saccades

Saccade amplitude

There was substantial evidence for impairments to anti-saccades after DLPFC cTBS in conditions involving the late PPC pulse, and for DLPFC cTBS alone for leftward anti-saccades (Table 4A). Strong evidence was found for a *greater* impairment from the combined perturbation effects for rightward anti-saccades after the late pulse relative to the DLPFC cTBS alone ($BF_{10} = 325.22$), but this was not found compared to the effects of the late PPC pulse alone ($BF_{10} = 0.75$) (Figure 5A).

Percentage correct direction

There was no evidence that anti-saccades were impaired by DLPFC cTBS, with, or without, the PPC pulse (Table 4B). (Bayesian t-tests revealed strong evidence for anti-saccade *benefits* to performance following DLPFC cTBS and late PPC pulses). There was also no evidence for greater impairment from a double compared to single perturbation (Figure 5B).

Saccade Reaction Times (SRT)

There was strong evidence for impaired reaction times at the late pulse time following DLPFC cTBS for right anti-saccades (Table 4C), and there was strong evidence that the combined effects of DLPFC cTBS and a late PPC pulse resulted in greater impairments relative

to DLPFC cTBS alone (Figure 5C), but there was no evidence for greater impairment in comparison to the PPC pulse.

FEF vs control cTBS conditions: pro-saccades

Saccade amplitude

Table 5A and Figure 6A show that there was not substantial evidence for effects of either TMS condition on pro-saccade amplitudes.

Percentage correct direction

Substantial impairments were found for rightwards pro-saccades following FEF cTBS during trials with the addition of a late PPC pulse (Table 5B; $BF_{10} = 4.53$). There was also substantial evidence that the impairments to leftwards pro-saccades were greater following FEF cTBS when there was a late PPC pulse (Figure 6B; $BF_{10} = 3.74$) compared to FEF cTBS alone. There was not substantial evidence for other impairments.

Saccade Reaction Times (SRT)

Substantial or greater evidence for pro-saccade reaction time impairments was observed for all PPC pulse conditions (Table 5C). There was also strong evidence that the combined effects of FEF cTBS and PPC pulses resulted in greater impairments relative to FEF cTBS alone (Figure 6C), however, there was not evidence for a greater impairment over the PPC pulse effects alone.

DLPFC vs control cTBS conditions: pro-saccades

Saccade amplitude

There was not substantial evidence for any effects to pro-saccade amplitudes (Table 6A, Figure 7A).

Percentage correct direction

There was substantial evidence that the impairments to rightwards pro-saccades were greater following DLPFC cTBS when the late PPC pulse was present (Figure 7B; $BF_{10} = 3.60$), but no other evidence for impairments was substantial (Table 6B).

Saccade Reaction Times (SRT)

There was decisive evidence for reaction time impairments at the late PPC pulse time following DLPFC cTBS, and substantial evidence for impairments at the early PPC pulse time for left-ward anti-saccades (Table 6C). Also, there was substantial evidence that the combined effects of DLPFC cTBS and PPC pulses resulted in greater impairments relative to DLPFC cTBS alone (Figure 7C).

Discussion

We found Bayesian evidence for impaired FEF and DLPFC anti-saccade amplitudes following a cTBS perturbation, and that compensation by PPC was possible after DLPFC cTBS perturbed ipsilateral anti-saccades. There was not evidence that cTBS impaired anti-saccade reaction times or correct directions, and we note that the impairments to anti-saccade amplitudes were not found in every condition following cTBS alone. Interestingly however, we did not find any Bayesian evidence for an "augmented" effect, whereby the two TMS perturbations built upon one another, suggesting instead the effects are generated at the network rather than nodal/regional level only.

Performance of pro- and anti-saccades involves cortical and sub-cortical regions including FEF, PPC, DLPFC, supplementary eye fields (SEF), anterior cingulate cortex, visual cortex, basal ganglia, cerebellum, superior colliculus, and brainstem reticular formation (Moschovakis et al., 1996; Munoz and Everling, 2004; Munoz and Schall, 2004; Everling and DeSouza, 2005; Ford et al., 2005; Medendorp et al., 2006; Schall, 2009). A frontoparietal, precuneus, and parietal-medio-temporal network have also been identified as being involved in anti-saccade generation by independent company analysis (ICA)-based fMRI, in addition to an eye-field network involved in both pro- and anti-saccades (Domagalik et al., 2012). This highlights the wide-ranging involvement of several brain networks with the implication that one may not always observe deficits after a TMS perturbation or lesion, given the potential for redundancy or "degeneracy" (Price and Friston, 2002). Nevertheless, key neurophysiological processes related to voluntary saccade programming, reflexive saccade inhibition, and attentional re-orienting processes point to important nodal roles for FEF, PCC, and DLPFC, explaining why deficits *can* result from single lesions or perturbations.

The Frontal Eye Fields

In FEF, "saccade" and "fixation" neurons could provide two substrates for saccade programming and saccade inhibition. First, some of the "saccade" neurons code for the motor goal of saccades, while others process visual and visuomotor information (Bruce and Goldberg, 1985; Schlag-Rey et al., 1992; Schall, 2002; Sato and Schall, 2003; Schall et al., 2011). Reversible FEF lesions by cooling probe in monkeys were shown to produce hypometria (Keating and Gooley, 1988; Peel et al., 2014), and patients with FEF lesions have shown reduced contralateral saccade amplitudes (Rivaud et al., 1994; Ploner et al., 1999), though not always (Terao et al., 2016). Second, FEF saccade neurons show decreased activity during the

preparatory phase of anti- compared to pro-saccade trials, (Everling and Munoz, 2000). FEF "fixation" neurons, on the other hand, show increased activity during fixation (even in the absence of a stimulus) (Hanes et al., 1998; Izawa et al., 2009), implying that they are substrates for stopping reflexive saccades (Munoz and Everling, 2004; Boucher et al., 2007; Schall and Godlove, 2012). Indeed, some patients with lesions encompassing FEF have shown difficulty in suppressing reflexive saccades (Guitton et al., 1985; Van der Stigchel et al., 2012; Terao et al., 2016), and increased voluntary saccade latencies (Terao et al., 2016). However, one patient with a highly circumscribed left FEF lesion showed no deficits in inhibiting reflexive saccades, but did have hypometria (Gaymard et al., 1999). Together this shows that FEF is important to voluntary saccade programming, but task, or lesion, specifics may dictate whether its role is critical given the potential for the contributions from other network regions with neuronal populations that can carry similar information. Evidence shows, for instance, that deficits following an FEF lesion become more severe if the superior colliculus is also lesioned (Schiller et al., 1979; Keating and Gooley, 1988).

TMS perturbations to FEF have largely produced similar effects. Like lesions, TMS perturbations lack the specificity to affect saccade neurons uniquely from fixation neurons, meaning that caution should be taken in attempts to interpret the effects on particular neuronal populations. A single TMS pulse to FEF increased the latency for ipsilateral anti-saccade trials, but did not increase pro-saccade errors (Müri et al., 1991; Olk et al., 2006). However, in another study, a single TMS pulse to FEF at 100 ms post stimulus-onset, increased anti-saccade latency *and* increased the frequency of contralateral pro-saccade errors (Terao et al., 1998). (This distinction may be due to the fact that single pulses during anti-saccade generation would perturb an ongoing process whereby anti-saccade processes are in competition with more automatic pro-

433 saccade signals, an effect that can explain our findings regarding pro- and anti-saccade reaction
434 times). Another study showed both latency increases in pro- as well as anti-saccade trials,
435 particularly late during preparation (at 200 ms) (Nagel et al., 2008). In a few studies, cTBS to
436 FEF was shown to increase reaction times (Nyffeler et al., 2006a, 2006b; Liu et al., 2011), but in
437 other cases cTBS was reported to affect saccade amplitudes instead (Jaun-Frutiger et al., 2013;
438 Cameron et al., 2015).

439 ***The Posterior Parietal Cortex***

440 In monkeys, the generation of anti-saccades recruits lateral intraparietal area (LIP)
441 neurons (the region of the primate PPC mostly associated with attention and eye movements)
442 (Gottlieb and Goldberg, 1999; Zhang and Barash, 2000; Bisley and Goldberg, 2010). LIP has
443 been described as a "priority" map for attentional orienting, either overtly (a gaze change) or
444 covertly (Bisley and Goldberg, 2010), integrating bottom-up visual information with top-down
445 goal-directed information. Some LIP neurons signaling a visual stimulus then show activity
446 during the motor component of vector inversion, which could be representing a remapped visual
447 response (Zhang and Barash, 2000). In humans, PPC bilaterally (along with FEF) is shown to
448 signal the vector inversion process (Medendorp et al., 2005; Moon et al., 2007; Collins et al.,
449 2008). Patients with lesions to PPC have demonstrated saccade hypometria (Duhamel et al.,
450 1992; Ptak and Müri, 2013), and those exhibiting neglect lesions often display erroneous
451 saccades to ipsilesional "distractor" stimuli (Ptak and Müri, 2013), or deficits in remapping a
452 saccade goal if the target changes position (Duhamel et al., 1992). Some patients display longer
453 latencies on reaction times for reflexive, visually guided saccades (Pierrot-Deseilligny et al.,
454 1991; Terao et al., 2016), fitting with evidence that the PPC may have a role in triggering
455 "express" saccades (Hamm et al., 2010; Chen et al., 2013). Altogether, this highlights and

456 important role of PPC in the *visuo*-motor aspects of saccade generation. Disruptive effects from
457 TMS on these visuo-motor aspects is also consistent with these observations: a TMS pulse to
458 PPC shortly after stimulus onset (100 ms) produces hypometric anti-saccades to the ipsilateral
459 (to TMS) direction, which then reverses to affect the motor vector in the opposite direction when
460 applied later (>333 ms) (Nyffeler et al., 2008b). Contralateral neglect is also reported from cTBS
461 to right PPC (Nyffeler et al., 2008a).

462 ***The Dorsolateral Prefrontal Cortex***

463 DLPFC is well known to be involved in cognitive control (Gazzaley and D'Esposito,
464 2007), and is therefore highly likely to be an important region in a network controlling voluntary
465 saccades. Human and monkey studies have indeed found "preparatory" signals during pro- or
466 anti- instruction periods in DLPFC (Everling and Munoz, 2000; Connolly et al., 2002; DeSouza
467 et al., 2003; Everling and DeSouza, 2005; Ford et al., 2005; Brown et al., 2007), and SC neurons
468 have been demonstrated to receive task-related signals from DLPFC (Johnston and Everling,
469 2006). There are also spatial signals in some DLPFC neurons, particularly important in visual
470 working memory: DLPFC neurons were shown to have receptive/response fields with a
471 contralateral bias (across the population) in working memory task delay-periods (Funahashi et
472 al., 1989; Ikkai and Curtis, 2011), which is not surprising if it shares information with FEF and
473 PPC. Indeed, findings from human neuroimaging suggest DLPFC is connected to FEF as well as
474 PPC functionally as well as anatomically (de Schotten et al., 2011; Vossel et al., 2014), and one
475 physiological study that recorded all three regions simultaneously in a sensorimotor decision task
476 showed sensory information "flows" from early visual regions, to LIP, FEF and DLPFC, and
477 task-related signals flows from DLPFC and LIP to FEF (Siegel et al., 2015).

Patients with DLPFC lesions exhibit increased pro-saccade errors on anti-saccade trials (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Ploner et al., 2005), suggesting it has a direct role in suppression. However it has been difficult to dissociate a suppression role specifically of DLPFC from a role in task set establishment (Johnston and Everling, 2006; Johnston et al., 2009), as reflexive saccade errors following a DLPFC lesion could be explained by disruption to anti-saccade task-set signals to overcome the pro-saccade bias. A TMS pulse to DLPFC during the preparatory phase in an anti-saccade task did result in increased pro-saccade errors (Nyffeler et al., 2007), and "intermittent" TBS (thought to have excitatory effects) (Huang et al., 2005) over DLPFC produced a reduction in pro-saccade errors (in patients with bipolar disorder) (Beynel et al., 2014). In another study however, a TMS pulse to DLPFC at the end of the preparatory period increased anti-saccade as well as pro-saccade latency, but not direction errors (Nagel et al., 2008).

TMS to DLPFC has also been shown to affect endpoint accuracy in memory-saccades (Brandt et al., 1998), and DLPFC lesions resulted in higher variability in memory-guided saccade endpoints, with non-significant reductions in amplitudes (Pierrot-Deseilligny et al., 2003), and a single pulse TMS study did find that DLPFC pulses disrupted contralateral saccade amplitudes during the target memory component of a delayed saccade task (Müri et al., 1996). However, it has also been concluded in one lesion study that DLPFC was not necessary for performing the spatial calculations in a memory-guided saccade task (Mackey et al., 2016), and a study employing cTBS to DLPFC did not find amplitude deficits to either ipsilateral or contralateral anti-saccades (Cameron et al., 2015).

Implications from the double perturbation

As outlined above, individual lesion or TMS studies have indicated that FEF, PPC and DLPFC are important to pro and anti-saccade tasks. However, there is a high level of variability across studies in the types of behavioral deficits one observes. This may be the result of relative unfocused effects of a TMS perturbation, or lesion, on the underlying populations, and/or network-level effects that extend beyond the role of an individual node. This implies that caution should be taken in assuming that any one TMS (or lesion) study can definitively define the role of an oculomotor region. In this study, we focus on the effects of a double compared to single perturbation in a single paradigm and environment, acknowledging that the specifics of the paradigm may make direct comparisons to other studies difficult.

FEF vs control cTBS conditions: anti-saccades

We did not find evidence to suggest an augmented impairment effect (Hypothesis A) from the double perturbation across any of the saccade behaviors. Substantial evidence did suggest impairments to anti-saccade amplitude in FEF cTBS conditions when PPC pulses were present; however, because there was not substantial evidence that PPC pulses on their own caused impairments, nor were the effects greater following the double perturbation relative to following FEF cTBS alone, we conclude that cTBS to FEF on its own was consequential to anti-saccade amplitudes. We suggest FEF cTBS had a "distributed" effect on processing in the network (Hypothesis B).

For saccade reaction times, we found evidence for greater impairments from the double perturbation compared to FEF cTBS on its own. The observation that a second perturbation produces a deficit that is not otherwise observed unless the first node is perturbed, is the argument to indicate compensation by that second node (Sack et al., 2005). We do not however

believe our findings here indicate compensation by PPC (the second node), because the combined FEF cTBS plus PPC pulse conditions did not actually reveal substantial evidence for impairing behavior (see Table 3B). In fact, the late PPC pulses on their own produced impairments that were *greater* than the double perturbation for contralateral anti-saccades (Hypothesis E). We conclude therefore that later PPC pulses were disruptive to the motor component of the anti-saccade. Following FEF cTBS however, a compensatory mechanism might be revealed by other network structures which aid in anti-saccade generation. One possibility is that after FEF cTBS, there is compensation by DLPFC-colliculus projections to contralateral SC saccade neurons (Everling and Johnston, 2013), reducing the disruptive effect from a PPC pulse on the same network structures. This is sensible, considering the PPC pulses also produced substantial anti-saccade performance benefits in percentage correct directions, and human EEG evidence has shown that the posterior parietal/occipital cortex is involved in triggering "express" pro-saccades (Hamm et al., 2010), possibly by a cortical-SC mechanism (Watanabe et al., 2010; Chen et al., 2013). A PPC pulse could therefore disrupt the bias towards stimulus-driven saccades thus indirectly facilitating anti-saccade performance.

Altered SC function could contribute to both the behavioral deficits, as well as to compensatory effects in either visuomotor or executive control for the following reasons: it receives widespread projections from the retina, subcortical and cortical brain regions including FEF, PPC, and DLPFC, and thus, its activity is influenced by the afferent signals it receives; it has a spatial map for programming a saccade to a particular spatial location; it has the internal architecture for directly translating visual information into the motor commands which it also sends to the brainstem saccade generator circuits, and finally, it has "fixation" and "saccade"

544 neurons which could play a similar role in to those described in FEF (Munoz and Everling, 2004;
545 Munoz and Schall, 2004; Boucher et al., 2007; Watanabe and Munoz, 2011).

546 However, we acknowledge that these effects could be driven in part by the auditory/or
547 somatosensory influence of the pulse (Duecker and Sack, 2013; Duecker et al., 2013), which
548 could engage a startle-like reflex that inhibits ongoing motor commands, by acting also on the
549 SC or brain stem saccade generator circuits (Xu-Wilson et al., 2011) (perhaps with less of a
550 consequence in cases of compensation). As the goal of this study was to compare hypotheses
551 regarding the double vs single perturbations situations, the important comparisons are those
552 between the PPC pulses following control versus verum cTBS, which both have the same
553 auditory/somatosensory influences of the PPC pulse.

554 *DLPFC vs control cTBS conditions: anti-saccades*

555 We found strong evidence for "compensation" by PPC (Hypothesis C) following DLPFC
556 cTBS for ipsilateral (rightward) anti-saccade amplitudes, but not substantial evidence for an
557 augmented effect (Hypothesis A). Importantly, there was not substantial evidence that the PPC
558 pulses alone produced an impairment. This finding *is* consistent with a compensatory
559 mechanism, in that the second perturbation impairs a node which has assumed a greater
560 contribution (Sack et al., 2005; Hartwigsen et al., 2016). We note that these effects were
561 lateralized, as compensation was only seen in this ipsilateral direction. cTBS to DLPFC alone
562 produced impairments in the contralateral direction, suggesting that DLPFC perturbations were
563 more consequential for contralateral anti-saccades. The finding on its own is interesting as it
564 suggests DLPFC may be part of the vector inversion process previously emphasized to involve
565 FEF and PPC (Munoz and Everling, 2004; Medendorp et al., 2005; Moon et al., 2007). However,
566 the mixed findings from previous TMS and lesions studies lend support to a hypothesis that the

spatial calculations for anti-saccades are performed by a distributed process. We can only speculate that compensation occurs in some circumstances depending on the particular task demands, such as spatial working memory complexity.

As with FEF cTBS, there was no evidence that any of the conditions impaired percentage correct direction, but there was evidence for greater SRT impairments from the combined double perturbation compared to DLPFC cTBS alone. As addressed, the late PPC pulse impaired SRT on its own, suggesting the effects are more related to that of the PPC pulse.

FEF vs control cTBS conditions: pro-saccades

There was no evidence to suggest that TMS to FEF or PPC impaired pro-saccade amplitudes, suggesting that other regions in a wider network are sufficient for the spatial calculations for a pro-saccade (Munoz and Schall, 2004). There were findings to suggest that the late PPC pulses following FEF cTBS impaired pro-saccade correct directions and that PPC pulses substantially increased reaction times, suggesting a detrimental effect of the PPC pulse, possibly by impairing PPC-SC signals (as described previously). We acknowledge, however, that because we rejected trials when reaction time was less than the PPC pulse time, the outcome measures of the late PPC pulse are biased as coming from pro-saccade trials with a slower latency.

DLPFC vs control cTBS conditions: pro-saccades

As with FEF cTBS, DLPFC appears not to be critical to pro-saccade amplitudes. Interestingly, the late PPC pulse following DLPFC cTBS impaired rightward pro-saccade performance compared to DLPFC cTBS alone, but it is difficult to interpret this as compensatory as this condition did not actually produce substantial evidence for an impairment ($BF10 < 3$, Table 6).

Conclusions

Our findings for a general lack of augmented effects from two TMS perturbations to critical nodes in anti-saccade programming suggest that these saccade behaviors are governed by distributed computations. Yet if these regions are critical for behavior, how can we reconcile a lack of augmented effects from a double perturbation? Given evidence that anti-saccade vector inversion is developed simultaneously in FEF and PPC neuronal populations, our cTBS effects may be interpreted as being consequential for the communication of information between nodes (Sporns et al., 2007; Bullmore and Sporns, 2009) rather than for perturbing nodal computations only. FEF, DLPFC and PPC are part of interconnected frontoparietal networks which are recruited when attentional control is needed (Dosenbach et al., 2008; de Schotten et al., 2011; Ptak, 2012; Vossel et al., 2014; Tschentscher et al., 2017). FEF and DLPFC may be critical nodes in terms of network-level processes, behaving as "connector hubs" for long-range information flow (Sporns et al., 2007; Bullmore and Sporns, 2009). A cTBS perturbation to FEF, or DLPFC, may therefore be consequential for the communication of information. Neuronal oscillations, (not addressed in this study), nevertheless have been shown to be modulated in a cortical oculomotor network by TMS (Marshall et al., 2015), and could represent a "collective-order process" in network-level representations and interactions (Buzsáki, 2006 p.25). Taken together, this study illustrates how network interactions are important, over summated contributions of individual nodes.

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Figure Legends

Figure 1: Hypotheses for the effects of TMS perturbations to two oculomotor network nodes (e.g., F: frontal eye fields / D, dorsolateral prefrontal cortex; and P, posterior parietal cortex) in the same hemisphere. A) "Augmented": augmented impairment from a double perturbation compared to a single perturbation to either node. B) "Distributed": no augmented effects (a single perturbation to the network is equally disruptive). C) "Compensatory": compensatory effect from second node that became more important. D) "Spreading": greater effect due to cTBS spreading through the network to influence the second node. E) "Boosting": additional network regions (region 'X') provide sources of compensation after cTBS leading to a boost to performance.

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 an SPM single-subject anatomical template. Mean coordinates are shown as large 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 PPC (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.

Figure 3: Derivation of the Early and Late PPC pulse bins based on anti-saccade reaction times. Reaction time distributions were calculated for correct and direction error anti-saccades in PPC 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 PPC pulses.

Figure 4: Effects on left and right anti-saccades when the double perturbation involved FEF cTBS and PPC TMS is compared to the single perturbation conditions. All data is normalized to the cTBS control condition (cTBS to S1, no PPC pulses). Error bars represent standard error of the mean across subjects (N=23), and dark grey represents the double perturbation conditions. Values between brackets indicate the Bayes Factor evidence for the alternative hypothesis that the combined effects from the double perturbation resulted in a greater impairment (more negative values, note the Y axis is reversed for saccade reaction times) compared to the effects of the single perturbations. Values > 3 provide substantial evidence for the alternative hypothesis that the combined effects resulted in a greater impairment than the single perturbation effects. Asterisks show the results from Bayesian one-sample t-tests for evidence that the values are < 0 for amplitude and percent correct, or > 0 for reaction time, where $BF_{10} > 3$.

Figure 5: Effects on left and right anti-saccades when the double perturbation involving DLPFC cTBS and PPC TMS is compared to the single perturbation conditions. PPC pulse conditions relative to S1 cTBS are shown in duplication as in Figure 4, and conventions are as in Figure 4.

Figure 6: Effects on left and right pro-saccades when the double perturbation involving FEF cTBS and PPC TMS is compared to the single perturbation conditions. Conventions as in Figure 4.

Figure 7: Effects on left and right pro-saccades when the double perturbation involving DLPFC cTBS and PPC TMS is compared to the single perturbation conditions. Conventions as in Figure 4.

Table Legends

Table 1: Regions Of Interest (ROI) information (average ± standard deviations (mm)).

Table 2: Statistical Table.

Table 3: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right anti-saccade trials relative to control cTBS.

Table 4: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right anti-saccade trials relative to control cTBS. (The effect of the PPC pulse relative to control cTBS is shown in duplication as in Table 3).

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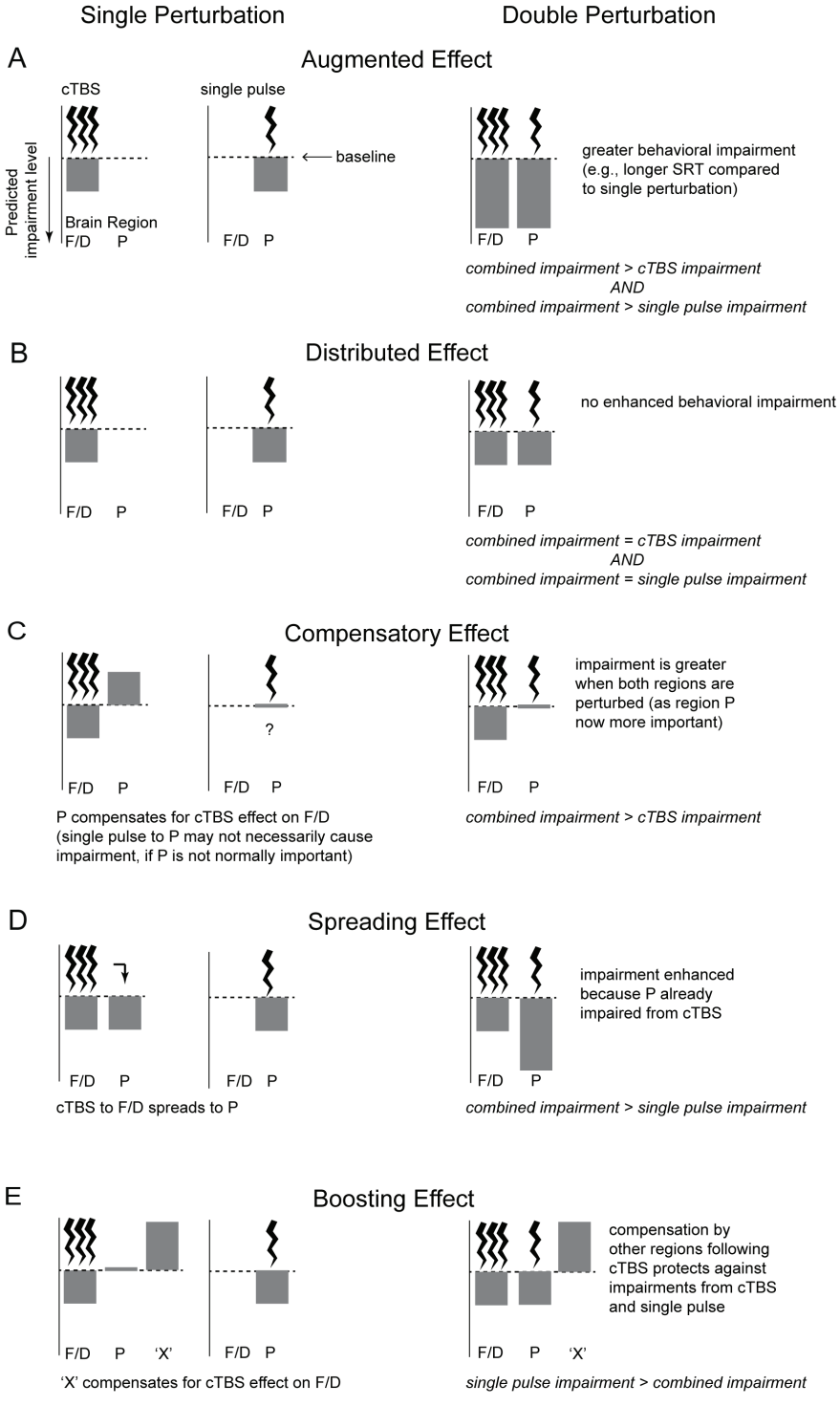
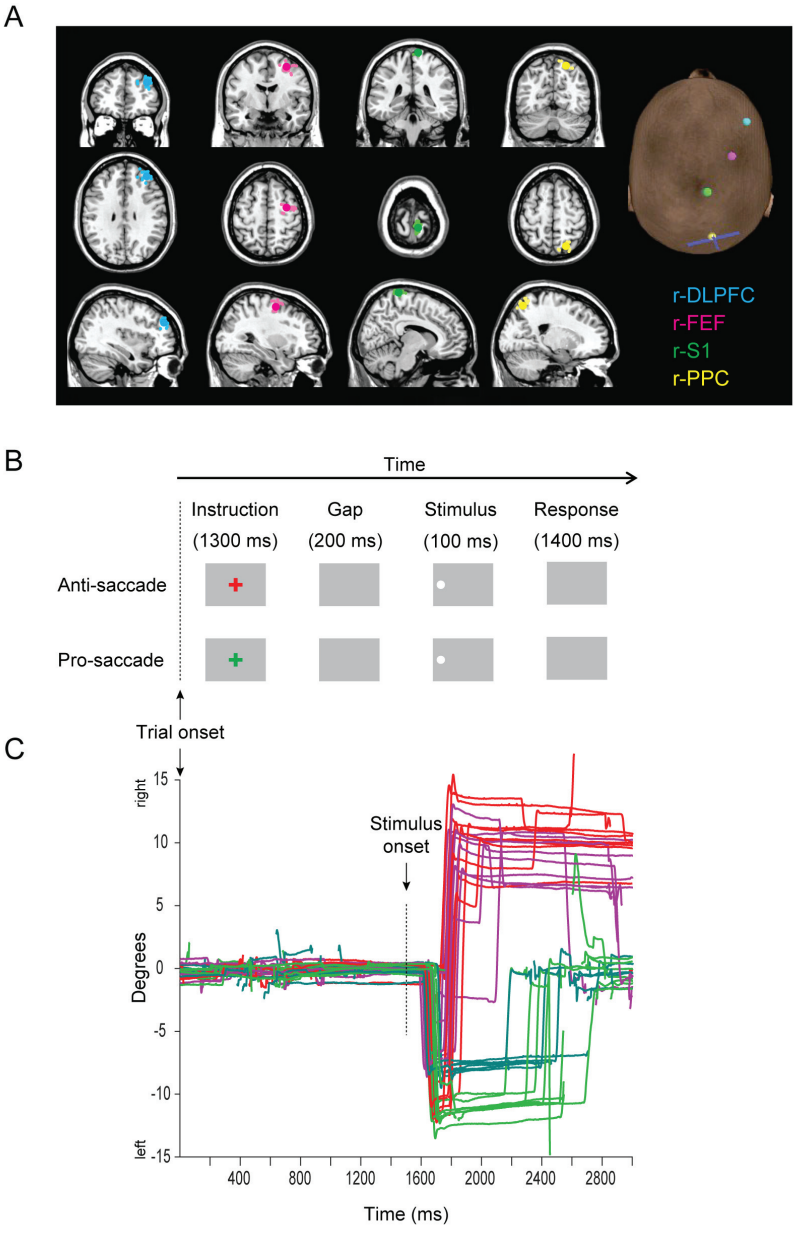
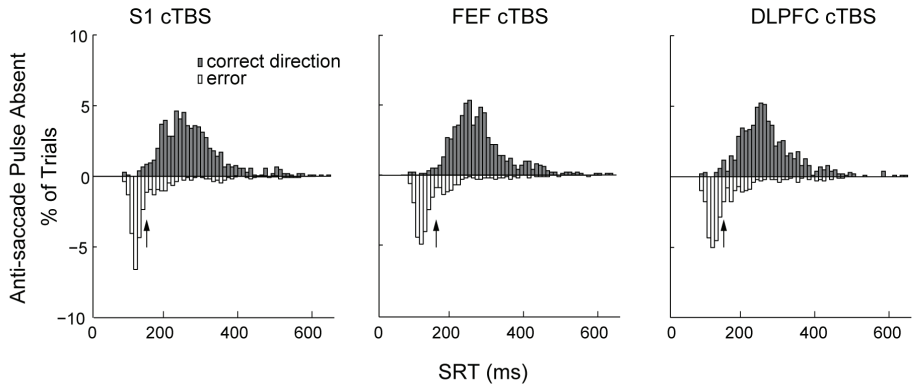
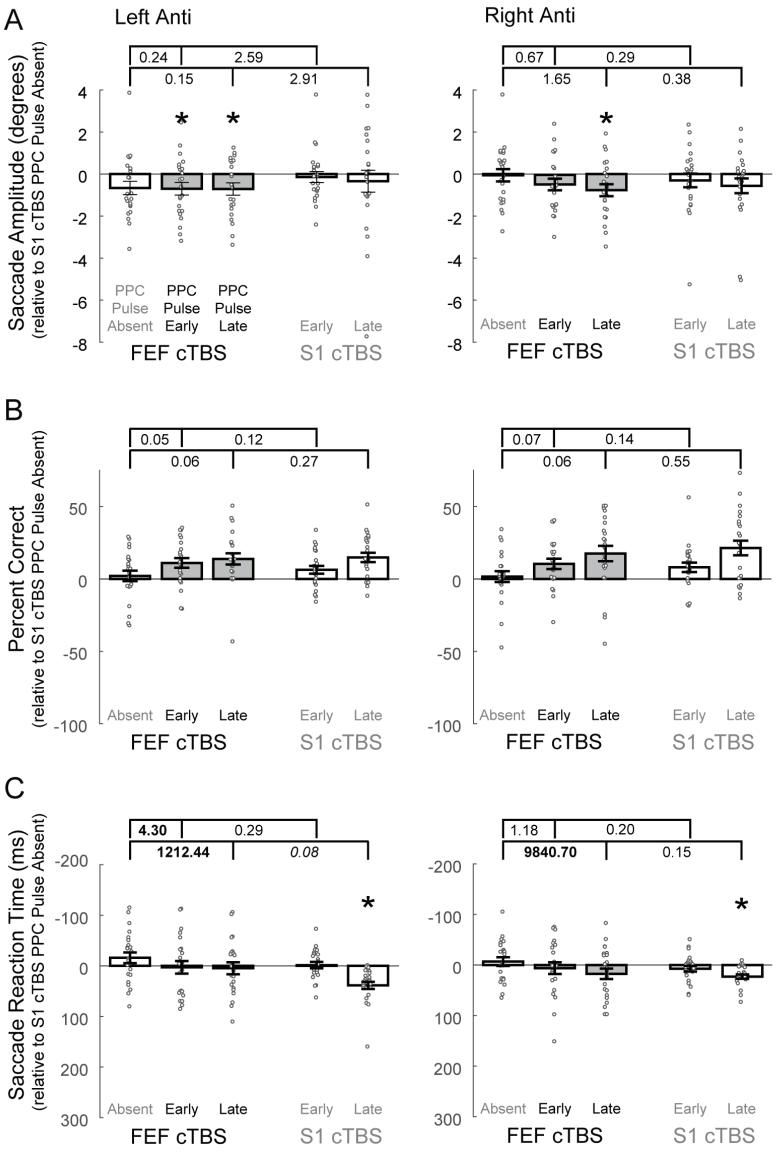
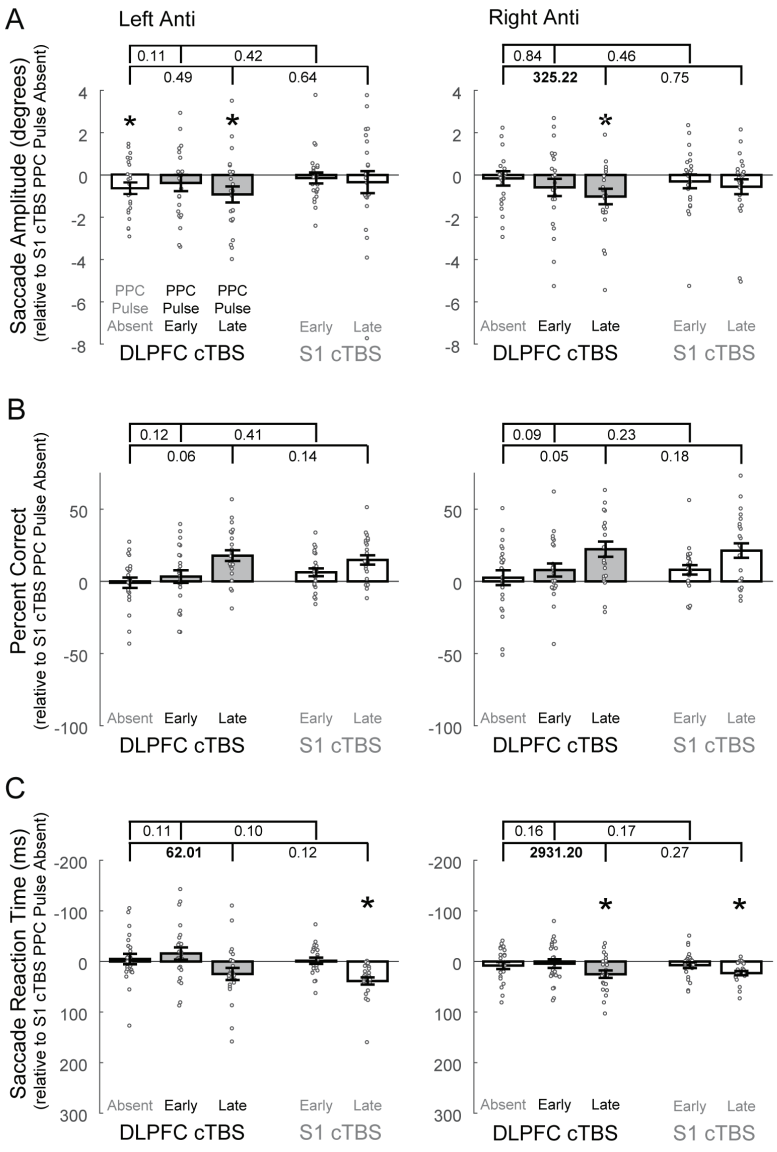




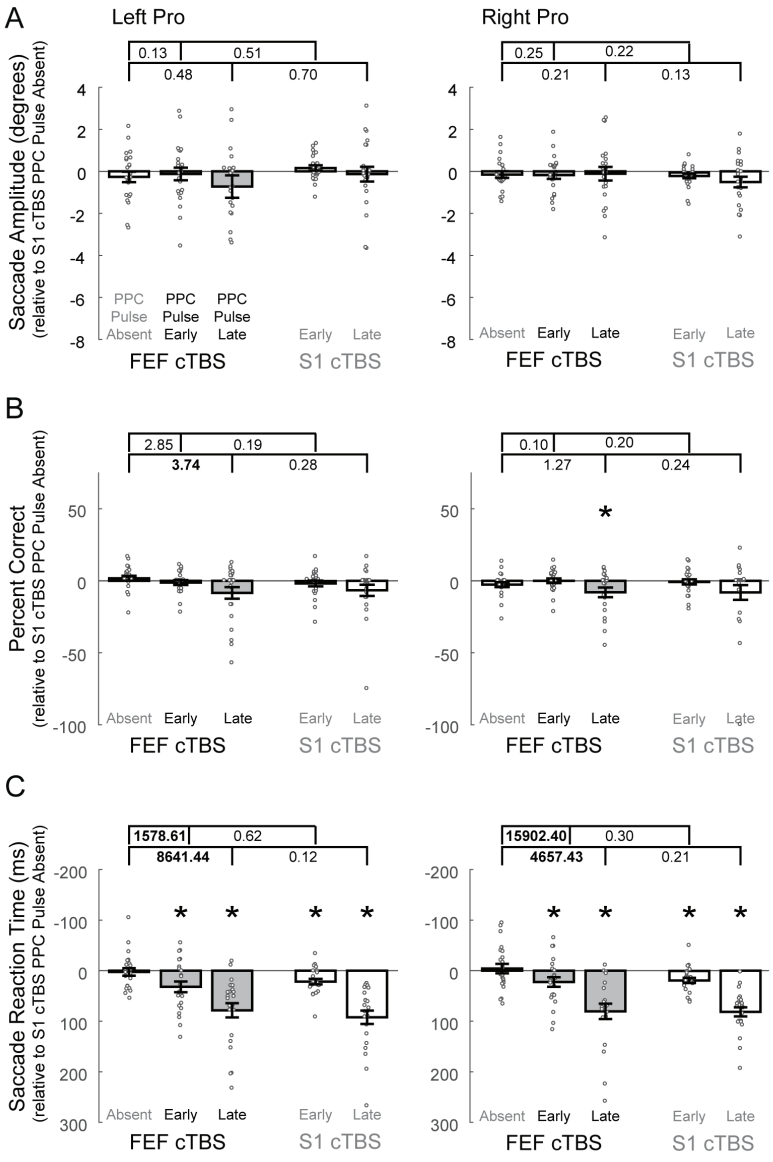


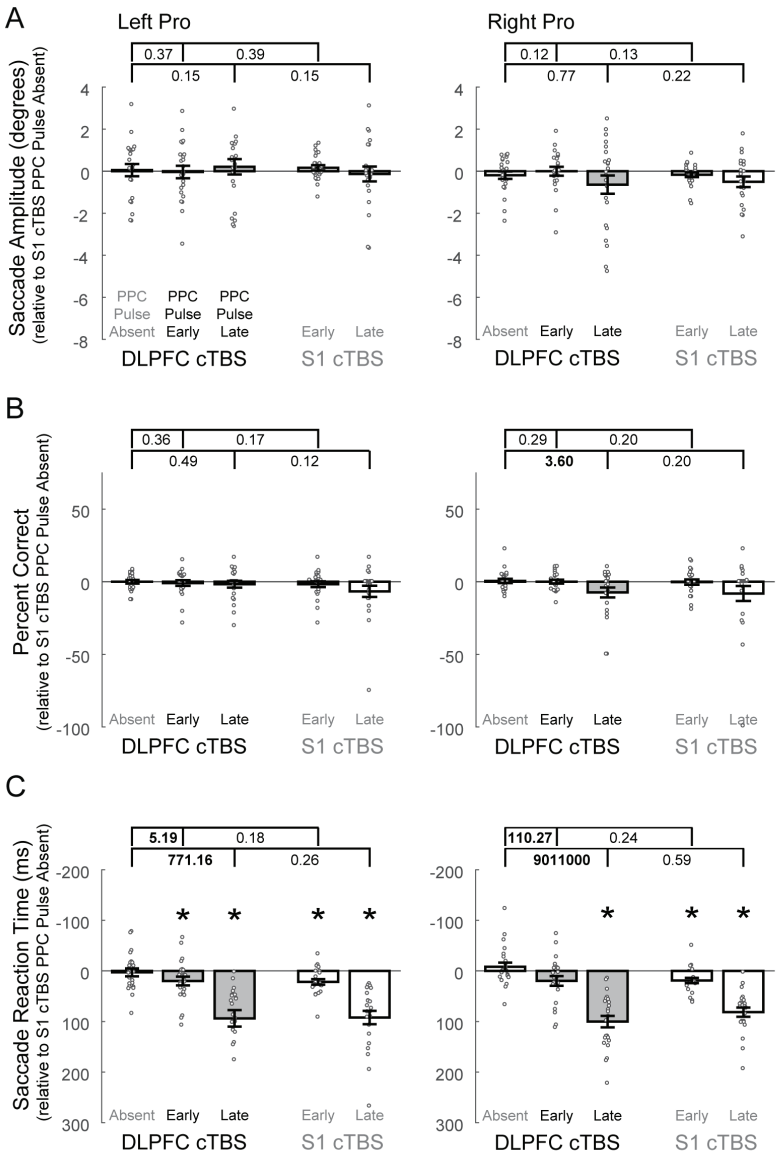


*, **Bold** values: $BF_{10} > 3$



*; **Bold** values: $BF_{10} > 3$





*, **Bold** values: $BF_{10} > 3$

Table 1: Regions Of Interest (ROI) information (average ± standard deviations (mm))

	Coordinates (MNI space)			Distance to scalp
	X	Y	Z	
r-DLPFC	35±7	45±10	31±7	19±4
r-FEF	30±5	-5±4	57±6	26±5
r-PPC	20±7	-66±6	60±5	22±4
r-S1	9±2	-38±5	79±2	20±3

Table 2: Statistical Table

	Data structure	Type of test	BF_{10}	Effect Size: Median of posterior distribution [95% C.I.]
Table 3A				
L.A., F., Absent	Assumed normal	Bayesian t-test	2.69	-0.40 [-0.82, -0.06]
L.A., F., Early			4.09	-0.45 [-0.86, -0.08]
L.A., F., Late			4.58	-0.47 [-0.90, -0.09]
L.A., S., Early			0.35	-0.18 [-0.53, -0.01]
L.A., S., Late			0.39	-0.19 [-0.54, -0.01]
R.A., F., Absent			0.26	-0.15 [-0.47, -0.01]
R.A., F., Early			1.31	-0.32 [-0.72, -0.03]
R.A., F., Late			7.60	-0.51 [-0.94, -0.11]
R.A., S., Early			0.52	-0.22 [-0.58, -0.02]
R.A., S., Late			1.21	-0.31 [-0.71, -0.03]
Table 3B				
L.A., F., Absent			0.15	-0.10 [-0.37, 0.00]
L.A., F., Early			0.06	-0.03 [-0.12, 0.00]
L.A., F., Late			0.06	-0.06 [-0.18, -0.01]
L.A., S., Early			0.08	-0.06 [-0.22, 0.00]
L.A., S., Late			0.05	-0.05 [-0.24, 0.00]
R.A., F., Absent			0.16	-0.11 [-0.38, -0.01]
R.A., F., Early			0.07	-0.05 [-0.22, 0.00]
R.A., F., Late			0.06	-0.04 [-0.14, 0.00]
R.A., S., Early			0.07	-0.06 [-0.22, 0.00]
R.A., S., Late			0.06	-0.10 [-0.13, -0.01]
Table 3C				
L.A., F., Absent			0.10	0.07 [0.00, 0.28]
L.A., F., Early			0.27	0.15 [0.01, 0.47]
L.A., F., Late			0.31	0.17 [0.01, 0.51]
L.A., S., Early			0.19	0.12 [0.01, 0.40]
L.A., S., Late			2299.54	1.04 [0.52, 1.59]
R.A., F., Absent			0.13	0.09 [0.00, 0.35]
R.A., F., Early			0.35	0.18 [0.01, 0.52]
R.A., F., Late			1.39	0.33 [0.03, 0.74]
R.A., S., Early			0.79	0.27 [0.02, 0.65]
R.A., S., Late			2619.87	1.05 [0.53, 1.60]

	Data structure	Type of test	BF_{10}	Effect Size
Table 4A				
L.A., D., Absent	Assumed normal	Bayesian t-test	4.21	-0.45 [-0.88, -0.08]
L.A., D., Early			0.55	-0.23 [-0.59, -0.02]
L.A., D., Late			4.84	-0.47 [-0.89, -0.08]
R.A., D., Absent			0.33	-0.17 [-0.51, -0.01]
R.A., D., Early			0.98	-0.29 [-0.67, -0.03]
R.A., D., Late			8.84	-0.52 [-0.96, -0.12]
Table 4B				
L.A., D., Absent			0.27	-0.15 [-0.47, -0.01]
L.A., D., Early			0.14	-0.09 [-0.35, 0.00]
L.A., D., Late			0.05	-0.01 [-0.01, -0.01]
R.A., D., Absent			0.16	-0.11 [-0.38, -0.01]
R.A., D., Early			0.09	-0.07 [-0.25, 0.00]
R.A., D., Late			0.05	-0.03 [-0.18, -0.01]
Table 4C				
L.A., D., Absent			0.16	0.10 [0.01, 0.39]
L.A., D., Early			0.11	0.07 [0.00, 0.31]
L.A., D., Late			2.52	0.39 [0.06, 0.81]
R.A., D., Absent			0.68	0.25 [0.02, 0.63]
R.A., D., Early			0.33	0.17 [0.01, 0.51]
R.A., D., Late			33.86	0.65 [0.22, 1.10]

	Data structure	Type of test	BF_{10}	Effect Size
Table 5A				
L.P., F., Absent	Assumed normal	Bayesian t-test	0.61	-0.23 [-0.60, -0.02]
L.P., F., Early			0.31	-0.16 [-0.50, -0.01]
L.P., F., Late			0.87	-0.28 [-0.66, -0.02]
L.P., S., Early			0.11	-0.08 [-0.32, 0.00]
L.P., S., Late			0.30	-0.16 [-0.50, -0.01]
R.P., F., Absent			0.54	-0.23 [-0.59, -0.01]
R.P., F., Early			0.56	-0.23 [-0.59, -0.01]
R.P., F., Late			0.30	-0.16 [-0.51, -0.01]
R.P., S., Early			1.07	-0.30 [-0.69, -0.03]
R.P., S., Late			2.32	-0.39 [-0.83, -0.05]
Table 5B				
L.P., F., Absent			0.12	-0.08 [-0.34, 0.00]
L.P., F., Early			0.41	-0.20 [-0.56, -0.01]
L.P., F., Late			2.63	-0.40 [-0.81, -0.06]
L.P., S., Early			0.48	-0.21 [-0.56, -0.01]
L.P., S., Late			1.44	-0.34 [-0.74, -0.04]
R.P., F., Absent			1.16	-0.31 [-0.69, -0.03]
R.P., F., Early			0.22	-0.13 [-0.43, -0.01]
R.P., F., Late			4.53	-0.47 [-0.91, -0.09]
R.P., S., Early			0.24	-0.14 [-0.46, -0.01]
R.P., S., Late			1.19	-0.31 [-0.71, -0.03]
Table 5C				
L.P., F., Absent			0.29	0.16 [0.01, 0.49]
L.P., F., Early			14.878	0.57 [0.15, 1.02]
L.P., F., Late			3314.92	1.08 [0.56, 1.63]
L.P., S., Early			110.56	0.77 [0.30, 1.25]
L.P., S., Late			52637.20	1.40 [0.79, 2.03]
R.P., F., Absent			0.16	0.10 [0.02, 0.38]
R.P., F., Early			4.08	0.44 [0.08, 0.86]
R.P., F., Late			1461.64	1.07 [0.53, 1.64]
R.P., S., Early			51.42	0.69 [0.25, 1.16]
R.P., S., Late			2165000.00	1.81 [1.09, 2.56]

	Data structure	Type of test	BF_{10}	Effect Size
Table 6A				
L.P., D., Absent	Assumed normal	Bayesian t-test	0.19	-0.12 [-0.41, 0.00]
L.P., D., Early			0.24	-0.14 [-0.47, -0.01]
L.P., D., Late			0.15	-0.10 [-0.36, -0.01]
R.P., D., Absent			0.62	-0.24 [-0.62, -0.02]
R.P., D., Early			0.22	-0.13 [-0.43, -0.01]
R.P., D., Late			1.03	-0.29 [-0.69, -0.02]
Table 6B				
L.P., D., Absent			0.22	-0.13 [-0.45, -0.01]
L.P., D., Early			0.32	-0.17 [-0.50, -0.01]
L.P., D., Late			0.42	-0.19 [-0.56, -0.01]
R.P., D., Absent			0.17	-0.11 [-0.39, -0.01]
R.P., D., Early			0.21	-0.13 [-0.44, -0.01]
R.P., D., Late			2.84	-0.41 [-0.82, -0.06]
Table 6C				
L.P., D., Absent			0.29	0.16 [0.01, 0.50]
L.P., D., Early			3.65	0.43 [0.07, 0.85]
L.P., D., Late			5089.32	1.12 [0.58, 1.67]
R.P., D., Absent			0.12	0.09 [0.00, 0.33]
R.P., D., Early			2.49	0.39 [0.05, 0.81]
R.P., D., Late			2344000.00	1.75 [1.07, 2.46]

	Data structure	Type of test	BF_{10}	Effect Size
Figure 4A				
L.A., F. Absent – F. Early	Assumed normal	Bayesian t-test	0.24	-0.14 [-0.45, -0.01]
L.A., F. Early – S. Early			2.59	-0.40 [-0.80, -0.06]
L.A., F. Absent – F. Late			0.15	-0.10 [-0.38, 0.00]
L.A., F. Late – S. Late			2.91	-0.42 [-0.85, -0.06]
R.A., F. Absent – F. Early			0.67	-0.25 [-0.62, -0.02]
R.A., F. Early – S. Early			0.29	-0.16 [-0.49, -0.01]
R.A., F. Absent – F. Late			1.65	-0.34 [-0.75, -0.05]
R.A., F. Late – S. Late			0.38	-0.18 [-0.53, -0.01]
Figure 4B				
L.A., F. Absent – F. Early			0.05	-0.05 [-0.25, 0.00]
L.A., F. Early – S. Early			0.12	-0.08 [-0.34, 0.00]
L.A., F. Absent – F. Late			0.06	-0.05 [-0.17, -0.01]
L.A., F. Late – S. Late			0.27	-0.15 [-0.47, -0.01]
R.A., F. Absent – F. Early			0.07	-0.05 [-0.23, 0.00]
R.A., F. Early – S. Early			0.14	-0.10 [-0.35, 0.00]
R.A., F. Absent – F. Late			0.06	-0.05 [-0.21, -0.01]
R.A., F. Late – S. Late			0.55	-0.23 [-0.59, -0.02]
Figure 4C				
L.A., F. Absent – F. Early			4.30	0.45 [0.09, 0.87]
L.A., F. Early – S. Early			0.29	0.15 [0.01, 0.49]
L.A., F. Absent – F. Late			1212.45	1.02 [0.49, 1.55]
L.A., F. Late – S. Late			0.08	0.06 [0.00, 0.28]
R.A., F. Absent – F. Early			1.18	0.31 [0.03, 0.71]
R.A., F. Early – S. Early			0.204	0.12 [0.01, 0.44]
R.A., F. Absent – F. Late			9840.70	1.17 [0.63, 1.75]
R.A., F. Late – S. Late			0.152	0.10 [0.01, 0.38]

	Data structure	Type of test	BF_{10}	Effect Size
Figure 5A				
L.A., D. Absent – D. Early	Assumed normal	Bayesian t-test	0.11	-0.14 [-0.45, -0.01]
L.A., D. Early – S. Early			0.42	-0.40 [-0.80, -0.06]
L.A., D. Absent – D. Late			0.49	-0.22 [-0.57, -0.02]
L.A., D. Late – S. Late			0.64	-0.24 [-0.62, -0.02]
R.A., D. Absent – D. Early			0.84	-0.25 [-0.62, -0.02]
R.A., D. Early – S. Early			0.46	-0.16 [-0.49, -0.01]
R.A., D. Absent – D. Late			352.22	-0.86 [-1.36, -0.38]
R.A., D. Late – S. Late			0.75	-0.25 [-0.64, -0.02]
Figure 5B				
L.A., D. Absent – D. Early			0.12	-0.08 [-0.31, 0.00]
L.A., D. Early – S. Early			0.41	-0.19 [-0.54, -0.01]
L.A., D. Absent – D. Late			0.06	-0.01 [-0.01, -0.01]
L.A., D. Late – S. Late			0.14	-0.10 [-0.34, 0.00]
R.A., D. Absent – D. Early			0.09	-0.07 [-0.26, 0.00]
R.A., D. Early – S. Early			0.23	-0.13 [-0.45, -0.01]
R.A., D. Absent – D. Late			0.05	0.00 [0.00, 0.00]
R.A., D. Late – S. Late			0.18	-0.11 [-0.41, -0.01]
Figure 5C				
L.A., D. Absent – D. Early			0.11	0.07 [0.00, 0.31]
L.A., D. Early – S. Early			0.10	0.07 [0.00, 0.32]
L.A., D. Absent – D. Late			62.01	0.71 [0.26, 1.18]
L.A., D. Late – S. Late			0.12	0.08 [0.00, 0.31]
R.A., D. Absent – D. Early			0.16	0.10 [0.01, 0.37]
R.A., D. Early – S. Early			0.17	0.11 [0.01, 0.40]
R.A., D. Absent – D. Late			2931.20	1.07 [0.55, 1.60]
R.A., D. Late – S. Late			0.27	0.15 [0.01, 0.47]

	Data structure	Type of test	BF_{10}	Effect Size
Figure 6A				
L.P., F. Absent – F. Early	Assumed normal	Bayesian t-test	0.13	-0.09 [-0.35, 0.00]
L.P., F. Early – S. Early			0.51	-0.22 [-0.59, -0.02]
L.P., F. Absent – F. Late			0.48	-0.21 [-0.56, -0.01]
L.P., F. Late – S. Late			0.70	-0.26 [-0.64, -0.02]
R.P., F. Absent – F. Early			0.25	-0.15 [-0.46, -0.01]
R.P., F. Early – S. Early			0.22	-0.13 [-0.44, -0.01]
R.P., F. Absent – F. Late			0.21	-0.13 [-0.44, -0.01]
R.P., F. Late – S. Late			0.13	-0.09 [-0.35, 0.00]
Figure 6B				
L.P., F. Absent – F. Early			2.85	-0.40 [-0.83, -0.06]
L.P., F. Early – S. Early			0.19	-0.12 [-0.41, -0.01]
L.P., F. Absent – F. Late			3.74	-0.44 [-0.86, -0.07]
L.P., F. Late – S. Late			0.28	-0.16 [-0.49, -0.01]
R.P., F. Absent – F. Early			0.10	-0.08 [-0.29, 0.00]
R.P., F. Early – S. Early			0.20	-0.12 [-0.41, -0.01]
R.P., F. Absent – F. Late			1.27	-0.33 [-0.74, -0.03]
R.P., F. Late – S. Late			0.24	-0.14 [-0.47, -0.01]
Figure 6C				
L.P., F. Absent – F. Early			1578.61	1.01 [0.50, 1.54]
L.P., F. Early – S. Early			0.62	0.24 [0.02, 0.60]
L.P., F. Absent – F. Late			8641.44	1.17 [0.62, 1.73]
L.P., F. Late – S. Late			0.121	0.09 [0.00, 0.35]
R.P., F. Absent – F. Early			15902.41	1.22 [0.67, 1.81]
R.P., F. Early – S. Early			0.30	0.16 [0.01, 0.50]
R.P., F. Absent – F. Late			4657.42	1.19 [0.63, 1.80]
R.P., F. Late – S. Late			0.21	0.13 [0.01, 0.49]

	Data structure	Type of test	BF_{10}	Effect Size
Figure 7A				
L.P., D. Absent – D. Early	Assumed normal	Bayesian t-test	0.37	-0.18 [-0.53, -0.01]
L.P., D. Early – S. Early			0.39	-0.19 [-0.54, -0.01]
L.P., D. Absent – D. Late			0.15	-0.10 [-0.38, 0.00]
L.P., D. Late – S. Late			0.15	-0.10 [-0.38, 0.00]
R.P., D. Absent – D. Early			0.12	-0.09 [-0.33, 0.00]
R.P., D. Early – S. Early			0.13	-0.09 [-0.35, 0.00]
R.P., D. Absent – D. Late			0.77	-0.26 [-0.64, -0.02]
R.P., D. Late – S. Late			0.22	-0.13 [-0.44, -0.01]
Figure 7B				
L.P., D. Absent – D. Early			0.36	-0.18 [-0.52, -0.01]
L.P., D. Early – S. Early			0.17	-0.11 [-0.40, -0.01]
L.P., D. Absent – D. Late			0.49	-0.21 [-0.58, -0.01]
L.P., D. Late – S. Late			0.12	-0.08 [-0.33, 0.00]
R.P., D. Absent – D. Early			0.29	-0.16 [-0.48, -0.01]
R.P., D. Early – S. Early			0.20	-0.13 [-0.42, -0.01]
R.P., D. Absent – D. Late			3.60	-0.43 [-0.85, -0.07]
R.P., D. Late – S. Late			0.20	-0.12 [-0.42, -0.05]
Figure 7C				
L.P., D. Absent – D. Early			5.19	0.47 [0.09, 0.90]
L.P., D. Early – S. Early			0.18	0.12 [0.01, 0.41]
L.P., D. Absent – D. Late			771.16	0.94 [0.45, 1.44]
L.P., D. Late – S. Late			0.26	0.15 [0.01, 0.46]
R.P., D. Absent – D. Early			110.27	0.76 [0.30, 1.24]
R.P., D. Early – S. Early			0.24	0.14 [0.01, 0.46]
R.P., D. Absent – D. Late			9011000.00	1.90 [1.18, 2.65]
R.P., D. Late – S. Late			0.59	0.24 [0.02, 0.60]

Table 3: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right anti-saccade trials relative to control cTBS

Left Anti	cTBS site	PPC pulse	BF_{10}	**Right Anti**	cTBS site	PPC pulse	BF_{10}
A) Amplitude							
	FEF	Absent	2.69		FEF	Absent	0.26
		Early	**4.09**			Early	1.31
		Late	**4.58**			Late	**7.60**
	S1	Early	0.35		S1	Early	0.52
		Late	0.39			Late	1.21
B) Percent Correct							
	FEF	Absent	0.15		FEF	Absent	0.16
		Early	0.06			Early	0.07
		Late	0.06			Late	0.06
	S1	Early	0.08		S1	Early	0.07
		Late	0.05			Late	0.06
C) Saccade Reaction Time							
	FEF	Absent	0.10		FEF	Absent	0.13
		Early	0.27			Early	0.35
		Late	0.31			Late	1.39
	S1	Early	0.19		S1	Early	0.79
		Late	**2299.54**			Late	**2619.87**

Bold values: $BF_{10} > 3$

Table 4: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right anti-saccade trials relative to control cTBS. (The effect of the PPC pulse relative to control cTBS is shown in duplication as in Table 3)

Left Anti	cTBS site	PPC pulse	BF_{10}	**Right Anti**	cTBS site	PPC pulse	BF_{10}
A) Amplitude							
	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
B) Percent Correct							
	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
C) Saccade Reaction Time							
	DLPFC	Absent	0.16		DLPFC	Absent	0.68
		Early	0.11			Early	0.33
		Late	2.52			Late	**33.86**
	S1	Early	0.19		S1	Early	0.79
		Late	**2299.54**			Late	**2619.86**

Bold values: $BF_{10} > 3$

Table 5: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right pro-saccade trials relative to control cTBS

Left Pro	cTBS site	PPC pulse	BF_{10}	**Right Pro**	cTBS site	PPC pulse	BF_{10}
A) Amplitude							
	FEF	Absent	0.61		FEF	Absent	0.54
		Early	0.31			Early	0.56
		Late	0.87			Late	0.30
	S1	Early	0.11		S1	Early	1.07
		Late	0.30			Late	2.32
B) Percent Correct							
	FEF	Absent	0.12		FEF	Absent	1.16
		Early	0.41			Early	0.22
		Late	2.63			Late	**4.53**
	S1	Early	0.48		S1	Early	0.24
		Late	1.44			Late	1.19
C) Saccade Reaction Time							
	FEF	Absent	0.29		FEF	Absent	0.16
		Early	**14.88**			Early	**4.08**
		Late	**3314.92**			Late	**1461.64**
	S1	Early	**110.56**		S1	Early	**51.42**
		Late	**52637.20**			Late	**2165000**

Bold values: $BF_{10} > 3$

Table 6: Bayes Factors for the alternative (impairment) vs. null (no impairment) hypothesis (BF_{10}) for left and right pro-saccade trials relative to control cTBS (The effect of the PPC pulse relative to control cTBS is shown in duplication as in Table 5)

Left Pro	cTBS site	PPC pulse	BF_{10}	**Right Pro**	cTBS site	PPC pulse	BF_{10}
A) Amplitude							
	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
B) Percent Correct							
	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
C) Saccade Reaction Time							
	DLPFC	Absent	0.29		DLPFC	Absent	0.12
		Early	**3.65**			Early	2.49
		Late	**5089.32**			Late	**2344000**
	S1	Early	**110.56**		S1	Early	**51.42**
		Late	**52637.20**			Late	**2165000**

Bold values: $BF_{10} > 3$