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Exploring the Role of the Dorsal Attention Network in Sustained Attention with rTMS

Hidefusa Okabe

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Abstract

Sustained attention that is effortful during challenging cognitive tasks has been associated with robust activity in brain areas involved with cognitive control, collectively referred to as the dorsal attention network (DAN). In contrast, the periods of optimal sustained attention have been associated with relatively less DAN activity than periods of struggle. Optimal sustained attention may be less dependent on DAN function and more dependent on brain networks related to task automation such as the default mode network (DMN). Alternatively, optimal sustained attention may be recruiting DAN function efficiently, thus resulting in less overall activity. These two hypotheses were examined by temporarily disrupting DAN activity by applying repetitive transcranial magnetic stimulation (rTMS) to the frontal eye fields (FEF) in the DAN and then measuring sustained attention to a cognitive task. Subjects randomly received real or sham rTMS to the left or right FEF and then performed a modified go/no-go sustained attention task referred to as the gradCPT. For subjects receiving real rTMS to the right FEF, response accuracy decreased and reaction time variability increased on the gradCPT during periods of optimal sustained attention. The findings suggest that optimal sustained attention to cognitive tasks is supported by the refined, economical recruitment of right hemisphere DAN function.

Dedication

To mom, Tanaka Kiyomi, and dad, Okabe Chiaki,

without whose love and support, this thesis would not have been possible.

Acknowledgments

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Chapter I

Introduction

Sustained attention is the cognitive process of maintaining a goal-directed state over time while ignoring distracting, task-irrelevant information (Corbetta & Shulman, 2002; Hilti et al., 2013). For this reason, sustained attention is crucial for monitoring task performance and avoiding error. Problems with sustaining attention are one of the most common deficits in a wide range of clinical populations. Sustained attention is also important in healthy populations. For example, drivers who send text messages while driving have a higher chance of getting into an accident, compared to drivers who remain focused while driving (Caird, Johnston, Willness, Asbridge, & Steel, 2014). Thus, this ability to sustain attention to tasks effectively and efficiently represents an important research topic as it underlies human sustenance and survival.

Research has focused on a critical determinant in the quality of sustained attention, namely, that it is hard to maintain and thus fluctuates (Langner & Eickhoff, 2013). Maintaining sustained attention is difficult because it is an effortful activity and can thus be depleted over time (Warm, 2008). Fluctuations in sustained attention can also result from attention straying from the task due to irrelevant thoughts (referred to as mind wandering; Killingsworth & Gilbert, 2010) or boredom (Smallwood & Schooler, 2006). Cognitive experimental approaches suggest that the ability to sustain attention can be disrupted by a variety of natural and pathological conditions. For example, mental fatigue (Lim et al., 2010), anxiety (Ode, Robinson, & Hanson, 2011), age (West, 2002), sleep deprivation (Doran, Van Dongen, & Dinges, 2001) and alcohol consumption (Dougherty

et al., 1999) have been found to exacerbate fluctuations. Additionally, clinical syndromes such as ADHD (Castellanos et al., 2005) and PTSD (Swick, Honzel, Larsen, & Ashley, 2013) are characterized by failures in sustained attention. While these findings highlight how fluctuations in sustained attention can contribute to a range of clinical problems, how these fluctuations in sustained attention vary within a person over time still needs to be considered. Accurately and reliably measuring this variability remains challenging, controversial, and multifaceted.

Behavioral tests known as continuous performance tasks have been developed to operationalize sustained attention. The study of vigilance became a priority during World War II when radar operators were failing to detect targets after working for extended hours (Mackworth, 2014). The Mackworth clock test was one early task devised to examine vigilance decrement, which is the tendency for attention to decline and lead to performance inefficiency over time (Grier et al., 2003). Participants would observe a blank clock for up to 2 hours and report any infrequent double jumps in the point's movement. Modern renditions typically present a stream of stimuli on a computer monitor in a short inter-stimulus interval that is not self-paced, and requires detection of rare targets (Corkum & Siegel, 2006; Klee & Garfinkel, 1983). Such task was devised with the idea that functional deficits in attention regulation (such as impulsivity, inattention, and hyperactivity) would manifest behaviorally as degraded performance on the CPT. When the CPT is administered to subjects with disorders of attention, task performance is significantly worse than typical populations. Importantly, CPT performance and brain activity (measured with neuroimaging) have been significantly correlated (Hilto, Jann, Heinemann, Federspiel, Dierks, Seifritz, & Cattapan-Ludewig,

2013). For example, reaction time to targets was positively correlated with brain activation measured with functional magnetic resonance imaging (fMRI). Longer reaction times were correlated with more extensive brain activation in areas associated with cognitive control, relative to shorter reaction times.

There are two main types of CPTs. X CPTs require a response only to rare targets while ignoring nontarget stimuli (Ballard, 2001). One limitation of this type is that moment-to-moment changes in sustained attention cannot be examined, as responses are relatively sparse in time. Another subtype, the not-X CPT, circumvents this limitation by requiring a response to a majority of nontarget stimuli while withholding responses to rare target stimuli (Smilek, Carriere, & Cheyne, 2010). Through rapid sampling of behavior, the not-X CPT can reveal fluctuations in reaction time across time to show how some consecutive trials have similar reaction times relative to other epochs (Forster & Lavie, 2013). Overall speed, and importantly, response time variability in these CPTs may account for differences in distractability or difficulty with goal-oriented tasks like task preparation (Gerlach, Spreng, Gilmore, & Schacter, 2011). Reaction time variability increases with age (Hultsch, MacDonald, & Dixon, 2002; O'Halloran, Finucane, Savva, Robertson, & Kenny, 2013) and is more pronounced in those with attention disorders such as ADHD or PTSD (Adams, Roberts, Milich, & Millmore, 2011; Avisar & Shalev, 2011; Kofler, et al., 2013; Epstein et al., 2013; Swick et al., 2013) relative to typical populations. In addition to fluctuations, like all CPTs, the not-X CPT also allows for the operationalization of vigilance decrement, which is measured as the increase in missed targets (errors of commission), missed non-targets (errors of omission) and reaction time to targets over time. It is expected that there will be more commission and omission

errors as the participants expend attention longer. According to resource theory (Helton & Warm, 2008; Grier et al., 2003; Lavie, 2010; Parasuraman, 1979; Smit, Eling & Coenen, 2004), attention is a finite resource that declines when the person processes information effortfully (during a challenging cognitive task such as the not-X CPT), with the depletion of attentional resources manifesting as task performance deterioration. Moreover, the frequent responding to nontarget stimuli in the not-X CPT is thought to induce mind-wandering (or task-unrelated thoughts) as well as habituation (mindless responding). The failure to inhibit a response to a rare target is seen as a lapse in attention – a moment of mindlessness. In this "underload" theory, vigilance decrement is thought to originate from insufficient arousal due to boredom or disinterest (Eichele et al., 2008). Additionally, the subjective perception of the task as taxing may decrease motivation towards the task as means of limiting the expenditure of executive function (Kurzban, Duckworth, Kable, & Myers, 2013). The not-X CPT's sensitivity to many aspects in sustained attention make it an optimal candidate for the current study.

Fluctuations in sustained attention are related to the recruitment of the dorsal attention network (DAN). Functional neuroimaging has identified brain areas that respond with an increase in activation to goal-oriented cognitive tasks. These brain areas exhibit higher activity during task engagement relative to resting state. In addition, the activity of these brain areas is highly synchronized during cognitive tasks, as well as when the person is at rest. These findings led to postulating theoretical brain constructs referred to as task-positive networks (TPN), which are thought to support cognitively demanding tasks (Fox et al., 2005). The task-positive networks consist of the dorsal attention network (DAN), dorsolateral and ventral prefrontal regions, insula, and

supplementary motor area. In particular, cognitive tasks requiring the directing of

sustained attention have been found to activate the dorsal attention network (DAN),

which consists of the frontal eye fields and inferior parietal sulcus (Fox et al., 2005). For

optimal task performance, the DAN must operate within a particular range. Either the

under- or over-engagement of the DAN has been associated with sub-optimal task

performance. Consistent with data on optimal level of arousal, when the DAN sends top-

down signals to the specific sensory systems needed for a particular task (such as vision,

hearing), task-relevant information can be processed preferentially, resulting in effective

task engagement (Corbetta, Patel, & Shulman, 2008). In contrast, insufficient recruitment

of the DAN can lead to failures of maintaining goal-directed attention and sensory

modulation, causing performance to suffer (Hedden & Gabrieli, 2006; Weissman et al.,

2006; Padilla, Wood, Hale, & Knight, 2006). On the other hand, excessive expending of

the DAN may deplete the attentional reserves necessary for prolonged task performance.

The consequence of this depletion is illustrated in the attentional blink task (Raymond et

al., 1992) – a type of rapid serial visual presentation (RSVP). Unlike a CPT, the

attentional blink task is self-paced, as each RSVP sequence, or trial, lasts approximately

10 seconds. While not a CPT, the attentional blink task illustrates the effects of

momentary attention depletion (on the order of milliseconds) as the processing of a first

target disrupts the ability to detect a second target that closely follows. Specifically, in the

attentional blink task, each set of stimuli consists of a series of successive black letters

presented rapidly in the center of a screen. The subject is instructed to press a button

when a white letter (the first target, T1) is displayed, then she or he must identify the

subsequent letter (the second target, T2). After a brief pause, the subject is presented with

a new set. When T2 is presented within 500 ms after T1, subjects are often unable to detect T2. This failure is thought to result when attention is focused onto T1, leaving insufficient resources to process T2.

While extreme fluctuations in DAN activity predict the decline of performance during goal-oriented activities, the relationship between the DAN and moment-to-moment fluctuations in sustained attention is less clear. A meta-analysis (Langner & Eickhoff, 2012) examining the neural activity of sustained attention suggested that the DAN was involved with "energizing" (p. 884) processes that brought the mind back on track during task disengagement or distractions. However, findings on the relationship between DAN activation and sustained attention tasks have been less consistent. For example, DAN activation has been observed in sustained attention tasks requiring responses to stimuli that are presented rapidly (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003) as well as slowly (Lim et al., 2010). While additional research is necessary to clarify the contributions of the DAN to optimal sustained attention, the contributions of other neural networks also inform sustained attention.

The default mode network (DMN) also contributes to fluctuations in sustained attention during goal-oriented tasks. A set of brain areas is more active during rest than when focused on cognitive tasks (Greicius et al., 2003). Functional neuroimaging has identified high coherence in activity between the brain areas, collectively referred to as the task-negative network or default mode network: the posterior cingulate cortex, ventromedial prefrontal cortex, inferior parietal lobule, medial prefrontal cortex, and hippocampal formation (Buckner et al., 2008). In contrast to the task positive network's role in directing sustained attention, the role of the task negative network is thought to be

involved in reorienting attention away from engagement with the cognitive task (Hampson, Driesen, Roth, Gore, & Constable, 2010). Activation of the DMN has been associated with interrupting thoughts, unrelated to the goal-oriented task. These may include internal mentation, self-referential thinking, and mind-wandering (Buckner, Andrews-Hanna, Schacter, 2008; Buckner & Carroll, 2006; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Gusnard, Akbudak, Shulman, & Raichle, 2001; Mason, et al., 2007). Not surprisingly, fluctuations in neural activity between the DAN and DMN have been found to be inversely correlated (Uddin et al., 2009). For example, novel cognitive tasks requiring effortful engagement have been associated with high DAN activity and suppression of DMN activity (Corbetta et al., 2008). Further, the level of task mastery also affects DMN activity. For example, well-practiced tasks performed effortlessly have been associated with higher DMN activity and lower DAN activity (Mason et al., 2007) relative to less mastered tasks. During effortless performance, however, high DMN activity – which may result from mind-wandering (Christoff et al., 2009) – has been associated with greater errors in performance. The spike in DMN activity is thought to reflect an attentional lapse where cognition unrelated to the task intrudes into the processes necessary to maintain optimal sustained attention (Helton, Kern, & Walker, 2009). Thus, DMN activity can be associated with optimal or failures of task performance depending on the nature of the task.

Using functional neuroimaging, Esterman et al. (2014b) correlated DAN activity with fluctuations in sustained attention. In addition to measuring brain activity through fMRI, the study used a novel not-X CPT task referred to as the gradual onset continuous performance task to measure accuracy and reaction time variability. The study found two

types of responses during task performance, each associated with differential brain

activity. An effortful mode of processing (when the participant is struggling to keep up)

referred to colloquially as "out of the zone" was associated with greater reaction time

variability, error proneness and excessive DAN activity. In contrast, a stable, efficient

mode (when the participant excels at the task) colloquially referred to as "in the zone"

was associated with higher DMN activity (Figure 1). Based on these findings, two

hypotheses have been proposed as to why DAN activity was lower during efficient task

performance (relative to inefficient task performance). The hypotheses suggest that the

optimal sustained attention for excelling at tasks effortlessly requires a balance between

the DAN and DMN. The "automaticity hypothesis" suggests that optimal sustained

attention is less dependent upon top-down control from the DAN and recruits more of the

DMN, which is associated with automation through task mastery (Mason et al., 2007).

However, top-down control through the DAN may be recruited when performance begins

to suffer (from mindlessness or boredom). In contrast, the "effective recruitment

hypothesis" suggests that optimal sustained attention is established through refined,

economical recruitment of the DAN. This pattern of brain activation is akin to a

phenomenon in studies on the elderly population. For a given task, the elderly population

shows greater activation in brain areas relative to the younger population, because it is

thought that the brain processes are accomplished less efficiently with age (Cabeza,

Anderson, Locantore, & McIntosh, 2002). Optimal sustained attention and lower DAN

activity are correlated because the phenomena are observed together. To determine

whether these phenomena are linked mechanistically, it is necessary to explore if one

phenomenon causes the other phenomenon. For example, if DAN activity could be

manipulated experimentally, subsequent changes in sustained attention could be measured to determine whether there is a causal relationship. The findings would provide further insight into the contributions of DAN activity to maintaining sustained attention efficiently.

The role of the DAN in optimal sustained attention can be examined by manipulating the DAN with transcranial magnetic stimulation (TMS). The neuroimagingstudy by Esterman et al. (2014b) illustrated the involvement of DAN function in efficient sustained attention. Beyond involvement, however, the study could not conclude whether optimal sustained attention was dependent upon DAN function. Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, could help overcome this limitation. One stimulation protocol, repetitive TMS, can temporarily induce neural plasticity known as long-term depression locally, reducing neural activation. The resulting decrease in cortical excitability creates a 'virtual lesion' that subtly disrupts functions subserved by that brain area (Pascual-Leone et al., 1999; Pascual-Leone, Wassermann, Sadato, & Hallett, 1995). The present study seeks to build upon Esterman (2014b) by applying TMS to the frontal eye fields (Amiez & Petrides, 2009) to examine the functional role of the DAN in efficient sustained attention. TMS can be used to explore whether the lower activation observed in the DAN during efficient sustained attention can be accounted for by the automaticity hypothesis or effective recruitment hypothesis. The effective recruitment hypothesis postulates that the DAN plays a critical role in providing fine-tuned support for efficient sustained attention (in the zone). Accordingly, if TMS to the DAN disrupts gradCPT performance while the participant is in the zone, this would be evidence for efficient recruitment hypothesis. In
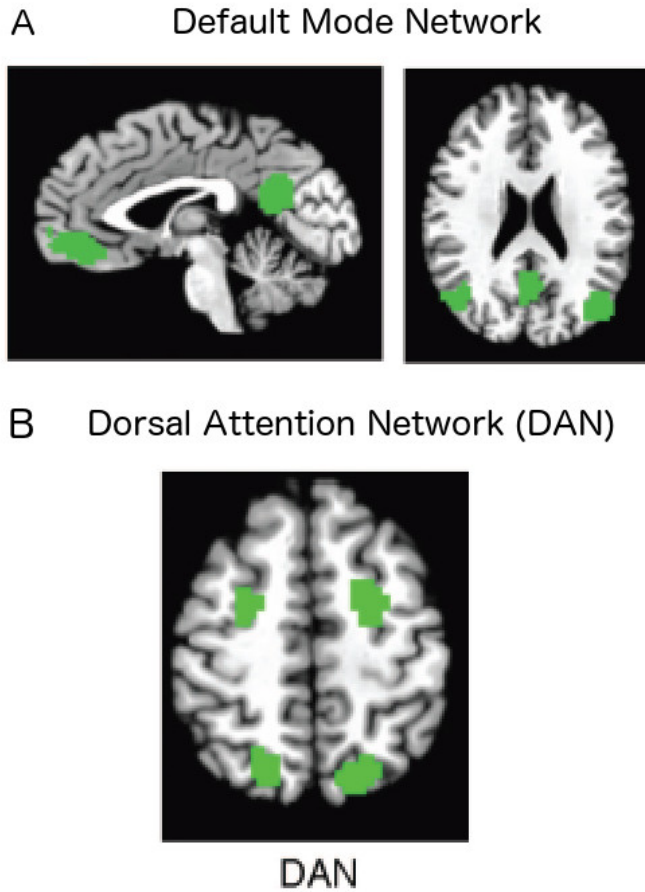
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A   Default Mode Network

B   Dorsal Attention Network (DAN)

DAN

Figure 1. Brain networks implicated in sustained attention (Esterman, Noonan, Rosenberg, & DeGutis, 2012). (*A*) Neuroimaging studies suggest that during rest (when there is no task engagement), activity in the default mode network is high, especially in the posterior cingulate, ventromedial prefrontal cortex, and bilateral lateral parietal cortex (Greicius et al., 2003). (*B*) In contrast, goal-directed task engagement is associated with suppression of the default mode network and increased activity in the dorsal attention network, with significant activations in the dorsal prefrontal cortex (frontal eye fields), inferior parietal sulcus (IPS), and dorsomedial frontal cortex (Szczepanski et al., 2013).

contrast, the automaticity hypothesis postulates that the DAN is less essential for

maintaining efficient sustained attention, and is recruited only when task performance is

suffering due to lapses in attention (out of the zone). As such, if TMS to the DAN

disrupts gradCPT performance while the subject is out of the zone, this would be

evidence in favor of the automaticity hypothesis.

Chapter II

Research Method

Participants

The target population in the current study was human subjects with no history of severe or persistent mental illness between the ages of 18 and 60 years old. Participants were recruited through online bulletin boards at Boston University and Northeastern University. Individuals were invited to contact the laboratory if interested in participating in a non-invasive brain stimulation study exploring attention. During the initial contact, the participant received a preliminary screening for TMS eligibility (See Appendix). After confirming eligibility, each participant was assigned a numeric code to protect confidentiality. Data from participants who were unable to complete the experiment were excluded from the final analysis. Subjects received compensation of $10 for travel and $25 per hour for receiving TMS, even if they did not complete the study.

Instruments

A behavioral task from an earlier study (Esterman et al., 2013) known as the gradual onset continuous performance task (gradCPT) was used to examine each participant's sustained attention. Specifically, the gradCPT measured the reaction time to target and non-target trials, and whether the responses were correct. A Macbook Pro running Matlab (The Mathworks Inc.) and Psychophysics Toolbox (Brainard, 1997) displayed stimuli to a 46-inch Sony flat-screen television display. The stimuli were 20

grayscale photographs cropped in a circle and presented on a white background. Half of the photographs were city scenes, and the other half were mountain scenes. Scenes were presented at random, such that in each trial, there was a 10% chance of a mountain scene (target), and 90% of a city scene (non-target). Each scene gradually transitioned into the next with a complete transition occurring over 800 ms. Subjects were instructed to respond to all city scenes by pressing the comma key on an Apple Bluetooth keyboard, and they were told to withhold responses from all mountain scenes. In addition, subjects were told to emphasize accuracy over speed.

FMRI data from an earlier experiment (Esterman et al., 2013) was used to guide TMS to the frontal eye field activations during target mountain trials. The presentation of mountain trials recruited transient activity in the frontal eye field, which is part of the DAN. The Brainsight 2 Neuronavigation System (Rogue-Research Inc.) detected the location of the TMS device relative to the subject's head in order to deliver TMS pulses to an intended brain area. This system consisted of an infrared sensor, a chair with a headrest, and a Macintosh computer (running Brainsight 2). TMS pulses were delivered from an Air Film Coil. The Air Film Coil is a handheld device that is shaped like a figure-of-eight (Rösler, Hess, Heckmann, & Ludin, 1989a), and contains magnetic coils that conduct electricity to emit electromagnetic pulses. The Air Film Coil was connected through a cable to a Magstim Super Rapid Plus repetitive stimulator, which is a device that stores electrical energy and generates the electromagnetic pulses. The infrared scanner detected the location of the Air Film Coil relative to the subject's head, and these coordinates were superimposed onto the subject's fMRI image loaded onto Brainsight 2. This ensured the accurate delivery of TMS pulses over a predetermined cortical area.

Procedure

Following approval by the Veterans Affairs (VA) Boston Healthcare System

Institutional Review Board and Harvard Committee on the Use of Human Subjects,

subjects were recruited from local universities. Next, subjects were asked to give written

informed consent and assured that all information gathered would be kept confidential.

Subjects also completed a health screening form to ensure eligibility for TMS based on

safety guidelines (See Appendix; Rossi, Hallett, Rossini, Pascual-Leone, & The Safety of

TMS Consensus Group, 2009). Specifically, subjects who were pregnant or had a history

of epileptic seizures or metal implants (such as cochlear implants, neurostimulators,

cardiac pacemakers) were excluded. Subjects were also informed about the rare reported

adverse reactions to TMS: seizures, headaches, muscle aches, and tinnitus. Data obtained

from each participant was assigned a unique identifier, with the master key stored in a

separate, secure location within the VA facility. The experiment was expected to take

under two hours to complete.

Localization

Prior to performing infrared neuronavigation (Sack et al., 2008) with the

Brainsight 2 apparatus, MRI images of prospective participants were loaded onto the

Macintosh computer running the Brainsight 2 software. Next, for each participant, the

brain areas to receive TMS were localized on each MRI image imported into Brainsight

2. As a guide, a functional activation map from a previous study (Esterman et al., 2013)

was used. This map illustrated brain activity, on average, among participants when

encountering target trials. Target trials recruited the DAN because detecting and

withholding the button press required cognitive control, and this functional activation as revealed through fMRI indicated the location of the FEF (which is part of the DAN). Using AFNI (Cox, 1996), this functional activation map was superimposed onto the brain of each prospective participant to determine the approximate location of the FEF. Next, the location of the left or right FEF was indicated on the participant's MRI loaded in Brainsight 2 in accordance to the participant's stimulation condition. In addition, using anatomical features (such as the central sulcus) as a guide, the brain area corresponding to the participant's right hand was marked on the MRI image loaded in Brainsight 2. This area was stimulated later to calibrate the power used for TMS to the participant.

Prior to actual stimulation, the subject's head was calibrated to MRI space using BrainSight 2 (Sack et al., 2008). Throughout the experiment, the subject was asked to wear a headband that was detected by the infrared sensor to determine the orientation of head movement. A metallic wand with a pointy tip, also detected by the infrared scanner, was placed on the surface of the subject's tip of nose, bridge of nose, and left and right intertragal notches of the ear. Brainsight 2 detected the headband and the metallic wand together to superimpose the coordinates of the participant's head onto the MRI image loaded into the system.

Motor Thresholding

Individual variability in cortical excitability affects participants' sensitivity to TMS (Bijsterbosch, Barker, Lee, & Woodruff, 2011). To ensure that individual differences in responsiveness to TMS do not confound with TMS effects, it is common pratice to equalize the effects of TMS across participants. The motor system was used as

a baseline reference because TMS pulses to the motor cortex results in an observable

effect (through muscle movement). This process is referred to as motor thresholding

(Rothwell, 1997). Each subject was asked to rest his or her right hand on his or her lap as

the coil head was placed on the scalp above the brain area marked for the right hand. A

single pulse was delivered to the subject starting at 65% power to determine whether any

movement of the fingers could be observed. Once a finger movement was observed for 5

out of 10 pulses, a single pulse was delivered at lower power until no finger movement

was observed. This level of power, referred to as the resting motor threshold, indicated

the baseline responsiveness to rTMS for that participant, and was used when delivering

rTMS pulses. Motor thresholding ensured that rTMS pulses had an equal effect across all

participants, despite between-subject differences in cortical excitability.

Design

To determine the number of participants, a power analysis was conducted using

the statistical program G*Power. The power was set to .8, a value commonly used in the

behavioral literature (Faul, Erdfelder, Lang, & Buchner, 2007). We examined three

studies with the most comparable stimulation protocols and behavioral procedures. A

similar study by Grosbras & Paus (2002) applied TMS to the left and right FEF to detect

changes in behavior (reaction time). The study used 5 subjects per FEF (10 total) to find a

significant three-way interaction, $F(1,8) = 6.03$, $p < .05$, Cohen's $d = 1.736$. To achieve

this effect size for the present study, a total of at least 7 subjects per group were needed

(14 total). Smith (2009) applied TMS to the right FEF to explore the effect of TMS on

reaction time in 15 subjects. The study found a significant effect for TMS condition and

validity, $F(1,10) = 5.86$, $p < .05$, Cohen's $d = 1.294$. To achieve this effect size for the present study, a total of at least 10 subjects per group were needed (20 total). Finally, a TMS study (Esterman, Verstynen, & Robertson, 2007) of the right intraparietal sulcus (which is also part of the DAN) detected significant differences in reaction time using 8 subjects, $F(1, 7) = 5.880$, $p < .05$, Cohen's $d = 1.833$. To achieve this effect size for the present study, a total of at least 7 subjects per group were needed (14 total). Given the large effects sizes and potential for publication bias in these cases, we chose the largest number of subjects in the power analysis and recruited 28 subjects as our total sample size (with 14 subjects to each frontal eye field group).

Each subject was randomly assigned to a left or right FEF condition, given that the FEF (which is part of the DAN) is located bilaterally (on the left and right hemispheres of the brain). Additionally, the sequence of real TMS and sham stimulation was randomly assigned in a counterbalanced (ABAB) design. During sham stimulation, the TMS coil head was oriented perpendicularly to the scalp, away from the neocortex. During stimulation, the TMS coil head was placed on the surface of the scalp, oriented towards the frontal pole (which is the forehead). Each stimulation session delivered 480 pulses of 1 Hz rTMS over 8 minutes. Each subject was offered optional earplugs during the stimulation.

Following a stimulation session, the subject placed his or her chin on the chin rest in front of a 46-inch Sony flat-screen television display. Subjects were handed an Apple Bluetooth wireless keyboard and were told to press any key when they were ready. Each gradCPT block (after TMS stimulation) took 5 minutes, thus within the window of time likely influenced by the rTMS. After completing two blocks (each consisting of a TMS

stimulation and a task), the physical coordinates of the subject's head were recalibrated to the MRI image in Brainsight 2. This ensured that the TMS coil head accurately delivered rTMS pulses over an intended brain area. Then, the remaining two blocks of TMS and task followed.

In the current study, the independent variables included stimulation condition, stimulation location, and state of attention. Only data from subjects who completed all sessions were included in the analysis. The dependent variable, commission error (CE), was automatically calculated by MATLAB as the percentage of correctly withheld responses to target trials. MATLAB also automatically calculated the variance time course (VTC) for each trial through taking the absolute value of the difference between the individual trial's reaction time and the mean reaction time. The VTC was used to examine each subject's trial-to-trial variation in reaction time. These results were then exported into a spreadsheet. The Statistical Package for the Social Sciences (IBM Corp.) was used to run a 2 x 2 x 2 ANOVA to determine whether TMS of the left or right FEF disrupted sustained attention performance accuracy and response stability, and further, if the effects interacted with attention state (in the zone vs. out of the zone performance) and side of stimulation (right vs. left FEF). Sustained attention recruits the DAN, which is lateralized to the right hemisphere of the brain (Ptak et al., 2010). Accordingly, it was expected that real TMS to the right FEF would degrade the quality of optimal sustained attention (in the zone), reflected in an increased VTC and CE. The experiment was expected to take less than two hours.

Chapter III

Results

Participants who were randomly assigned to receive TMS to the left FEF

consisted of 10 males and 4 females. The group of participants in the right FEF group

consisted of 5 males and 10 females. The groups differed significantly by distribution of

gender, χ^2 (1, $N = 28$) = 4.21, $p < .05$, with more males than females in the left FEF

group and more females than males in the right FEF group. The groups also differed

significantly by age, $t(26) = -2.37$, $p < .05$, with participants in the left FEF group being

older ($M = 21.50$, $SD = 2.79$) than the right FEF group ($M = 19.43$, $SD = 1.70$).

TMS Over the Right FEF

There was no significant difference in the CE rate by stimulation condition, $F(1,$

$13) = .0030$, $p > .05$. There was a significant difference in CE rate by attentional state,

$F(1, 13) = 19.92$, $p < .01$, with the CE rate being less while in-the-zone than out-of-the-

zone. Additionally, there was a significant interaction between stimulation condition and

attentional state, $F(1, 13) = 8.67$, $p < .05$, where there was a significant difference for in-

the-zone CE rate between real stimulation and sham stimulation, $t(13) = 3.02$, $p < .05$,

where the in-the-zone CE rate was significantly higher after real stimulation relative to

sham stimulation. In contrast, the out-of-the-zone CE rate was not significantly different

whether receiving real stimulation or sham stimulation, $t(13) = 1.61$, $p > .05$ (Figure 2).
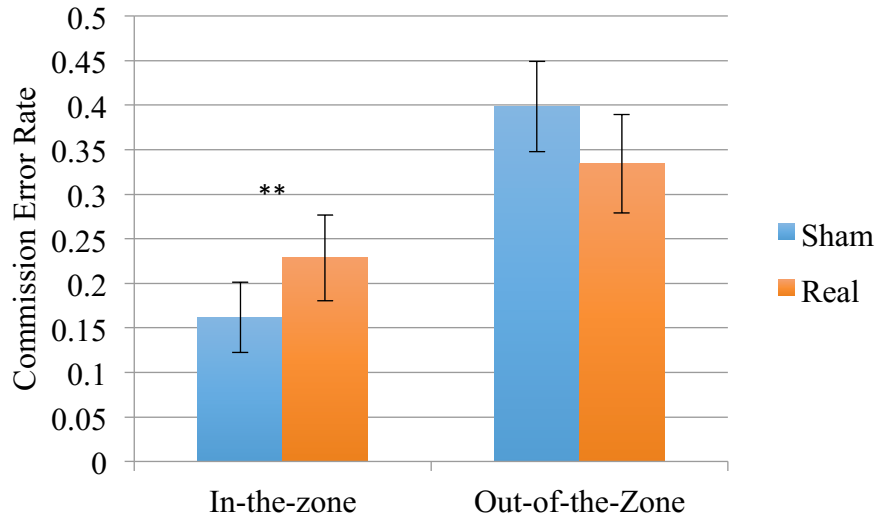
Figure 2. CE Rate After TMS to the Right FEF. There was a significant interaction (with the doule astericks denoting p < .01) between stimulation condition (sham, real) and attentional state (in-the-zone, out-of-the-zone). There was no significant main effect of stimulation condition, but there was a significant main effect of attentional state.

There was no significant difference in the CV by stimulation condition, $F(1, 13) = 1.263$, $p > .05$.

Additionally, there was a significant difference in the CV between in-the-zone and out-of-the-zone attentional states, $F(1, 13) = 102.910$, $p < .001$. Specifically, there was a significant difference in the CV depending on the attentional state, $t(13) = 2.79$, $p < 0.05$, where the CV was significantly higher during out-of-the-zone relative to in-the-zone attentional state. There also was no significant interaction between attentional state and stimulation condition, $F(1, 13) = .94$, $p > .05$ (Figure 3). As a whole, real stimulation to the right FEF significantly increased the CE rate and the CV rate while in-the-zone.
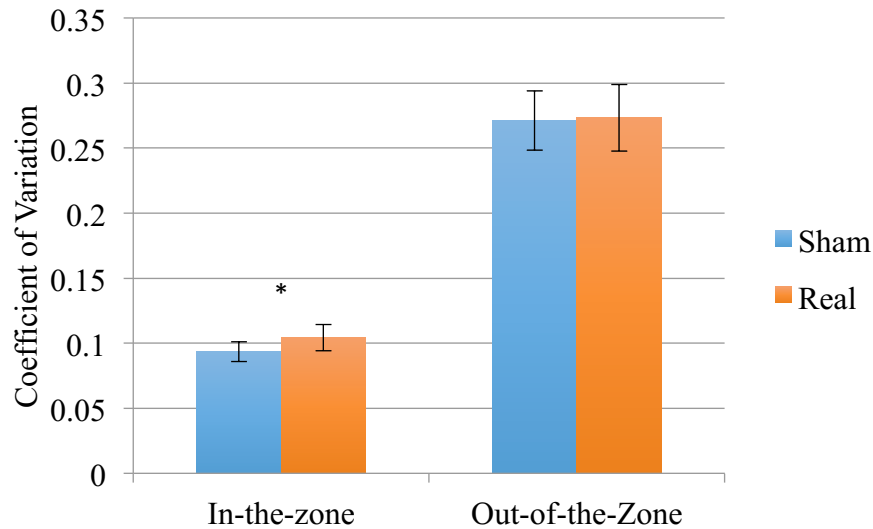
Figure 3. CV Rate After TMS to the Right FEF. There was no significant interaction between stimulation condition (sham, real) and attentional state (in-the-zone, out-of-the-zone). There was a significant main effect of stimulation condition (denoted by an asterick, $p < .05$), but there was no significant main effect of attentional state.

TMS Over the Left FEF

There was no significant difference in the CE rate by stimulation condition, $F(1, 13) = 3.81$, $p > .05$, but the difference was trending towards significance with real stimulation improving the CE rate when compared with sham stimulation. There was a significant difference in CE rate by attentional state, $F(1, 13) = 15.63$, $p < .05$, with the CE rate being less while in-the-zone relative to out-of-the-zone. There was no significant interaction between attentional state and stimulation condition, $F(1, 13) = .55$, $p > .05$ (Figure 4).

There was no significant difference in the CV rate by stimulation condition, $F(1, 13) = .27$, $p > .05$. There was a significant difference in the CV rate based on attentional
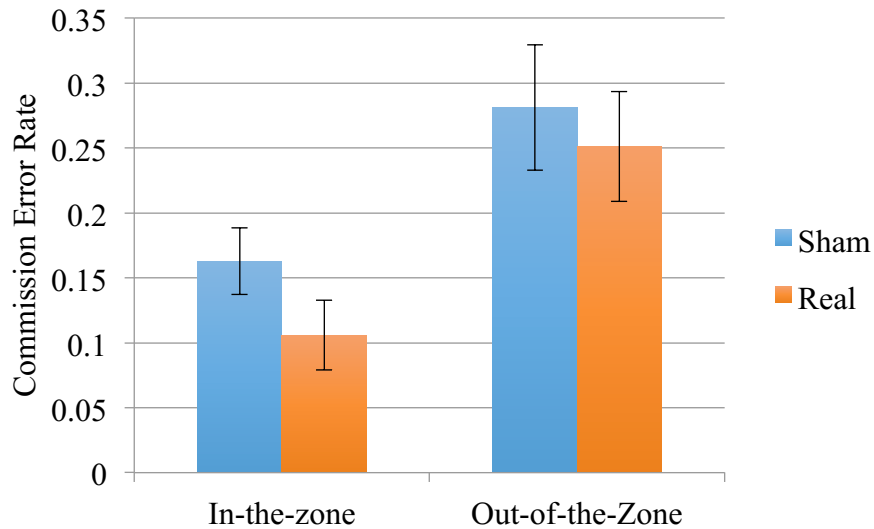
Figure 4. CE Rate After TMS to the Left FEF. There is no significant interaction between stimulation condition (sham, real) and attentional state (in-the-zone, out-of-the-zone). There was no significant main effect of stimulation condition, but there was a significant main effect of attentional state.

state, $F(1, 13) = 104.19$, $p < .001$, with the CV rate being significantly less while in-the-zone compared to out-of-the-zone. There was no significant interaction between stimulation condition and attentional state, $F(1, 13) = .48$, $p > .50$. In sum, real stimulation to the left FEF did not significantly affect the CE rate or the CV rate whether a subject was in-the-zone or out-of-the-zone (Figure 5).

Comparing TMS Over the Right FEF and Left FEF

There was no significant difference in the CE rate by stimulation condition, $F(1, 26) = 1.72$, $p > .05$, or side, $F(1, 26) = 2.461$, $p > .05$. However, there was a significant difference in the CE rate by attentional state, $F(1, 26) = 35.54$, $p < 0.001$, with the CE
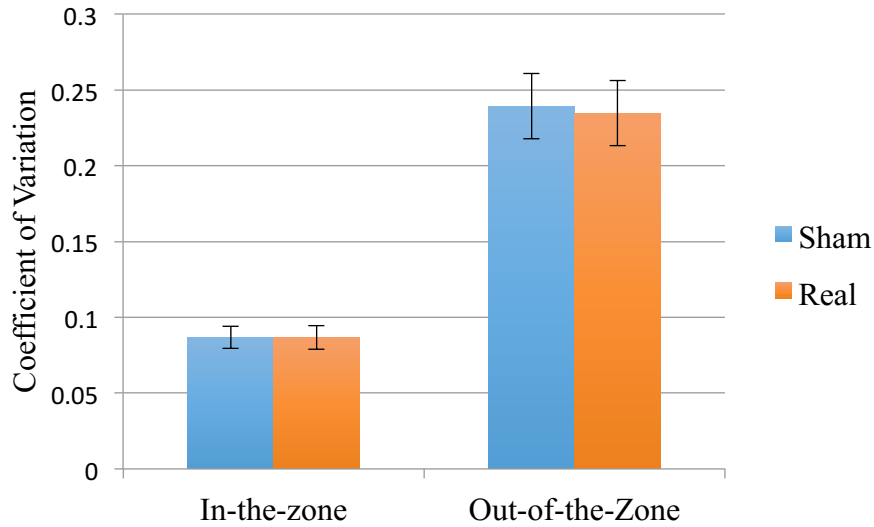
Figure 5. CV Rate After TMS to the Left FEF. There is no significant interaction between stimulation condition (sham, real) and attentional state (in-the-zone, out-of-the-zone). There was no significant main effect of stimulation condition, but there was a significant main effect of attentional state.

rate being greater while out-of-the-zone than in-the-zone. There were no significant interactions between attentional state and stimulation condition, $F(1, 26) = 3.25, p > .05$, attentional state and side, $F(1, 26) = .60, p > .05$, or attentional state and stimulation condition, $F(1, 26) = 3.25, p > .05$. However, there was a significant interaction between stimulation, attentional state, and side, $F(1, 26) = 7.52, p < .05$, where the CE rate while in-the-zone was higher after TMS to the right FEF relative to the left FEF.

There was no significant difference in the CV rate by stimulation condition, $F(1, 26) = .328, p > .05$, or side, $F(1, 26) = 1.27, p > .05$. There was a significant difference in the CV rate by attentional state, $F(1, 26) = 205.86. p < .001$, with the CV rate being less while in-the-zone relative to out-of-the-zone. There were no significant interactions

between stimulation and side, $F(1, 26) = 1.45$, $p > .05$, attentional state and side, $F(1, 26)$ $= 1.05$, $p > .05$, stimulation and attentional state, $F(1, 26) = 1.42$, $p > .05$, or between stimulation, attentional state, and side, $F(1, 26) = .16$, $p > .05$. In conclusion, real stimulation to the right FEF increased the CE rate and the CV rate while in-the-zone.

<p style="text-align:center">Controlling for Individual Differences</p>

Baseline gradCPT ability was measured as performance on the gradCPT after sham stimulation. To determine if the effects of real TMS on in-the-zone performance reported earlier could be accounted for by individual differences in gradCPT ability, baseline gradCPT performance was correlated to in-the-zone gradCPT performance following real TMS stimulation. The effects of real TMS on in-the-zone gradCPT performance was quantified as the difference in the CE rate while in-the-zone between real stimulation and sham stimulation, which was not found to correlate significantly with baseline CE rate while in-the-zone, $r = -.16$, $n = 28$, $p > .05$, or with overall baseline CE rate (averaging performance while in-the-zone and out-of-the-zone), $r = .08$, $n = 28$, $p > .05$.

When baseline gradCPT ability was compared between the left FEF group and the right FEF group, there was no significant difference in the CE rate, $F(1, 26) = 2.46$, $p > .05$, however the left FEF group had a marginally lower CE rate than the right FEF group. Additionally, while the CV rate did not differ significantly between the left FEF group and the right FEF group, $F(1, 26) = 1.27$, $p > .05$, the left FEF group had a more consistent reaction time than the right FEF group.

If the distribution of gender, age, or gradCPT capability differed between the left FEF group and the right FEF group, this sampling bias could have affected the statistical findings. However, including age as a covariate in a three-way repeated measures ANOVA (attentional state, stimulation condition, and side) still resulted in a three-way significance, $F(1, 25) = 6.32$, $p < .05$, such that the CE rate while in-the-zone was significantly higher after TMS to the right FEF relative to the left FEF. Additionally, including gender as a covariate in a three-way repeated measures ANOVA (attentional state, stimulation condition, and side) still resulted in a three-way significance, $F(1, 25) = 4.30$, $p < .05$, where the CE rate while in-the-zone was higher after TMS to the right FEF relative to the left FEF. The finding that real TMS to the right FEF disrupted in-the-zone gradCPT performance was not due to individual differences in age, gender, or gradCPT ability.

Chapter IV

Discussion

This study employed TMS to examine the functional contributions of the DAN during optimal sustained attention (i.e., in-the-zone) while performing a continuous performance task. Two hypothetical mechanisms were proposed on the basis of observing low DAN activity while a subject was in-the-zone. According to the automaticity hypothesis, efficient sustained attention is maintained by the DMN which facilitates automation through task mastery, and the DAN is recruited for top-down control only when struggling to maintain performance on the task (i.e., during out-of-the-zone attentional state). Thus, if TMS to the DAN impairs gradCPT performance while out-of-the-zone, this would be evidence for the automaticity hypothesis. In contrast, the efficient recruitment hypothesis suggests that optimal sustained attention requires refined, economical DAN recruitment. If TMS to the DAN impairs gradCPT performance while in-the-zone, this would be evidence for the efficient recruitment hypothesis. The current study found that TMS to the right DAN significantly increased comission errors and response time variability on the gradCPT while subjects were in-the-zone. These findings suggest that optimal sustained attention is dependent on the refined recruitment of the DAN in the right hemisphere.

Following TMS to the right DAN, in-the-zone gradCPT performance deteriorated, suggesting evidence for the efficient recruitment hypothesis for optimal sustained attention. Building on the finding that DAN activity was low during optimal sustained

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attention (Esterman et al. 2014a), this study used TMS to establish that the right FEF was essential for maintaining response accuracy and response consistency on the gradCPT. In other words, the low DAN activity during periods of optimal sustained attention can be interpreted as a refined, economical recruitment of cognitive control. During optimal sustained attention, the DAN may be exerting top-down cognitive control to make fine adjustments to task engagement (e.g., redirecting attention from a distracting thought back to the task). In contrast, when task performance is suffering, the DAN exerts maximum top-down cognitive control to direct full attention resources towards recovering task performance (Lock and Braver, 2008). The role of the right FEF in the precision control of sustained attention may be evidenced more in continuous performance tasks over trial-based tasks. In trial-based tasks (e.g., Posner cueing task), exerting maximum top-down control may be an effective task strategy because the periods of rest between the discrete trials may promote the replenishment of attentional reserves. In the case of a continuous performance task (e.g., not-X CPT) however, constant monitoring and frequent responding are required, so the exertion of maximum top-down control throughout the task may excessively expend attentional reserves (Olivers and Nieuwenhuis, 2006; Sadaghiani et al., 2009), leading to attentional depletion as manifested through a deterioration in task performance (Smit et al., 2004; Warm et al., 2008). This study demonstrated that optimal sustained attention is subserved by delicate top-down control by the right DAN in continuous performance tasks.

Out-of-the-zone gradCPT performance was not affected by TMS to the right DAN. When task engagement on the gradCPT is effortful (i.e., out-of-the-zone attentional state), DAN activity is high (Esterman et al., 2013). Accordingly, TMS to the

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DAN should disrupt the ability to recruit additional attentional resources when task performance is struggling. In contrast, it was found that TMS to the right FEF had no significant impact on out-of-the-zone gradCPT performance. This finding may be explained by the relationship of the FEF with respect to the DAN as a whole. Brain activation that extends beyond the FEF across the DAN may illustrate a reactive, inefficient strategy that aims to maximize the recruitment of top-down cognitive control in the face of deteriorating task performance (Hedden and Gabrieli, 2004; Paxton et al., 2008). As a result, the application of TMS to one structure within the right DAN (i.e., right FEF) may have been insufficient to affect gradCPT performance because other cortical regions within the DAN (e.g., inferior parietal sulcus) were compensating for right FEF functionality.

Applying TMS to the left FEF did not affect gradCPT performance. This finding may relate to known functional differences between the left FEF and right FEF. While the left FEF possesses a topographical map representing contralateral (i.e., right) visual space, the right FEF may possess a topographical map representing bilateral (i.e., left and right) visual space. The role of the left and right FEF may also differ specifically in visual sustained attention. TMS studies exploring the detection of visual stumili have suggested that the right FEF is more involved in the modulation of visual processing than the left FEF (Grosbras & Paus, 2003; Hung et al., 2011; Silvanto et al., 2006). In line with these findings, gradCPT performance deteriorated after TMS was applied specifically to the right FEF (as opposed to the left FEF), suggesting the right FEF's critical role in excelling at the task.

TMS to the right FEF may be disrupting the balance in DAN activity between the

brain hemispheres, leading to impairment in gradCPT performance. High performers on the gradCPT have a low commission error rate, meaning they successfully withhold responses to target stimuli (i.e., mountain scenes). Correctly refraining to press to a mountain scene was associated with more right DAN activation and less left DAN activation (Esterman et al., 2013). However, this idea of attentional control being right-hemisphere lateralized has been implicated more to the ventral attention network (VAN) (Corbetta and Shulman, 2011) and less to the DAN (Szczepanski et al., 2010; Vandenberghe et al., 2005), through studies relating brain injury to attentional control. For example, a lesion to the right hemisphere VAN may induce a condition known as hemispatial neglect where sustained attention and arousal are significantly impaired. Further, lesion studies have revealed that damage to neural tracts connecting the right VAN and right DAN is a common finding in hemispatial neglect. It is thought that the disruption of balance between these two networks in the right hemisphere results in a state where activity in the left DAN exceeds the right DAN, resulting in impaired sustained attention and arousal (Corbetta and Shulman, 2011). In the curent study, TMS to the right FEF could have temporarily depressed right DAN function, leading to a state of imbalance where left DAN activity was greater than the right DAN. The finding that TMS to the left FEF lead to a marginal improvement in gradCPT performance strengthens this possibility. The left FEF and right FEF share reciprocal neural projections to one another through the corpus callosum for the purpose of maintaining interhemispheric balance. Thus, TMS to the left FEF may have decreased the left DAN's ability to inhibit the right DAN. As a result, right DAN activity may have become disinhibited, engendering the observed subtle increase in gradCPT performance.

The findings from this study should be interpreted in the context of several limitations. When the power of the TMS pulse was adjusted to each subject, visible hand movement was used as a marker to determine the threshold of power for eliciting a motor response. While the right hand was observed carefully, future studies could achieve more precise calibration using objective, sensitive measures such as event-related potentials. Additionally, after calibrating the power of the TMS pulse to the motor cortex, the prefrontal cortex was stimulated with the same level of power with the assumption that the effect would be the same. Future studies could verify whether TMS altered brain activity by having participants do the gradCPT in an fMRI machine immediately after receiving TMS. Further, brain activity at the time of calibration could have been variable among participants (e.g., lack of sleep the night before, anxiety towards receiving TMS pulses, consumption of coffee before the experiment), thus affecting the efficacy of the TMS pulses (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008). Another concern was whether the effects of real TMS had subsided by the time the subject finished receiving sham TMS and was beginning the gradCPT. Studies have shown that the effects of TMS persist for the duration of stimulation (Nyffeler et al., 2006; Thut and Pascual-Leone, 2010). In the current study, the 8 min of TMS stimulation was followed by a washout period of at least 14 min (consisting of 5 min of gradCPT and the 8 min of sham TMS), dispelling concerns of real TMS affecting gradCPT performance after receiving sham TMS. Lastly, this between-subject study design compared gradCPT performance between left FEF subjects to right FEF subjects. Individual differences in gender, age, and capacity for gradCPT performance may have added additional variability to gradCPT performance or

responsiveness to TMS. While controlling for these individual differences using statistical analysis did not alter the conclusions of the study, future studies should adopt a within-subject design (where each subject receives stimulation to the left FEF and right FEF in random order) would have controlled for individual differences.

In this study, repetitive TMS pulses to the right FEF disrupted gradCPT performance while in-the-zone, suggesting that moderate activity in the right DAN is critical for maintaining optimal sustained attention during cognitive tasks. Other studies have applied rTMS to the inferior parietal cortex (Lee et al., 2013) or used a different type of neurostimulation known as transcranial direct current stimulation (TDCS; McIntire, McKinley, Goodyear & Nelson, 2014; Nelson, McKinley, Golob, Warm & Parasuraman, 2014). The findings from this study contribute to existing literature by establishing that it is possible to illustrate the neuromodulatory role of the DAN by applying rTMS pulses to the left and right FEF. Research on the modulation of attention using brain stimulation could inform and improve existing treatments that have been found to allay the symptoms in attentional disorders such as hemispatial neglect (Van Vleet & DeGutis, 2013). Additional research on this area will help develop more efficacious treatments for persons with attentional disorders.

Appendix

1. Do you have a history of epilepsy, convulsions, or seizures?   Yes   No
2. Do you have a history of fainting, or syncopes?   Yes   No
3. Have you ever had a consussion, traumatic brain injury, or head injury where you lost consciousness (car accident, sports injury, fall, etc)?   Yes   No
    If yes, describe: _____   Age _____
4. Do you experience ringing in the ears, or is your hearing impaired in any way?
          Yes   No
    If yes, describe: _____
5. Do you have cochlear implants?   Yes   No
6. Are you pregnant? (female only)   Yes   No
7. Do you have metal in your brain, skull, or anywhere in your body?   Yes   No
    If yes, describe: _____
8. Do you have an implanted neurostimulator (deep brain stimulation, epidural/subdural, vagus nerve stimulation)?   Yes   No
9. Do you have a cardiac pacemaker or intracardiac lines?   Yes   No
10. Do you have a medication infusion device?   Yes   No
11. Are you currently taking, or have you ever taken, tricyclic antidepressants or neuroleptic agents?   Yes   No
    If yes, describe when these medications were taken: _____
    _____
12. Are you currently taking any other medications?   Yes   No
    If yes, please list: _____
13. Have you experienced problems with TMS in the past?   Yes   No
14. Have you experienced problems with MRI in the past?   Yes   No
15. Do you have a history of frequent headaches, such as migraines?   Yes   No
16. Do you have a history of electroconvulsive treatment?   Yes   No
17. Are you left handed, right handed, or ambidextrous? (circle one)
          Right   Left   Ambidextrous
18. What is your first language? _____
19. Are you interested in participating in a study that uses TMS, a safe and non-invasive technique where a magnetic coil delivers low-level magnetic pulses above your scalp?
          Yes   No

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