Controlling brain state prior to stimulation of parietal cortex prevents deterioration of sustained attention

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Contributions
GE & LB designed the research. GE, FC, & LKB performed the experiments. GE analyzed the data. GE, FC, & LB wrote the manuscript.

Competing financial interests
The authors declare no competing financial interests.

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Abstract

Sustained attention is a limited resource which declines during daily tasks. Such decay is exacerbated in clinical and aging populations. Low-frequency transcranial magnetic stimulation (LF-rTMS) to the intraparietal sulcus (IPS) has potential to upregulate neural activity within the attention network, evidenced by increased activation and functional communication. Attributed to functional compensation for the inhibited node, this boost outlasts the stimulation for tens of minutes. Despite the neural change, no behavioral effect has been found in healthy subjects, a necessary direct evidence of functional compensation. To understand the functional significance of neuromodulatory induced fluctuations on sustained attention, we sought to boost the impact of LF-rTMS through controlling neural excitability prior to LF-rTMS, with the goal to impact behavior. Brain state was controlled using high-frequency transcranial random noise stimulation (HF-tRNS), based on the evidence that HF-tRNS increases and stabilizes neuronal excitability. In male and female human participants, we tested several fMRI-guided stimulation protocols combining HF-tRNS and LF-rTMS. Sustained attention was recorded post-stimulation via a multiple object tracking task (MOT). Whilst attention deteriorated across time in the control condition, HF-tRNS followed by LF-rTMS maintained attention performance up to 94 minutes, doubling the length of successful sustained attention. These results suggest controlling brain state can increase the impact of LF-rTMS in bilateral sustained attention. Used in a cognitive domain dependent on network-wide neural activity, this tool may be effective in causing neural compensation important for clinical rehabilitation.

Significance Statement

Sustained attention decreases 45 minutes after the onset of a task. Here, we prevent decrement of sustained attention for 94 minutes through applying multi-method brain stimulation. Our stimulation protocol aimed to boost sustained attention through harnessing functional compensation previously found in the attention network following low-frequency rTMS (LF-rTMS) to the IPS, a node of the network. To date, this functional compensation has not provoked behavioral benefit. In our study, controlling brain state with high-frequency transcranial random noise stimulation (HF-tRNS) prior to LF-rTMS resulted in a lasting sustained attention, a crucial effect that could be beneficial to both healthy and clinical populations. Furthermore, given the feasibility of real-world application, this stimulation protocol could be employed ubiquitously to augment cognitive processes.

Introduction

Sustained attention is fundamental for cognitively interacting with the environment (DeGangi & Porges, 1990), however it progressively deteriorates over time (Sarter et al., 2001; Berardi et al., 2001; Whitehurst et al., 2019). This deterioration increases with age (Berardi et al., 2001) and in cognitive disorders, such as ADHD and bipolar disorder (Barkley, 1997; Clark et al., 2005). Thus, a protocol that stabilizes sustained attention for prolonged durations has population-wide application.

Non-invasive brain stimulation can significantly boost cognitive function (Herpich et al. 2019; Reinhart & Nguyen, 2019; Freedberg et al., 2019; Hermiller et al., 2019) indicating that favorable behavioral changes following stimulation may be due to lasting network-wide fluctuation of regions functionally connected to stimulation site (Battelli et al., 2017; Freedberg et al., 2019; Hermiller et al., 2019). In visual attention, low frequency repetitive transcranial magnetic stimulation (LF-rTMS) to the intraparietal sulcus (IPS) results in a cascade of network-wide effects (Capotosto et al., 2012; Szczepanski & Kastner, 2013; Plow et al., 2014; Petitet et al., 2015; Capotosto et al., 2017). For example, inhibition of the IPS with LF-rTMS causes increased functional communication between nodes of the dorsal attention network, 48 minutes post-stimulation (Battelli et al., 2017). One hypothesis is that network-wide functional change compensates for the inhibited node following LF-rTMS (Paus et al., 1997; Grefkes et al., 2009; Lee & D'Esposito, 2012; Plow et al., 2014; Battelli et al., 2017). Functional compensation should predict behavioral benefit lasting the duration of the functional change (Grefkes et al., 2009), yet such behavioral impact has not been found in healthy participants (Plow et al., 2014; Battelli et al., 2017). Enduring behavioral change is crucial for non-invasive brain stimulation to be considered in clinical intervention.

Multi-method brain stimulation to the motor cortex has successfully boosted the impact of LF-rTMS, inhibiting physiological response an hour after stimulation (Iyer et al., 2003). The lasting inhibition is achieved by applying high-frequency prior to low-frequency stimulation, with the aim of extending the long-term depressive effect (Stanton & Sejnowski, 1989; Christie & Abraham, 1992; Iyer et al., 2003). The influence of neuronal

activation history on subsequent neuronal activity has been termed “metaplasticity” (Abraham & Bear, 1996). To date, multi-method stimulation for enduring cortical inhibition have been tested physiologically in the motor (Iyer et al., 2003; Siebner et al., 2004; Lang et al., 2004; Fricke et al., 2010), and visual cortex (Bocci et al., 2014), but never in the parietal cortex using a cognitive task as the outcome measure. In order to harness the predicted behavioral benefit to sustained attention from functional compensation of the dorsal attention network, we aimed to boost the impact of LF-rTMS over the IPS.

Here, we adapted the multi-method approach to modulate the dorsal attention network and recorded sustained attention for 94 minutes post-stimulation. In the first experiment, we primed bilateral IPS with high-frequency transcranial random noise stimulation (HF-tRNS), shown to increase cortical excitability (Terney et al., 2008; Moliadze et al., 2012; Herpich et al., 2018). Following HF-tRNS we applied LF-rTMS to initiate long-term inhibition (Iyer et al., 2003). In the second experiment, we aimed to replicate experiment one, and boost the effectiveness of priming with the addition of a task during HF-tRNS, based on the premise that cortical excitation and engagement increases significantly with task during the stimulation (Silvanto et al., 2007; Cappalletti et al., 2013; Edwards et al., 2019).

Whilst sustained attention decreases with time in the control condition, we expect functional compensation following multi-method stimulation to maintain sustained attention. We conjecture multi-method stimulation would result in sustained inhibition of the IPS, similar to the findings in the motor and visual cortex (Iyer et al., 2003; Bocci et al., 2014) and functional compensation from other nodes of the attention network in response (Paus et al., 1997; Grefkes et al., 2009; Lee & D’Esposito, 2012; Plow et al., 2014; Battelli et al., 2017). We expected HF-tRNS alone to elicit cortical excitation (Herpich et al., 2018), resulting in an increase in sustained attention, while LF-rTMS was expected to only initially decrease contralateral attention (Battelli et al., 2009).

Methods & Materials

Participants. Forty-one volunteers (nineteen females; age range 20-40 years), participated in the two experiments. All participants gave written informed consent, and the study was approved by Harvard University's Institutional Review Board: The Human Research Protection Program. In the first experiment, five participants' data was not analyzed due to incomplete attendance to experiment sessions, leaving sixteen participants in total. All twenty participants were included in data analysis for experiment 2. All participants had normal to corrected-to-normal vision.

Experiment 1: Priming the Parietal Cortex at Rest

Experiment 1 was a multi-session within subjects design with five sessions. Participants attended an fMRI session first to localize the stimulation sites, and then attended four separate sessions of non-invasive brain stimulation followed by behavioral testing.

Stimuli. During the localizer runs in the fMRI in experiment 1, participants viewed the stimulus on an fMRI compatible screen positioned in the bore of the magnet at a distance of 104 cm. The screen projected the stimulus from a 13-inch MacBook Pro (Retina; screen resolution: 1280 x 800). During behavioral testing after stimulation in experiment 1, participants viewed the stimulus on the same 13-inch MacBook Pro at a distance of 60 cm. All stimuli were presented using the psychophysical toolbox PsychoPy.

Standard bilateral Multiple Object Tracking Paradigm (MOT). Participants performed a multiple object tracking paradigm (MOT) for both experiments. MOT is a well-established paradigm for recruiting bilateral attention (Pylyshyn & Storm, 1988), and functionally activating bilateral parietal cortices (Culham et al.,1998). On each trial, participants were presented with four objects (black dots, radius 0.25°) either side of a central fixation (Figure 1a). Two objects on either side of the fixation cross flashed (2 Hz for 2 sec) to cue the participant to track these objects amongst the other identical distractors. All objects then moved at a constant speed (degrees per second) for three seconds within a 6 x 6-degree region and centered 2 degrees to the left and right of the fixation. Speed was set

according to the individual participants' threshold (see *Thresholding* section). Each object repelled one another to maintain a minimum space of 1.5°, never crossed the midline and bounced off of invisible edges within each visual field. After three seconds, the objects stopped moving, one object was highlighted in red, and the participant was asked to respond with a key press to indicate if the highlighted object was the "target" or "distractor" to the objects flashed at the beginning. Importantly, the participant was unaware of which visual field would be tested, necessitating central fixation and tracking within both visual fields simultaneously. After each trial, the fixation point changed to red to indicate incorrect, or green to indicate correct response.

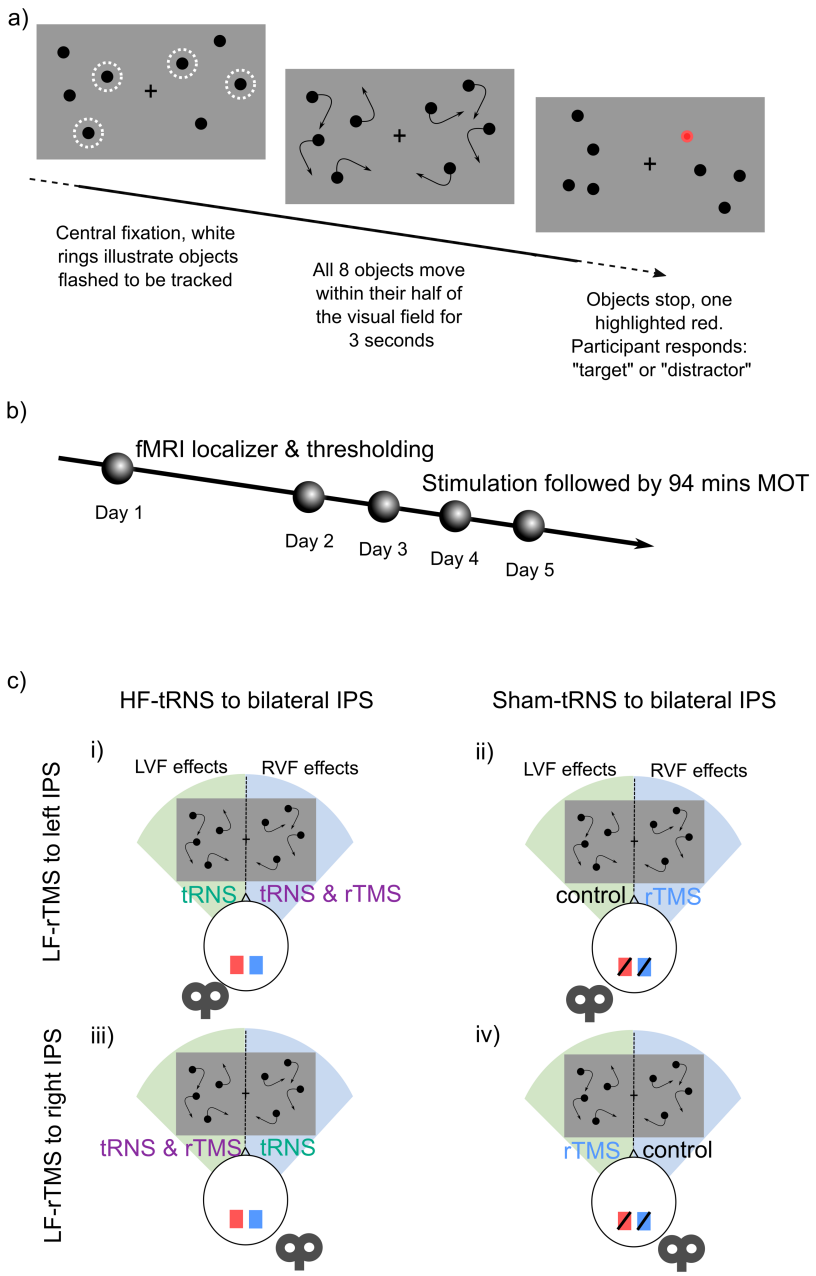

Figure 1: Sustained attention task & multi-stimulation protocol and procedure for experiment 1. 1a) Bilateral multiple object tracking (MOT) was used to record participants sustained attention across time after stimulation. 1c) Depiction of each stimulation session for experiment 1. Note all left visual field stimulation effects were compared with left visual field control in c.ii), and right stimulation effects with right control in c.iv).

Localizer stimuli. Unilateral MOT was used to localize the posterior portion of the intraparietal sulcus (IPS) in both the right and left cortex for experiment 1. Posterior IPS is typically localized using fMRI with covert attention to the right and left visual field separately (Gitelman et al., 1999). The posterior IPS is involved in lateralized attention in

the contralateral visual field (i.e. right posterior IPS is involved in attention of the left visual field). During the localizer scan in the MRI, participants performed unilateral MOT for one run of 8.5 minutes. Each trial was performed similarly to the standard MOT described above, but only two objects were cued to be tracked from one visual field only, rather than two objects in each visual field. Therefore, attention was diverted to one visual field from fixation point in each trial.

Thresholding stimuli. During the first session, participants performed bilateral MOT in a staircase procedure to establish each participants' 75% correct threshold (Cornsweet, 1962). Participants first practiced MOT for 16 trials when the dots moved at the slow speed of 2 deg/sec. After the practice block, participants' threshold was determined by changing the speed of the moving dots on each trial. Participants completed eight interleaved 3/1 staircases to assess their individual speed thresholds. The staircases increased the speed after three correct trials and reduced it following a single incorrect response. The staircases terminated after a combined 16 reversals, with threshold parameters estimated from the last 3 reversals. Speed was adjusted to yield 75% accuracy in the target/distractor judgments. Participants then performed bilateral MOT at their 75% correct threshold speed (degrees per second) for the duration of the experiment. In order to determine a behavioral change with stimulation, all participants should perform below ceiling at the same baseline prior to stimulation. Our participants 75% correct speed ranged from 5 – 12.75 deg/sec for experiment 1 (Figure 2a experiment 1).

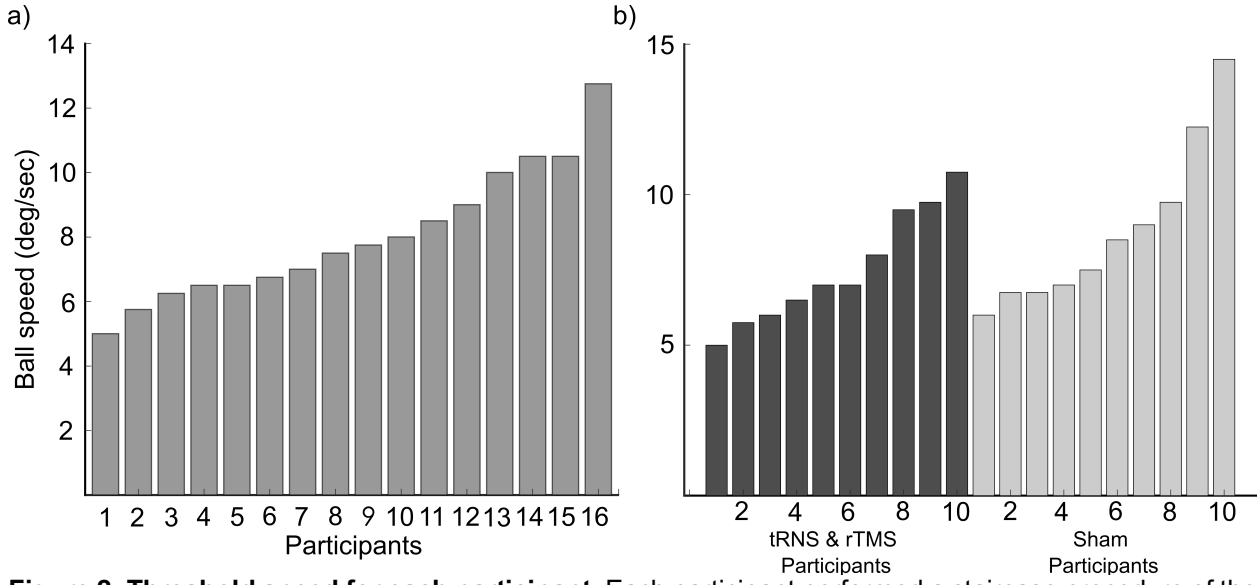

Figure 2: Threshold speed for each participant. Each participant performed a staircase procedure of the bilateral MOT to locate the speed at which performance was 75% correct. Data sorted lowest to highest for each group of participants. The speeds range from 5 – 14.5 degrees per second across experiments 1 (Figure 2a) and 2 (Figure 2b).

Experimental Designs & Statistical Analyses. The experiment was performed as a within-subjects design, each participant performed all conditions of the experiment. The experiment consisted of five sessions separated by at least 48 hours (Figure 1b). On day one, participants performed unilateral MOT in the fMRI to localize the IPS for the following stimulation session, and subsequently perform the bilateral MOT using the staircase procedure to determine individual threshold speed at which each subject performed the task at 75% correct. Day two to day five were counterbalanced across subjects using Balanced Latin Squares. On each day the participant received one of four stimulation protocols (Figure 1c): 20 minutes of (i) high-frequency transcranial random noise stimulation (HF-tRNS) or (ii) sham tRNS to bilateral posterior IPS, followed by 15 minutes of low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) to *left* IPS; or 20 minutes of (iii) HF-tRNS or (iv) sham ftRNS to bilateral posterior IPS, followed by 15 minutes of LF-rTMS to right IPS.

After stimulation, the participant performed bilateral MOT for 94 minutes, twelve blocks of six minutes separated by two minutes of rest between each block. Each block comprised of 19 trials in which objects in the left visual field were probed, and 19 trial in which objects in the right visual field were tested. The order of the tested visual field was randomized.

Embedded within each stimulation day are two conditions: object tracking in the visual field contralateral to the LF-rTMS, or object tracking in the hemifield ipsilateral to the LF-rTMS. On days with active bilateral tRNS, tracking performance in the ispilateral visual field served as a control for evaluating the impact of tRNS alone. Likewise, on days in which participants received sham tRNS, the visual field ipsilateral to the LF-rTMS received no direct stimulation, serving as the control to evaluate the impact of rTMS alone on behavioral responses.

Although data was collected in 12 six-minute bins, we collapsed the data every two bins to increase the number of trials per bin for analysis, resulting in six 14-minute bins. We analyzed our data in two ways: 1) data was collapsed across left and right LF-rTMS stimulation days, and tracking accuracy was calculated independently of the stimulated hemisphere, 2) data was split into the two visual fields to determine the hemifield-specific impact of stimulation. Stimulation effects were measured by normalizing performance after stimulation relative to baseline control behavior in the same visual field. It is important to consider the stimulation effects compared to control per visual field, as each subject tends to have a performance bias in one visual field. Our data is depicted in four stimulation conditions for each analysis: 1) tRNS & rTMS, 2) tRNS alone, 3) rTMS alone, 4) control. First a three-way repeated measures ANOVA was run to determine an interaction between visual field, stimulation, and time. After which, the data was split by visual field, and follow-up two-way repeated measures ANOVAs were run on each visual field to determine the effect of stimulation and time on behavior. Repeated measures ANOVAs attain the impact of stimulation and time on MOT accuracy, whilst accounting for multiple responses from one subject. We run FDR-corrected t-tests to determine the time-point at which a stimulation protocol was significantly different from our control condition.

Experiment 2: Combining Priming the Parietal cortex and Behavior

Experiment 2 was a between-subjects design, with only one session per participant.

Stimuli. In experiment 2, participants viewed the stimuli on the 13-inch MacBook Pro set-up as reported for experiment 1, both during tRNS and after stimulation.

Standard bilateral Multiple Object Tracking Paradigm (MOT). Performed in the exact format as that of experiment 1.

Thresholding stimuli. Performed at the beginning of the session for each participant in the same staircase procedure as described for experiment 1. Our participants 75% correct speed ranged from 5 – 14.5 deg/sec for experiment 2 (Figure 2b experiment 2).

Experimental Designs & Statistical Analyses. Experiment 2 was a between-subject design, therefore each subject received just one stimulation protocol. In the experimental session, participants first performed bilateral MOT in a staircase procedure in order to determine 75% correct speed threshold for each participant. This speed was used for the remainder of the experiment. Prior to stimulation, participants underwent six minutes bilateral MOT to ensure equal performance across groups before stimulation. Each participant was randomly assigned to one of two stimulation protocols (Figure 3: i) 20 minutes of high-frequency transcranial random noise stimulation (HF-tRNS) to bilateral posterior IPS followed by 15 minutes of low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) to right IPS, ii) 20 minutes sham HF-tRNS to bilateral IPS followed by 15 minutes sham rTMS to right IPS. None of the participants had experienced brain stimulation previously, and therefore were unable to determine if they received real or sham stimulation. Importantly, participants performed bilateral MOT during HF-tRNS stimulation. This part of the protocol was different from experiment 1, where subjects received HF-tRNS while they were at rest. After stimulation, participants performed 94 minutes of MOT across 12 blocks of 6 minutes each, with two minutes break between each block (see procedure of *Experiment 1* for details).

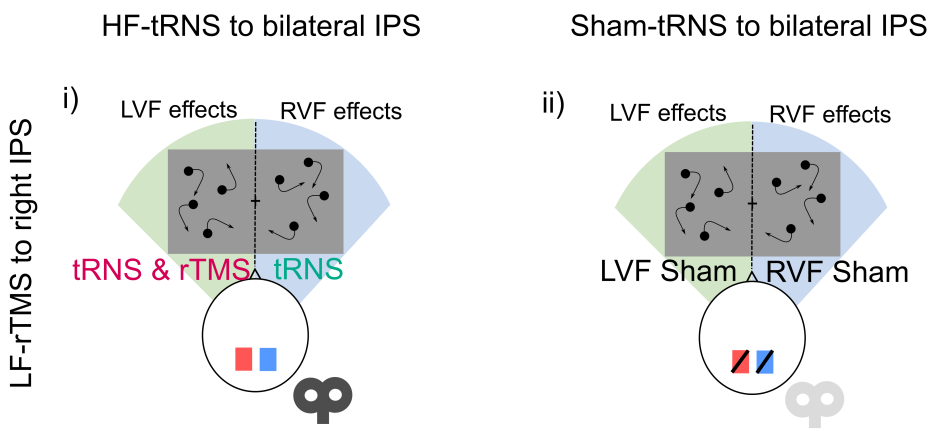

Figure 3: Multi-stimulation protocol – Experiment 2. Depiction of each stimulation protocol for experiment 2. Stimulation effect was compared to behavior in corresponding visual field of the sham condition.

Embedded within each stimulation protocol are two conditions defined by the visual fields (Figure 3). After HF-tRNS to bilateral IPS followed by LF-rTMS to right IPS, the behavior in the left visual field, contralateral to rTMS, showed the effect of both the tRNS and rTMS. Ipsilateral to the rTMS stimulation, in the right visual field, the behavior was affected by the tRNS alone. After sham tRNS to bilateral IPS and sham rTMS to the right IPS, behavior in both visual fields was unaffected by stimulation.

The data was analyzed for each visual field separately. A mixed ANOVA was run to determine the effect of stimulation and time for each condition. In one mixed ANOVA, the tRNS & rTMS stimulation effect in the left visual field was compared to the behavior in the left visual field following sham, across time. In a second mixed ANOVA, tRNS stimulation effects in the right visual field were compared to sham condition in the right visual field, across time. In order to determine a replication of experiment 1, an *a priori* analysis was performed to compare post-stimulation behavior in the tRNS & rTMS condition with sham baseline at the 80-94 minutes time-point. An *a priori* comparison was also planned for tRNS alone versus sham at 48-62 minutes after stimulation to determine replication of experiment 2. Post-hoc t-tests were also run for each time-point and corrected for multiple

comparisons to determine if any other stimulation effects were present. Confidence intervals (CI) will be reported with every t-test.

MRI acquisition. In experiment 1, functional and anatomical MRI data were acquired using a 32-channel phased-array head coil with a 3 Tesla MRI system (Siemens Prisma) at the Harvard Center for Brain Sciences. For the functional scans, contrasts of blood oxygenation level-dependent (BOLD) activity were obtained using an echo-planar imaging sequence (parameters: 65 slices; slice thickness = 2.40 mm; FOV = 211 mm; 2.4 x 2.4 x 2.4 voxel size; Flip Angle = 64; TR = 1; TE = 32.60 ms; multi-band accelerator factor of 5). High-resolution T1 scans were acquired using 3D MPRAGE protocol (parameters: 176 slices; FOV = 256 mm; 1x1x1 mm voxel resolution; gap thickness = 0 mm; TR = 2200 ms; TE = 1.69 ms).

MRI Analysis & localization of posterior IPS. The functional and anatomical data from experiment 1 were analyzed using BrainVoyager QX®. The first two volumes of each functional run were discarded to avoid saturation effects. Low-frequency noise and drift was removed using high-pass filtering during 3D-motion correction. The functional data was then aligned to the high-resolution anatomical data in native space. We convolved event timing with a hemodynamic model to generate predicted brain responses, with the associated beta weights estimated using a general linear model. To localize left and right posterior IPS, we contrasted the beta estimates for the unilateral MOT attend right > unilateral MOT attend left. With this contrast, activity in left IPS indicates lateralized attention to the right visual field, and activity in right IPS indicates lateralized attention to the left visual field (Figure 3). The most activated voxel within left and right posterior IPS was selected as the region for stimulation, individually measured for each subject (averaged coordinates across all subjects: Left IPS: x=-21.33(4.83), y=-83.53(3.01), z=19.00(4.87); Right IPS x=20.54(4.80), y=-83.35(4.19), z=17.96(5.56); depicted by red spheres in Figure 4). This data was saved in native space and retained for tRNS and TMS coil positioning.

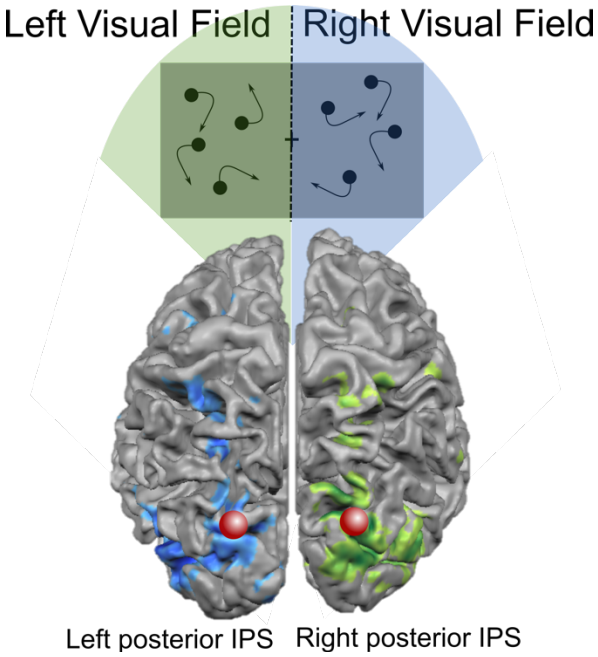

Figure 4: fMRI localizer for posterior bilateral intraparietal sulcus. Participants were presented with unilateral MOT in a fast-event related design. In each trial the participant had to fixate centrally and attend to targets in either the left or the right visual field, never both visual fields simultaneously. Right posterior IPS was localized through unilateral tracking in the left visual field, and left posterior IPS localized with unilateral tracking in the right visual field. The red spheres depict the average coordinates across all participants from experiment 1.

Stimulation Equipment & Coil Positioning. HF-tRNS was delivered using electrodes and a DC-Stimulator (Eldith-Plus, Neuroconn), at 1mA at random frequencies between 101-640 Hz. LF-rTMS was delivered using a MagPro® by MagVenture with a figure-8 coil with an inbuilt cooling system. Stimulation was performed at 1Hz with 65% machine output intensity (Battelli et al., 2009). In experiment 1, stimulation position was selected based on fMRI data which localized each participants' left and right posterior IPS (see *MRI Analysis & localization of posterior IPS* and Figure 4). Brainsight Frameless Stereotaxy System (Rogue Research, Montreal, Canada) was used to align the participant with their native space functional MRI data. In experiment 2, the averaged coordinates from experiment 1 were used to guide stimulation target. Participants were then aligned to the model brain within Brainsight Frameless Stereotaxy System (Rogue Research, Montreal, Canada), and then the averaged coordinates were selected for target. Once aligned, position of left and right posterior IPS in relation to the participants' head was used for positioning the electrodes for the tRNS, and the coil for the TMS. The coil was held with

the handle pointing backward, in a tangential orientation over the either left or right posterior IPS (Ruff et al., 2008; Battelli et al., 2009; Edwards et al., 2017).

Results

Experiment 1: Priming the Parietal Cortex at Rest

We examined the effect of multi-method non-invasive brain stimulation on bilateral attention, independent of visual field. After HF-tRNS to bilateral IPS, followed by LF-rTMS to IPS, we expected to prevent attention deterioration across time contralateral to the LF-rTMS stimulation, and we hypothesized this prolonged benefit to last beyond behavioral performance without stimulation intervention.

Stimulation effects collapsed across visual field. We first determine if stimulation impacts occur regardless of stimulation hemisphere.

Control behavior: Sustained attention without direct stimulation. The speed of the moving objects in the MOT was adjusted for each subject to perform at 75% correct. We examined our data to ensure our thresholding worked as designed, and indeed we found participants performed at 75% correct for the first 46 minutes after stimulation, with a decreasing trend in performance towards 94 minutes post-stimulation (Figure 5). At no time was the control condition significantly different from 75% correct ($p>0.05$).

Stimulation impact on sustained attention. Participants performed bilateral multiple object tracking (MOT) for 94 minutes after each stimulation protocol. The recordings provided MOT accuracy after: 1) tRNS & rTMS, 2) tRNS alone, 3) rTMS alone, and 4) control stimulation condition. We found a main effect of stimulation on behavior ($F(3,15)=3.22$, $p=0.02$), but no main effect of time on behavior ($F(5,15)=1.43$, $p=0.21$). We also found no interaction between stimulation and time on MOT ($F(3,15)=0.88$; $p=0.59$; RM ANOVA; Figure 5). Sustained attention is known to decrease as a function of time (Whitehurst et al., 2019), therefore we expected our stimulation effects to be most prominent late after stimulation. Furthermore, previous research has found the impact of the stimulation on

behavior following potential functional reorganization to be slow (Agosta et al., 2014), therefore, we examined the data for latent behavioral change.

tRNS & rTMS stimulation effects. To further investigate the impact of stimulation, we analyzed behavioral change between control and stimulation condition from 75 minutes onwards following stimulation (Whitehurst et al., 2019). We found participants performed 6.58% better following multi-method stimulation in comparison to control stimulation between 80-94 minutes post-stimulation ($t(15)2.75$, $p=0.015$, CI (1.48, 11.67); corrected t-test). No other time-point was significantly different from the control baseline performance ($p>0.05$).

tRNS- and rTMS-alone stimulation effects. In the single stimulation conditions (tRNS alone and rTMS alone), we found no significant difference in attention ability from control baseline. We expected to see an initial decrease in contralateral attention following LF-rTMS stimulation, but found no significant change in performance 0-14 minutes post-stimulation ($t(15)0.892$, $p=0.387$, CI (-3.66, 8.92)). Behavior was also not significantly different from baseline for the remaining 80 minutes ($p>0.05$). We also hypothesized a boost in attention capability at a time-point following HF-tRNS, and equally found no change in behavior ($p>0.05$). At 48 to 62 minutes post-stimulation the improvement in attention approached significance ($t(15)1.839$, $p=0.086$, CI(-0.54, 7.28)).

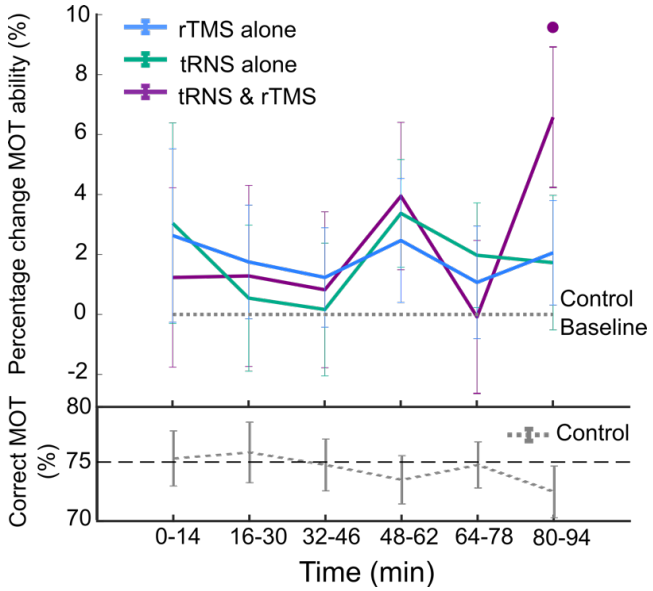

Figure 5: Experiment 1: Stimulation impact on MOT performance across time, collapsed across visual field. The grey dotted line at the bottom of the image depicts the percentage control MOT performance across time. In the top of the image, control data act as the baseline, and the percentage change in performance is presented in comparison to control after each stimulation condition. The • indicates $p<0.05$. The time-bins are each 14 minutes: two six-minute blocks, plus a two-minute break between each block.

Stimulation Effect by Visual Field. We compared directly the stimulation effects in the left and right visual fields using a three-way ANOVA across the stimulation conditions. In this analysis, the stimulation effects in each visual field were normalized to performance expected without stimulation, as observed in the hemifield not targeted by rTMS.

We found a marked difference between participant's attentional ability in left and right visual fields in the control baseline (t(15)2.43, p=0.028, CI(0.93, 14.20); t-test; Figure 5a). Although calibrated for a mean accuracy of 75% across both visual fields, visual tracking is more accurate in the left visual field as compared to the right visual field.

A three-way repeated measures ANOVA showed no significant interaction between visual field x stimulation x time (F(1,150)1.62, p=0.11), meaning that the interaction between stimulation and time does not seem to vary as a function of visual field. To determine the effects of stimulation in each visual field we run individual repeated measures ANOVAs on stimulation and time.

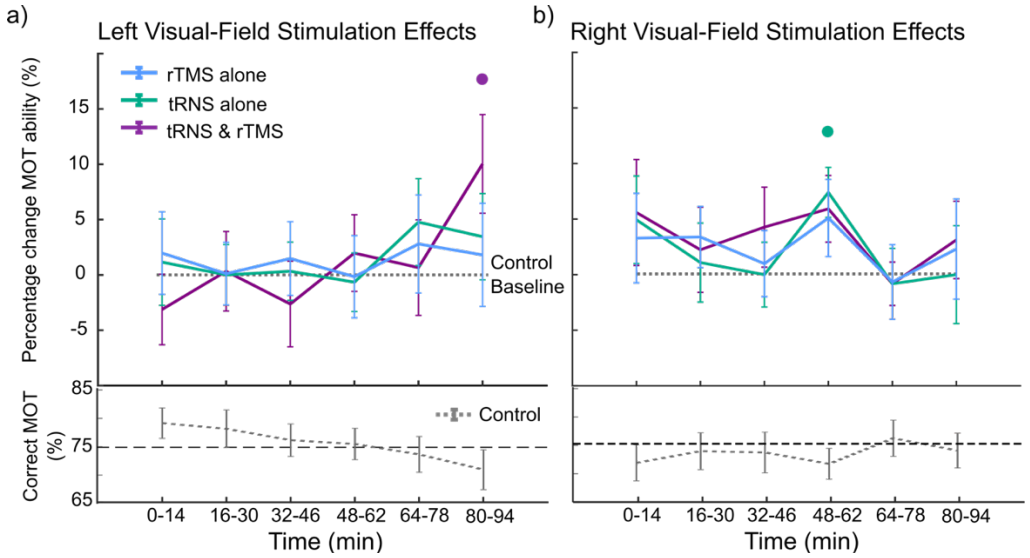

Figure 6: Experiment 1: Stimulation impact on MOT performance in each visual field across time. a) Stimulation impact on MOT in the left visual field. b) Stimulation impact on MOT in the right visual field. The grey dotted line at the bottom of the image depicts the percentage control MOT performance across time. The percentage change in performance after each stimulation condition is then presented above. The • indicates p<0.05. The time-bins are each 14 minutes: two six-minute blocks, plus a two-minute break between each block.

Left visual field stimulation effect. We found no main effect of stimulation on tracking performance (F(1,3)0.81, p=0.491), but a main effect of time (F(1,5)3.15, p=0.009; RM ANOVA). Moreover, MOT was significantly impacted by the interaction between stimulation and time (F(3,15)1.74, p=0.046; Figure 6a). When examining stimulation impact in comparison to control at individual time-points, we found a significant increase in attention between 80-94 minutes after tRNS & rTMS stimulation compared to control (t(15)2.21, p=0.04, CI(0.34, 19.72); corrected t-test). No other stimulation time-point was significantly above the control baseline.

Right visual field stimulation effect. In the right visual field, we found a main effect of stimulation on tracking accuracy (F(1,3) 2.74, p=0.04), but no main effect of time (F(1,5) 0.17, p=0.972). The interaction between stimulation and time had no significant impact on MOT (F(3,15)0.6, p=0.873; Figure 6b). Examining the stimulation impact at individual time-points in comparison to baseline, we found tRNS alone prevented attention deterioration in the right visual field at 48-62 minutes (t(15) 3.23, p=0.006, CI(2.51, 12.29);

corrected t-test). No other stimulation condition significantly affected behavior at each timepoint ($p>0.05$).

Experiment 2: Boosting Priming the Parietal cortex with Behavior

In Experiment 2 we expected to replicate the lack of attention deterioration up to 94 minutes after stimulation with priming prior to LF-rTMS. Importantly, we controlled the pre-stimulation brain state with HF-tRNS *and* behavior. We expected the additional behavioral priming to increase the potency of the LF-rTMS effect, beyond the priming benefit we found in experiment 1 with HF-tRNS alone.

Stimulation effects. Each participant received one type of stimulation, after which they performed 94 minutes of bilateral MOT. The recordings provided MOT accuracy after: 1) tRNS & rTMS in the left visual field, 2) tRNS alone in the right visual field, 3) sham in the left visual field and 4) sham in the right visual field. We found a significant interaction between stimulation and time in the left visual field ($F(1,11)=4.034$, $p=0.002$, mixed ANOVA; Figure 7a). This indicates that there is a difference between sham and tRNS & rTMS which is dependent upon time after stimulation in the left visual field. There was also a main effect of time ($F(1,11)7.20$,$p=0.00001$, mixed ANOVA), but no main effect of stimulation ($F(1,18)1.175$, $p=0.293$, mixed ANOVA). Therefore, time from stimulation significantly impacts the change in behavior. In the right visual field, we also found a significant interaction between stimulation and time ($F(1,11)3.551$, $p=0.006$, mixed ANOVA; Figure 7b), demonstrating behavior is affected differently for sham and tRNS alone across time, after stimulation. There was a significant main effect of time ($F(1,11)$ 4.864, $p=0.0006$, mixed ANOVA), but no main effect of stimulation ($F(1,18)0.224$, $p=0.627$). Therefore, behavior is modulated by time from stimulation in the right visual field.

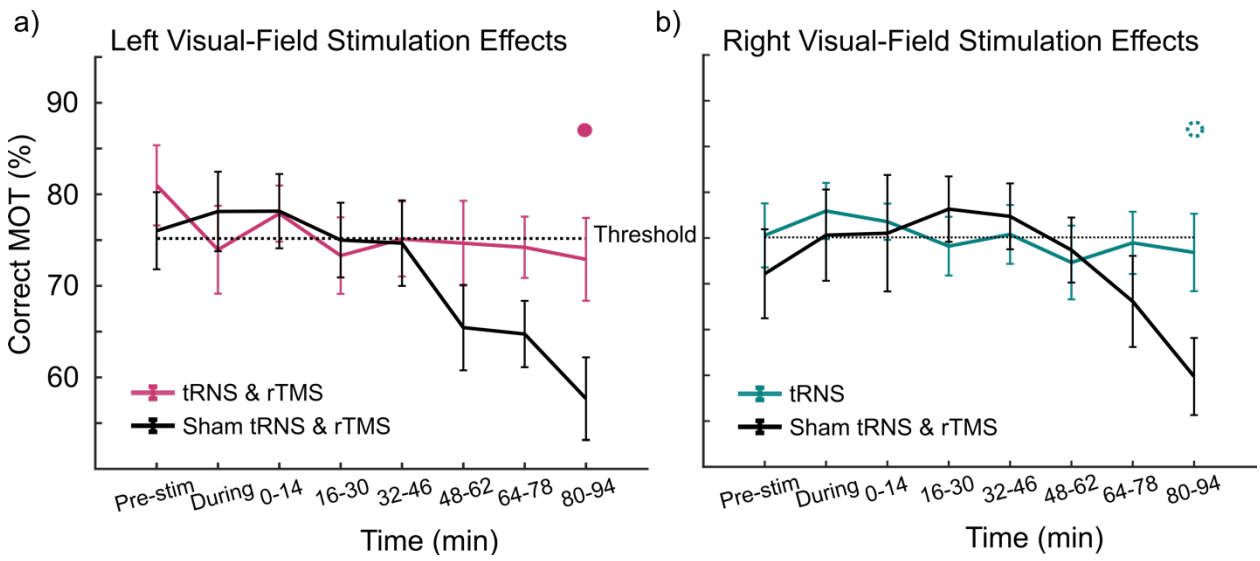

Figure 7: Experiment 2: Stimulation impact on MOT performance in each visual field across time. 6a) tRNS & rTMS stimulation impact on MOT relative to sham in the left visual field. 6b) tRNS alone stimulation impact on MOT in comparison to sham in the right visual field. The • indicates p<0.05. The dashed ° indicates p<0.05 after multiple comparisons. The figures depict the pre-stimulation performance, the performance during HF-tRNS/sham-tRNS, and the performance after stimulation – see the x-axis. The time-bins after stimulation are each 14 minutes: two six-minute blocks, plus a two-minute break between each block.

Multi-method stimulation effects. Our *a priori* hypothesis was a late effect of tRNS & rTMS, specifically 80-94 minutes post-stimulation. A comparison at that time-point showed a significant difference between tRNS & rTMS and sham (t(18)2.38, p=0.029, CI(1.79, 28.64), uncorrected between-subjects t-test). The post-hoc comparisons did not yield any significant differences between stimulation conditions at each time-point when corrected for multiple comparisons.

Single stimulation effects. The *a priori* comparison between behavior at 48-62 minutes after tRNS alone and sham was not significant (t(18)0.253, p=0.803, CI (-9.92, 12.64)). Although the difference between tRNS alone and sham in the right visual field was similar to tRNS & rTMS in the left visual field, no stimulation difference survived multiple comparisons. When the p-values were not corrected for multiple comparisons, tRNS alone did prevent attention deterioration between 80-94 minutes post-stimulation (t(18)2.27,p=0.036, CI (1.01, 26.09); uncorrected t-test).

Pre-stimulation performance. Due to the between subjects design, we ran a post thresholding, pre-stimulation block of trials to ensure there were no differences between the sham and stimulation groups. There was no significant pre-stimulation difference between tRNS alone and sham in the right visual field (t(18)0.817, p=0.425, CI (-17.72, 7.80); t-test) nor between tRNS & rTMS and sham in the left visual field (t(18)1.511, p=0.148, CI (-23.63, 3.85); t-test).

Discussion

We investigated the use of multi-method brain stimulation as an intervention to prevent decrement of sustained attention over time. In two experiments, we found multi-method stimulation maintained sustained attention at 75% correct, or above, up to 94 minutes post-stimulation. This is the first evidence to suggest multi-stimulation has a lasting impact on cognitive behavior, complementing the previous studies demonstrating lasting impact to physiological response (Iyer et al., 2003; Siebner et al., 2004; Lang et al., 2004; Fricke et al., 2010; Bocci et al., 2014). In previous experiments, high-frequency stimulation immediately followed by low-frequency stimulation has resulted in lasting inhibition, demonstrated physiologically by low amplitude MEPs (Iyer et al., 2003) and VEPs (Bocci et al., 2014). Our effect shows multi-method stimulation prevented attention deterioration, seemingly at odds with the previous inhibitory multi-method physiological responses. It is important to restate that our effect is likely due to a dynamic change of excitatory-inhibitory balance across the whole dorsal attention network. Like previous multi-method experiments, we expected multi-method stimulation to inhibit IPS, but unlike previous multi-method experiments, we expected the inhibition to cause compensatory activity from other nodes of the dorsal attention network (Paus et al., 1997; Grefkes et al., 2009; Lee & D'Esposito, 2012; Plow et al., 2014; Battelli et al., 2017). Importantly, our study demonstrated the impact of HF-tRNS followed by LF-rTMS to right IPS resulted in attentional compensation specific to the left visual field, directly targeted by the stimulation. The compensatory mechanism could have boosted visual field wide attention, but our data suggests the boost is more specific to the function of the targeted site. Experiments recording the impact of a single method protocol of LF-rTMS to the IPS have

shown a late boost in attention capability in patients (Brighina et al., 2003; Agosta et al., 2014) and a functional reorganization of the attention network beginning 36 minutes and lasting for 50 minutes after stimulation in healthy participants (Battelli et al., 2017). We believe that the lack of attention deterioration following multi-method stimulation, is a result of functional reorganization, like that of Battelli et al., (2017). Although behavioral change was not previously detected with network-wide function change following LF-rTMS alone (Battelli et al., 2017), multi-method stimulation may have caused a sustained enough inhibitory effect to result in behavioral impact. The lateness of the behavioral impact is likely due to the lasting sustained attention in our control conditions. Previous studies have demonstrated that sustained attention can deteriorate within 75 minutes (Whitehurst et al., 2019).

Along with a late boost in attention, one might expect an initial decrease in attentional capability following HF-tRNS and LF-rTMS multi-method stimulation. The initial decrement in attention could demonstrate the magnified inhibition expected directly following stimulation, however a decrease in attention capability was not found. The lack of behavioral decrement could be explained by the interaction of posterior IPS and its homotopic counterpart in the other hemisphere following targeted inhibitory brain stimulation. Using a different, but mechanistically similar, method to inhibit cortical function, researchers have found that an eye deprived of visual stimuli (through eye patching) *strengthens* in perceptual response directly after deprivation (Mrsic-Flogel et al., 2007; Lunghi et al., 2015; Kim, Kim and Blake 2017). Long-term potentiation (LTP) following deprivation and non-invasive brain stimulation hinge on similar underlying mechanisms including activation of NMDA receptors, concomitant GABAergic inhibition, and the production of acetylcholine neurotransmitter (Boroojerdi et al., 2001; Cheeran et al., 2009). This strengthening following monocular deprivation is in contrast to the usual functional decline associated with cortical inhibition. Even a short deprivation of 15 minutes can produce temporary strengthening of the deprived eye resulting in a change in perceptual behavior (Kim, Kim & Blake 2017). Similar to the mutual inhibition found between visual field specific attentional processing regions in temporoparietal areas, bistable perception between the two eyes is controlled via mutual inhibition between the

eyes in early visual areas (Binda et al., 2018). In monocular deprivation, a boost in performance of the deprived eye was thought to be due to the subsequent lack of inhibition from the functioning eye (Lunghi et al., 2011). This lack of inhibition is demonstrated by the overall decrease in GABA concentration in the early visual cortex which correlates with post-deprivation perceptual performance of the deprived eye (Lunghi et al., 2015). Therefore, the boost in functionality may be a method for stabilizing homeostatic gain response, where the deprived cortex attempts to restore balance between the homotopic brain regions (such as binocular balance, Zhou, Clavagnier, & Hess, 2013). This theory could indeed account for the effects we find following multi-stimulation of the posterior IPS. Posterior IPS is reliant on mutual inhibition with its homotopic counterpart to adequately induce lateralized attention (Corbetta et al., 2005). It may be that the multi-method stimulation still has an inhibitory effect, but this is mitigated in the behavior by the reduction of mutual inhibition from homotopic posterior IPS. Together these effects could cancel one-another, resulting in no change in behavior.

Interestingly, there is also no effect of LF-rTMS to the posterior IPS directly after stimulation, further supporting our interpretation of the initial null effect in the multi-method condition. LF-rTMS can result in an acute inhibitory behavioral or physiological response directly after stimulation (e.g. Battelli et al., 2009; Edwards et al., 2017), but has also been reported to have a null effect after stimulation in posterior IPS (Plow et al., 2014; Agosta et al., 2014; Edwards et al., 2017).

HF-tRNS alone also reduced the decrement of attention across time in the left visual field. In experiment 1, 48-60 minutes after stimulation, attention was maintained following HF-tRNS. Previous HF-tRNS studies have demonstrated almost an instantaneous boost in cognitive or physiological response following stimulation (Snowball et al., 2013; Herpich et al., 2018; Tyler et al., 2018). One main difference between our study and previous studies is the 15 minutes time-difference between the end of stimulation and the recording of behavior, a factor of our design. This factor may be sufficient to wash out an immediate excitatory effect on behavior following tRNS, while maintaining its late developing impact on the dorsal attention network, boosting attention ~90 minutes post stimulation. The

break between stimulation and recording was unavoidable due to the subsequent Sham- or LF-rTMS stimulation. We are unable to determine if the break between stimulation and recording alone would have been sufficient to reduce the impact of tRNS. A previous study found behavioral effects following HF-tRNS dissipated immediately after stimulation (Tyler et al., 2018) or can take multiple sessions to build sufficiently for behavioral impact (Herpich et al., 2019). Importantly, across our two experiments, we modulated task during HF-tRNS. In experiment 1, priming was performed with tRNS alone, but in experiment 2, participants performed bilateral MOT during tRNS. The addition of the task seemed to increase the longevity of tRNS, although not significantly following multiple comparisons. Previous research indicates the task may boost cortical excitability during stimulation, changing the impact of tRNS on cognitive performance (Snowball et al., 2013; Cappelletti et al., 2013; Edwards et al., 2019).

Our first experiment elucidated a visual field specific stimulation effect. Multi-method stimulation seemed to impact the left visual field, whereas HF-tRNS effect on cognitive performance was evident in the right visual field only. Left and right parietal cortex have been suggested to perform asymmetrically in attention across the visual fields, however there is variable evidence of the utility of these functional asymmetries in the parietal cortex (Corbetta et al., 2005; Szczepanski, & Kastner 2013; Sheremata et al., 2010). Leading theories suggest that the left parietal cortex attends predominately to the contralateral visual field (Kinsbourne 1977; Kim et al., 1999), while the right parietal cortex directs attention bilaterally (Kim et al., 1999; Corbetta et al., 1993; 1995). Along these lines, our study demonstrates that under specific conditions such as using a taxing task during bilateral attention (a function that we normally use during daily activities), we find a visual field specific response to stimulation that is likely due to the functional asymmetry of posterior parietal cortex (Sheremata et al., 2010: Sheremata & Silver 2015). This warrants further investigation, as it might suggest new strategies to sustain and improve attention in healthy and neurological populations.

Conclusion

Sustained attention is a limited resource, necessary across multiple cognitive tasks (DeGangi & Porges, 1990). Maintenance of attention across time is sought after in both

the clinical and healthy populations. Here, we demonstrate attention can be maintained without decrement for up to (and potentially beyond) 94 minutes following multi-method brain stimulation. Future research should be focused on the underlying network changes following multi-method stimulation. Network based compensation for inhibition of one focal node of a network using multi-method stimulation may prove useful in other cognitive domains, such as working memory (Compte et al., 2000). Efficiency of network-wide communication has been demonstrated to be of utmost importance in conserving cognitive reserve with age (Weiler et al., 2018).

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