



## Review article

# Hypothesis for cognitive effects of transcranial direct current stimulation: Externally- and internally-directed cognition

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## ABSTRACT

A comprehensive explanation is lacking for the broad array of cognitive effects modulated by transcranial direct current stimulation (tDCS). We advanced the testable hypothesis that tDCS to the default mode network (DMN) increases processing of goals and stored information at the expense of external events. We further hypothesized that tDCS to the dorsal attention network (DAN) increases processing of external events at the expense of goals and stored information. A literature search (PsychINFO) identified 42 empirical studies and 3 meta-analyses examining effects of prefrontal and/or parietal tDCS on tasks that selectively required external and/or internal processing. Most, though not all, of the studies that met our search criteria supported our hypothesis. Three meta-analyses supported our hypothesis. The hypothesis we advanced provides a framework for the design and interpretation of results in light of the role of large-scale intrinsic networks that govern attention.

## 1. Introduction

Non-invasive methods of stimulating the human brain have the potential to reveal causal relations between cognitive behavior and regional brain activity. The method of transcranial direct current stimulation (tDCS) in particular has advantages of accessibility, low cost, and low risk. The growing literature from tDCS is characterized not only by a large range of cognitive findings but also by a dearth of explanatory hypotheses on the relation between site of stimulation and effects on cognitive performance. Effects of tDCS have been observed across a spectrum of cognitive functions, e.g., motion perception (Blumberg et al., 2015b), complex task acquisition (Scheldrup et al., 2014), vigilance (Nelson et al., 2014), and working memory (WM) (Fregni et al., 2005). However, there has been little effort focused on interpreting the large range of findings obtained from a relatively small number of stimulation sites.

The lack of explanatory hypotheses is particularly important insofar as cognitive tDCS studies are commonly interpreted according to the putative function of cortex directly under the stimulating electrode. There are several problems with that approach. First, the few studies that have measured the BOLD signal under the anodal electrode during stimulation have observed both decreased activation (Meinzer et al., 2013, 2012) and increased activation (Alekseichuk et al., 2016). Second, meta-analyses of this literature reveal a complex relation between site of stimulation and cognitive function. Regarding studies that stimulated prefrontal cortex, Brunoni's meta-analysis on n-back tasks

concluded from 33 studies that F3 or F4 anodal stimulation modulated speed (but not accuracy) of WM (Brunoni and Vanderhasselt, 2014). Another meta-analysis (Mancuso et al., 2016) compared effects of F3/F4 anodal stimulation during WM training with effects of stimulation on WM task performance (after training). They found effects from F3 stimulation but not from F4 stimulation (Mancuso et al., 2016). However, if stimulation of F3/F4 activates PFC selectively, then performance of tasks mediated in other areas should be unaffected. Dedoncker's meta-analysis on 61 studies, which included a large range of tasks, found that the same F3 or F4 anodal stimulation speeded responding not just for memory tasks but also across a number of non-memory tasks in healthy individuals (Dedoncker et al., 2016). It is evident then that tDCS over PFC affects a range of tasks. On the other hand, effects of tDCS do not appear to be general. The meta-analysis of Mancuso found no effect of parietal tDCS on WM (Mancuso et al., 2016), despite established evidence of an important role for parietal cortex in WM storage (Postle, 2006).

These meta-analyses show that interpretations based solely on what is known of the function of the cortex directly under the anode cannot satisfactorily account for the empirical findings. In attempting to understand this literature, it is important to consider the growing evidence that cognitive functions are not solely mediated in isolated brain regions but rather in large-scale intrinsic functional connectivity networks (Bressler, 1995; Dosenbach et al., 2008; Fuster, 2006; Ridderinkhof et al., 2004; Smith et al., 2009). Based on this evidence, we advance the testable hypothesis that much of the cognitive tDCS

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literature can be interpreted as reflecting selective activation of a fundamental organization of neurocognitive function – internally and externally directed cognitive states mediated by the default mode and dorsal attention networks, respectively (Fornito et al., 2012; Fox et al., 2005; Greenwood and Parasuraman, 2016; Spreng et al., 2013). We examine this hypothesis in light of the existing literature including meta-analyses. We do not provide another meta-analysis, but rather we interpret the sizeable and confusing literature in light of what is known of neurocognitive functioning.

The method of tDCS involves the application of small amounts of direct current (0.5–2 mA) through the skull and scalp into cortex. In animals, this induces a change in the resting state potential of pyramidal neurons directly under the electrode (Radman et al., 2009). In humans, tDCS over motor cortex modulates motor evoked potentials, allowing assessment of causal relations between tDCS and the functioning of motor cortex under the stimulating electrode. However, in contrast to motor behavior, for human cognitive behavior the relation between site of stimulation and cognition is more tenuous. With tDCS we know where the current initially enters the brain but we do not know all the brain structures affected. Finite element models (FEM) make claims about effects of tDCS on specific brain regions (Datta et al., 2009), but these models make a number of assumptions about the flow of the electrical field through cortex that have not been rigorously tested. Yet, the few studies that have actually measured cortical activation directly under the stimulating electrode have observed both decreased (Meinzer et al., 2013, 2012) and increased (Aleksichuk et al., 2016) activation following tDCS, revealing complex effects of stimulation. There is empirical evidence that tDCS affects large-scale networks (Callan et al., 2016; Keeser et al., 2011; Meinzer et al., 2012). Yet, most cognitive tDCS studies have interpreted their findings only with reference to the putative function of cortex directly under the electrodes (e.g. Blumberg et al., 2015a,b; Fregni et al., 2005). Few studies have interpreted their findings with reference to intrinsic networks (e.g. Callan et al., 2016).

There is growing evidence that neurocognitive function is dominated by adaptive alternation between two cognitive states: internally-directed and externally-directed (Fox et al., 2005; Singh and Fawcett, 2008; Smith et al., 2009). That evidence maps onto a taxonomy of attention recently advanced by Chun et al. which summarizes evidence that attention operates on information which is either already stored in memory (internally-directed) or enters through the sensory system (externally-directed, Chun et al., 2011). The internally-directed state is associated with activation of the default-mode network (DMN) with nodes in medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and posterior inferior parietal lobule (IPL) (Greicius et al., 2003). The DMN is active during memory retrieval, introspection, planning, and self-referential processing and appears to suppress externally directed attention (Buckner et al., 2008; Christoff et al., 2009; Harrison et al., 2011; Ridderinkhof et al., 2004; Sestieri et al., 2011). The externally-directed state is associated with activation of the dorsal attention network (DAN), which has nodes in intraparietal sulcus (IPS), superior parietal cortex (SPC), and frontal eye fields (FEF; Corbetta et al., 2008). The DAN is active during processing of external events and appears to suppress both internally-directed attention and regions associated with the DMN (Fornito et al., 2012; Fox et al., 2005).

Importantly, the alternation affects the brain globally. The alternation between internally- and externally-directed states has been found to involve coherence of the BOLD signal globally across 66 regions of interest of the brain (Hellyer et al., 2014). Consistent with a global effect of these two states on the brain, efficient alternation between externally- and internally-directed states is associated with better cognitive processing. Stronger negative correlation between DAN and DMN was associated with lower variability in cognitive task performance (Kelly et al., 2008). One study found greater DMN activity was associated with poor encoding but successful retrieval while greater DAN activity was associated with successful encoding but poor retrieval

(Kim et al., 2009). Further, DMN deactivation is important for successful performance in tasks requiring external attention (Weissman et al., 2006) and error monitoring (Eichele et al., 2008). Several investigators have argued from functional connectivity data that the anticorrelated DMN and DAN networks are modulated by a third network, the “fronto-parietal control” network (FPN) which includes lateral prefrontal cortex, precuneus, anterior inferior parietal lobule, medial superior PFC, and anterior insula (Niendam et al., 2012; Vincent et al., 2008). By this view, the FPN can flexibly connect functionally with either the DMN or the DAN, depending on task demands (Cole et al., 2013; Spreng et al., 2013). Thus, the FPN may play a role in rapid switching between DAN and DMN.

### 1.1. Hypothesis

We hypothesize that tDCS applied over prefrontal cortex (PFC) and parietal cortex (PC) facilitates activation of the specific stimulated network. This is based on evidence reviewed above that internally- and externally-directed cognitive states mediated by the DMN and DAN, respectively, can be alternated dynamically. During a task that relies on the DMN and the internally-directed state, tDCS over nodes of the DMN (namely, mPFC) heightens activity in that network which, in turn, suppresses activity in the DAN. Thus, stimulation of nodes of the DMN results in heightened processing of goals and stored information and reduced processing of external events. During a task that relies on the DAN and the externally-directed state, tDCS applied over nodes of the DAN (namely, PC) heightens activity in that network which, in turn, suppresses activity in the DMN. Thus, stimulation of nodes of the DAN heightens processing of external events at the expense of processing of goals and stored information.

Our hypothesis assumes that effects of stimulation are greatest when administered in conjunction with a task that activates the targeted network (e.g., stimulation of superior parietal node of the DAN during a task requiring external processing). Therefore, stimulation to either the PFC or PC during the performance of an internally or externally-directed task could elicit tDCS-induced effects, but the size of the effects would be contingent upon the compatibility between the task demands and stimulation site. Within this framework, we argue that tDCS simultaneously heightens networks already active from task demands and suppresses activity in anticorrelated networks. Consistent with that hypothesis is evidence from Hellyer et al. that the DAN and DMN “tune” the brain globally across 66 regions of interest in the brain (Hellyer et al., 2014). The effect of tDCS over nodes in each network may strengthen that tuning. In this paper we examine the existing tDCS literature to determine the extent to which this hypothesis can explain a range of results.

It is important to distinguish between modeled tDCS electric fields and measured cortical activation shown to affect behavior. What is the evidence that a given tDCS electrode montage (combination of anode and cathode location) can induce an electric field selective for a specific node and/or network? Models of tDCS electric fields (Datta et al., 2012; Miranda et al., 2006; Sadleir et al., 2010) show distribution of activation that extends some distance beyond the active electrode. For example, Fig. 1 shows that an anode at F3 (and cathode over FP2) induces modeled electric fields (NIC software) that appear to include both mPFC (a node in the DMN) and FEF (a node in the DAN, Hsu et al., 2015). However, modeled electric fields may not predict patterns of functionally meaningful activation and de-activation in regions of cortex or in networks in light of the strongly anti-correlated relation between DMN and DAN networks (Fornito et al., 2012; Fox et al., 2005). Further, DAN and DMN are both networks with hierarchical organizations in which not all nodes in a network are equally able to drive the network. Certain nodes exert a causal top-down influence over other nodes in the same network (Fig. 2). For the DMN, both Granger causality and dynamic causal modeling show a causal relation in which the medial PFC node drives the PCC (Fig. 2B) but not vice versa (Di and Biswal, 2014;

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