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Network-targeted cerebellar transcranial magnetic stimulation improves attentional control

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ABSTRACT

Developing non-invasive brain stimulation interventions to improve attentional control is extremely relevant to a variety of neurological and psychiatric populations, yet few studies have identified reliable biomarkers that can be readily modified to improve attentional control. One potential biomarker of attention is functional connectivity in the core cortical network supporting attention - the dorsal attention network (DAN). We used a network-targeted cerebellar transcranial magnetic stimulation (TMS) procedure, intended to enhance cortical functional connectivity in the DAN. Specifically, in healthy young adults we administered intermittent theta burst TMS (iTBS) to the midline cerebellar node of the DAN and, as a control, the right cerebellar node of the default mode network (DMN). These cerebellar targets were localized using individual resting-state fMRI scans. Participants completed assessments of both sustained (gradual onset continuous performance task, gradCPT) and transient attentional control (attentional blink) immediately before and after stimulation, in two sessions (cerebellar DAN and DMN). Following cerebellar DAN stimulation, participants had significantly fewer attentional lapses (lower commission error rates) on the gradCPT. In contrast, stimulation to the cerebellar DMN did not affect gradCPT performance. Further, in the DAN condition, individuals with worse baseline gradCPT performance showed the greatest enhancement in gradCPT performance. These results suggest that temporarily increasing functional connectivity in the DAN via network-targeted cerebellar stimulation can enhance sustained attention, particularly in those with poor baseline performance. With regard to transient attention, TMS stimulation improved attentional blink performance across both stimulation sites, suggesting increasing functional connectivity in both networks can enhance this aspect of attention. These findings have important implications for intervention applications of TMS and theoretical models of functional connectivity.

Introduction

Attentional control, the ability to select and maintain task-relevant information processing, is critically important for many essential activities of daily life, from effectively accomplishing work/school activities (Kalechstein et al., 2003; Lam and Beale, 1991) to driver safety (Ball et al., 1991; Edkins and Pollock, 1997; Schmidt et al., 2009), and is impaired in a wide range of neurological and psychiatric populations. As attention underlies many other higher-level cognitive functions, attentional impairments can result in deficits of diverse cognitive functions (Fortenbaugh et al., in press). Thus, improvement of attentional control has widespread clinical appeal.

Converging evidence directly implicates a set of frontal and parietal regions, termed the dorsal attention network (DAN), in attentional control (i.e., preparing, initiating, and maintaining goal-directed attention; e.g., Corbetta et al., 2000; Kastner et al., 1999; Langner and Eickhoff, 2013; Fortenbaugh et al., in press). Recently, the DAN has been shown to include both cortical and cerebellar nodes (Brissenden et al., 2016). In contrast, during active engagement of the DAN, the medial prefrontal cortex, the precuneus and lateral inferior parietal regions, known as the default mode network (DMN), are commonly found to be deactivated (Buckner et al., 2008; Raichle

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et al., 2001; Raichle and Snyder, 2007). Thus, there is evidence that successful completion of attentional tasks requires some form of upregulation of the DAN and concomitant decreased response within the DMN.

Functional connectivity (FC) in the DAN is also related to attentional control. Specifically, increased FC within the DAN at rest corresponds with improved task performance (Hampson et al., 2006). Further, when attention is engaged, it dynamically modifies FC in the DAN. For example, studies have found greater within-DAN FC during the performance of a sustained attention task compared to rest (Bray et al., 2015). Critically, increased connectivity within the DAN, especially between cerebellar and cortical network nodes, corresponds to increased activation during multiple attentional tasks, suggesting a clear link between connectivity and cognitive performance (Brissenden, et al. 2016). In addition, greater resting connectivity between DAN and DMN is associated with poor attentional control and greater distractibility (e.g., Poole et al., 2016). In contrast, within-DMN FC has been less consistently linked with attention (Barber et al., 2015; Bonnelle et al., 2011). Together, FC data suggests that internal communication within the DAN, as well as distinctiveness from task-negative DMN, are reliable markers associated with better performance during tasks requiring voluntary attentional control.

Transcranial magnetic stimulation (TMS), a non-invasive intervention, might have the potential to enhance attention or ameliorate attention deficits due to its unique ability to modulate both brain activity and connectivity (Walsh and Pascual-Leone, 2003; Eldaief et al., 2011; Halko et al., 2014; Wang et al., 2014; Wang and Voss, 2015). Specifically, a key feature of TMS is that the effects are not limited to the stimulated region, but are further distributed to anatomically-connected sites (Ilmoniemi et al., 1997; Bohning et al., 1999; Morishima et al., 2008). These distributed effects of TMS, achieved through trans-synaptic activation (Amassian et al., 1990; Paus et al., 1997), can induce changes in functional connectivity (FC) between regions that include both the stimulated region (Eldaief et al., 2011; Halko et al., 2010; Wang et al., 2014; Wang and Voss, 2015), and its connected networks (Grosbras and Paus, 2002; Taylor et al., 2006; Silvanto et al., 2006; Ruff et al., 2006; Halko et al., 2014). Thus, effective therapeutic TMS interventions must rely upon an understanding of the targeted network, distributed effects (Dubin et al., 2017; Drysdale et al., 2017), as well as the state of the stimulated neuronal population (Silvanto et al., 2008; Miniussi et al., 2010).

TMS applied to regions of the DAN, such as the frontal eye field (FEF) and other frontal-parietal regions, has shown to decrease performance of orienting, distractor suppression, visual detection, and sustained attention (Chambers and Mattingley, 2005; Capotosto et al., 2012; Esterman et al., 2015). Stimulation of the FEF has also been found to increase BOLD responses in distal, but connected visual cortex, improving visual detection and enhancing excitability of visual areas (Grosbras and Paus, 2002; Taylor et al., 2006; Silvanto et al., 2006; Ruff et al., 2006). In contrast to the DAN, no work to our knowledge has considered the effects of DMN stimulation on attentional performance; this may partially be due to the inaccessibility of the core cortical regions of this network. Notably, an increase in the resting FC within the DAN and the DMN occurred after stimulation of distinctly localizable regions of the cerebellum (Halko et al., 2014), although this study did not measure cognition. Specifically, intermittent theta burst TMS (iTBS) increased resting FC within the DAN or within the DMN (Halko et al., 2014) after stimulation that targeted midline and lateral regions of the cerebellum respectively, regions exhibiting functional connectivity with cortical DAN and DMN regions. This stimulation of the cerebellum could induce these network-specific modulations by virtue of an indirect connection to brain networks via the thalamus (Schmahmann and Pandya, 1997; Strick et al., 2009) which can be observed with resting state FC (Buckner et al., 2011).

As attentional performance has been associated with FC within the DAN (Hampson et al., 2006; Bray et al., 2015; Brissenden et al., 2016), we examined whether TMS applied to the cerebellar node of the DAN could enhance attention. Since attentional performance is less associated with FC within the DMN, we contrasted cerebellar DAN stimulation to cerebellar DMN stimulation (as an active control). Specifically, we compared performance on a sustained attention task, the gradual onset continuous performance task (gradCPT), and a transient attention task, the attentional blink task pre/post iTBS. ITBS was applied at the midline cerebellar node of the DAN and the right cerebellar node of the DMN. We accessed the DAN/DMN via a network-based localization method (see localization approach in method section). Behavioral blocks preceding cerebellar-iTBS served as baseline performance measures. Given the importance of DAN activity and FC for sustained and selective aspects of attention, we hypothesized that stimulation of the DAN cerebellar node would improve attentional performance. Specifically, following cerebellar DAN stimulation, we predicted 1) reduced commission errors on the gradCPT, particularly while in the zone (Esterman et al., 2015), 2) enhanced ability to overcome the attentional blink as measured by fewer errors in reporting the second target, and 3) absence of attentional modulation following DMN cerebellar stimulation.

Method

Participants

Fifteen healthy participants (11 males, mean age = 22.27, SD = 3.69) were recruited from Northeastern University and Boston University. All participants met the screening criteria for TMS (Rossi et al., 2009) and reported to be free of neurologic and psychiatric conditions. Subjects gave informed consent and the study was approved by the VA Boston Healthcare System IRB.

Overall experimental procedure

Using a within-subjects cross-over design, participants completed two 1–2 h TMS sessions separated by a washout period of 48 hours to 2 weeks. Participants received stimulation to two different cerebellar sites (Fig. 1; based on DAN or DMN connectivity, see Localization below) with order randomly counterbalanced across participants. Note the current study considered DMN an active control, which has distinct advantages to using sham (Duecker and Sack, 2015).

At both sessions, immediately pre- and post- TMS, participants completed 1) the gradual onset continuous performance task (gradCPT), a go/no-go sustained attention task, and 2) the attentional blink task, a measure of selective attention. GradCPT was always performed before the attentional blink task (Fig. 2). The average time

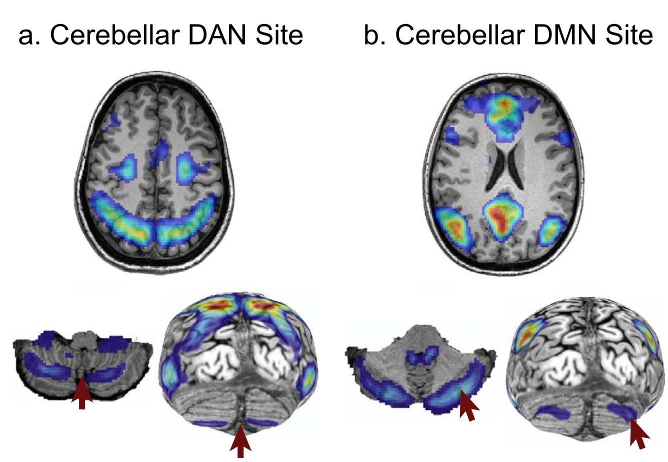

Fig. 1. TMS targets (arrows) localized using individual resting-state cortical functional connectivity with (a) cortical dorsal attention network (DAN) and (b) default mode network (DMN).

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