Exploring the physiological effects of transcranial direct current stimulation in traumatic brain injury patients.

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Mom, Dad, Max, Sarah, and Alex: this is possible because of you.

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Abbreviations

Choice reaction task (CRT)

Default mode network (DMN)

Fractional anisotropy (FA)

General linear model (GLM)

Independent component analysis (ICA)

Montreal Neurological Institute (MNI)

Mean reaction time (MRT)

Posterior cingulate cortex (PCC)

Psychophysiological interaction (PPI)

Region of interest (ROI)

Right anterior insula - dorsal anterior cingulate cortex/pre-supplementary motor area (rAI-dACC/pre-SMA)

Right inferior frontal gyrus (rIFG)

Salience network (SN)

Standard deviation (SD)

Stop Signal Task (SST)

Traumatic brain injury (TBI)

Transcranial direct current stimulation (tDCS)

Ventromedial prefrontal cortex (vmPFC)

Von Economo neurons (VENs)

White matter (WM)

Abstract

Transcranial direct current stimulation (tDCS) is a form of noninvasive brain stimulation that has been studied as a potential cognitive therapy. Its popularity has continued to grow as further behavioral benefits are uncovered. Yet reports of inter-individual behavioral variability and an insufficient understanding of the mechanisms influencing the effects of tDCS hinders its translation as an effective therapy. Studies have demonstrated parameters of brain state and stimulation polarity are drivers of the effects of tDCS, and an additional study by Li and her colleagues demonstrated the influence of white matter (WM) structure on the effects of stimulation. In light of these results, this study sought to address these deficits in understanding and deployed an experimental paradigm of combined stimulation and fMRI acquisition to measure the direct effects of stimulation on two brain networks relevant to cognition. The salience network (SN) and the default mode network (DMN) display robust, reliable, anticorrelated network activity during the choice reaction task (CRT). Concurrent stimulation of the right inferior frontal gyrus (rIFG) and fMRI acquisition determined the physiological effects of three parameters of stimulation: brain state (either task or rest), stimulation polarity (anodal, cathodal, or sham), and WM structure. The investigation of WM structure as a parameter influencing the effects of stimulation used mean fractional anisotropy (FA) values for the whole skeleton and two WM tracts linking nodes of the networks of interest. The right anterior insula – dorsal anterior cingulate cortex/pre-supplementary motor area (rAI-dACC/pre-SMA) tract connected nodes of the SN, and the bilateral cingulum connected nodes of the DMN. The inclusion of traumatic brain injury (TBI) populations served as a model for impaired WM structure, as TBI patients suffer from traumatic axonal injury (TAI) as a result of their primary pathologies. We found brain state and stimulation polarity influenced the physiological effects of stimulation in TBI patients. Specifically, stimulation served to highlight underlying network activity, with stimulation during task further activating SN activity, and stimulation in the absence of task further deactivated the same regions active during the task. Cathodal stimulation had stronger effects on brain networks relevant for cognition during task in TBI patients. FA influenced the effects of stimulation in TBI patients as well as healthy controls, and the influence of FA on the physiological effects of stimulation differed between patients and healthy controls. Furthermore, we found rAI-dACC/pre-SMA FA in healthy controls influenced improvements in task performance due to anodal stimulation.

This investigation of brain state, stimulation polarity, and WM structure has confirmed their role as parameters influencing the effects of tDCS in both TBI patients and healthy controls. Future stimulation studies are advised to consider these parameters of stimulation.

Word Count: 10,094

1 Introduction

1. 1 Noninvasive stimulation is an attractive option to boost cognition.

TDCS is a form of noninvasive stimulation and works by delivering a low electrical current between two scalp electrodes, from the anodal electrode to the cathodal. The directionality of current results in two simulation polarities, either anodal or cathodal stimulation. In-vitro studies have shown that, on a cellular level, tDCS works to alter neuronal excitability, thus altering the probability of producing an action potential. Anodal stimulation increases the likelihood of an action potential, whereas cathodal stimulation decreases the probability (Purpura and McMurty, 1965; Stagg and Nitsche, 2013).

The first recorded clinical use of noninvasive, direct current stimulation dates to 1744, administered by Dr. Christian Kratzenstein. A woman presented with a painfully contracted finger, which he shocked using a Leyden jar- a primitive means of generating and delivering direct current. Noting its success, Kratzenstein went on to predict that electricity would prove useful "not only in physical, but also mental patients whose wealth, worries, and anxieties prevent them from sleeping" (Coffman et al 2014). Though we have yet to realize all of Dr. Katzenstein's hoped therapeutic potential, use of noninvasive electrical stimulation still poses an attractive clinical option. A recent a meta-analysis by Gonzalez and colleagues found tDCS improves memory in dementia patients in the short term; it also has a mild, positive effect on memory and language in patients with mild cognitive impairment (Gonzalez et al 2018). A study by Li and colleagues determined tDCS improves task performances in healthy controls (Li et al 2019b). There are several studies showing behavioral improvements as a result of tDCS in TBI patients (Kang et al 2012; Lesniak et al 2014; O'Neil-Pirozzi et al 2017; Sacco et al 2016).

Though tDCS is an attractive option for boosting cognitive function, we have a limited understanding of its mechanisms of action in cognition. Additionally, we have little understanding of the reasons underpinning the inter-individual behavioral variation observed in tDCS studies. Multiple papers and meta-analysis have criticized the lack of reproducibility and variability in tDCS studies (Manusco et al 2016; Horvath et al 2015; Dedoncker, Josefien, et al 2016, 2014; Hill et al 2016; Li et al 2017). It is likely this variability results from deployment of tDCS without a sufficient understanding of the mechanisms influencing its effects.

1.2 There is a need to further develop a mechanistic understanding of tDCS.

Recent studies have worked to develop a mechanistic understanding of tDCS in order to effectively deploy its use as a cognitive therapy. Li and colleagues described the parameters of brain state and stimulation polarity as parameters driving the effects of tDCS in healthy controls. This study sought to replicate these findings, as well as investigate the effects of WM structure on the effects of tDCS.

TDCS induces network-specific modulations in activity (Li et al 2019a; Polania et al 2018; Polania et al 2011). For example, a study by Polania et al stimulated the posterior cingulate cortex (PCC), a seed region of the DMN. fMRI analysis revealed increased functional connectivity (FC) between the PCC, ventromedial prefrontal cortex (vmPFC), retrosplenial cortex, inferior parietal lobule and hippocampal formation- otherwise known as the DMN (Polania et al 2011; Buckner et al. 2008). Additionally, a study by Li also demonstrated tDCS increased psychophysiological interactions (PPI) among anatomically distant, functionally connected regions (Li et al 2019a). Therefore, stimulation results in modulation of activity and connectivity in brain networks related to the node of stimulation.

Rising gyri and plunging, sulcal depths form a cortical landscape that hosts collections of nodes. As stars scattered across the night sky are connected into twinkling constellations, nodes of synchronous activity are united and deemed a network. Networks are often state specific; for example, the DMN is characterized by patterns of activity that are representative of a task-inactive or "rest" state (Buckner et al 2008). An additional network with tightly coupled, anticorrelated activity to the DMN is the frontoparietal control network (FPCN) (Seeley et al 2007; Fox et al 2005). The SN is a subset of the FPCN (Fox et al 2005). The SN consists of the rIFG, the underlying anterior insula, and the dACC/pre-SMA (Seeley et al 2007). The anticorrelated activity between the DMN and SN is due to the contrasting nature of the network roles; the SN is activated during cognitive tasks, particularly those with attentional or inhibitory demands. This contrasts with the DMN, which is most active in the absence of task (Bonnelle et al 2012).

Within the SN, the rIFG has most commonly been characterized for its role in response inhibition and attentional control (Jilka et al 2014; Hampshire et al 2010). It is also a "control seat" region in the SN, mediating its activity and the switch from the DMN to a task-active state (Jilka et al 2014; Sridharan 2008). Additionally, the WM track connecting the rIFG and dACC/pre-SMA is responsible for network switching and modulating the deactivation of the DMN, particularly in

tasks requiring inhibitory control (Bonnelle et al 2012). We selected the rIFG as our node of stimulation for its central role in modulating DMN/SN activity, and its role in attention and cognition.

Two studies conducted by Li and colleagues determined tDCS of the rIFG reinforces underlying optimal network activity (Li et al 2019a; Li et al 2019b). The study demonstrated that during the task tDCS increased SN activation and decreased DMN activation, with cathodal effects more pronounced than the effects of anodal stimulation. Conversely, during rest tDCS increased DMN activation, decreased SN activation, and anodal stimulation produced stronger effects. These briefly summarized results are striking as they provide evidence that tDCS works through reinforcing underlying network activity, and its effects are driven by both brain state and stimulation polarity.

1.3 Traumatic brain injury patients are models of impaired WM structure

TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force." (Menon et al 2010). This definition serves to tie together a range of pathologies, whose origins- stroke, blast injury, falls, road traffic accidents- are almost as varied as their primary pathologies. Yet a ubiquitous pathology arising from TBI is traumatic axonal injury (TAI) (Hill et al 2016; Sharp et al 2014). TAI results from axonal shearing, where forces (particularly rotational) tear delicate WM axons in half. The central nervous system is an environment ill-suited for regeneration, and the torn or damaged axons form retraction bulbs and necrose (Gentleman et al 1995). Inflammation may have neurotoxic effects on the vulnerable regions immediately surrounding the shorn axons, resulting in further WM loss (Sharp et al 2014). The loss of axons due to the initial injury or subsequent neurodegenerative immune/inflammatory responses result in damaged WM physiology; therefore, TBI patients serve as models of impaired WM structure.

1.4 Impaired WM structure results in both cognitive deficits and abnormal brain network activity.

Moderate/severe TBI patients suffer impaired performance on cognitive, executive, and attentional tasks as a result of their injuries (Bonnelle et al 2012; Jilka et al 2014; Caeyenberghs et al 2014; Spitz et al 2013; Kinnunen et al 2010). The links between damaged WM structure and

deficits in behavior are extensive and well-characterized (Sharp et al 2014; Bonnelle et al 2011; Jilka et al 2014; Caeyenberghs et al 2014; Spitz et al 2013; Kinnunen et al 2010). Furthermore, these impairments in cognition are linked to disrupted networks dynamics.

TAI disrupts WM tracts connecting nodes in a brain network (Jilka et al 2014; Sharp et al 2014). The damaged tracts then disturb underlying network activity, resulting in disrupted network dynamics. For example, TBI induced damage of the tract responsible for DMN and SN modulation, the rAI-dACC/pre-SMA tract, leads to poorer performance on the stop signal task (SST), a cognitive task assessing inhibitory control (Jilka et al 2014; Li et al 2019 in press). WM tract damage induces inappropriate DMN activation during cognitive tasks, engendering poorer task performance (Bonnelle et al 2012). The deactivation of the DMN during a task is crucial to task performance. In both healthy controls and TBI patients a failure to decrease DMN activity is associated with worse performance in cognitive tasks (Bonnelle et al 2011; Weissman et al 2006). Therefore, tract damage connecting two nodes in a network hinders task performance (a measure of cognition) by proxy of network disruption caused by structural damage. This was further demonstrated by Li and colleagues who demonstrated FA of the rAI-dACC/pre-SMA as a driver for improved behavioral performance in a cognitive task due to anodal stimulation, and that anodal stimulation suppressed inappropriate DMN activity in poor task performers (Li et al 2019b).

1.5 Impaired WM structure influences the effects of tDCS

Several modelling studies have demonstrated the importance of WM structure in distributing the electric field of stimulation (Shahid et al 2013; Sadleir et al 2010; Metwally et al 2012; Shahid et al 2014). Modelling studies have determined changes WM conductivity may slightly alter distribution of current densities in brain regions (Sadleir et al 2010). Additional modelling shows alterations in WM structure measured by FA drive current densities, and the variations in FA strongly correlate with variation of current density distribution (Shahid et al 2013).

The importance of optimal WM structure in distributing the effects of stimulation make it an important parameter of tDCS. However, there are few studies that investigate the interaction among several parameters of tDCS, such as brain state, stimulation polarity, and WM structure, and both the physiological and behavioral effects of stimulation.

1.6 Aims and hypothesis

We investigated the effects of brain state, stimulation polarity, and WM structure on the physiological and behavioral effects of stimulation using a combined tDCS and fMRI experimental paradigm. We hypothesized that (1) stimulation of rIFG, a key region of the SN, leads to changes in brain network activity, and (2) that these changes depend on brain state (task or rest) and stimulation polarity (anodal or cathodal). We hypothesized that (3) effects of stimulation are influenced by WM structure, and that (4) these effects will differ between TBI patients and healthy controls. Through this investigation we will further develop a mechanistic understanding of the parameters influencing the physiological effects of tDCS.

2 Methods

2.1 Participants

We recruited thirty-five TBI participants (n=35, 5F:30M) with moderate-severe TBI as classified by Mayo classification system (Malec et al 2007). Exclusion criteria included contraindications to MRI or tDCS, prior neurosurgery, pre-TBI history of psychiatric or neurological illness or other TBI, or current drug and alcohol abuse. One participant was excluded due to distortion in fMRI preprocessing. Therefore, thirty-four patients were included in the analysis. Patient mean age was 39.7 (s.d. 10.3 years, range 21-56 years old). All participants were in the chronic, post-acute stage after their TBI (mean 48.9 months, range 6.5 to 367 months). A cohort of healthy control participants completed this study as published in (Li et al 2019a) (n=24, 12F:12M, mean age 39 years, s.d. 15.8 years). Healthy control participants had no contraindications to MRI or tDCS, prior neurosurgery, history of psychiatric or neurological illness, or current drug and alcohol abuse. All participants were naïve to tDCS, and gave written informed consent. The study conforms to the Declaration of Helsinki and ethical approval was granted through the local ethics board (NRES Committee London – West London & GTAC).

2.2 tDCS-fMRI task and paradigm

The CRT paradigm is detailed extensively in (Li et al 2019a). The task consists of 12 task blocks lasting 36 seconds with 24 trials and 12 rest blocks. The 12 rest blocks consisted of a white fixation cross on a black screen, and were interspersed with a blank screen presented for an interval ranging from 4.87 to 3.11 seconds to introduce jitter. During each task block participants selected whether the arrow was pointing left or right with their index finger on the corresponding hand (Fig 1b). Responses were recorded using a fiber-optic response box (NordicNeuroLab, Bergen, Norway). Participants had a maximum of 1.3 seconds to respond. The task was programmed in MATLAB (MathWorks, Natick, MA) using Psychtoolbox (Brainard, 1997) and presented via PC.

Prior to the tDCS-fMRI paradigm, participants performed a shorter blocked CRT to determine BOLD activity during CRT (Li et al 2019a). The tDCS-fMRI experimental paradigm consisted of blocked epochs of CRT and rest. Each block of CRT or rest were presented in a pseudo-randomized order consistent across all participants. During the task and rest blocks participants received anodal, cathodal, or sham TDCS, creating six different conditions of combined brain state and stimulation polarity: “rest” + sham; “rest” + anodal; “rest” + cathodal;

CRT + sham; CRT + anodal; CRT + cathodal (Fig 1c). All participants performed three runs interspersed with a brief rest to prevent fatigue. This resulted in a total of 18 minutes of full intensity tDCS.

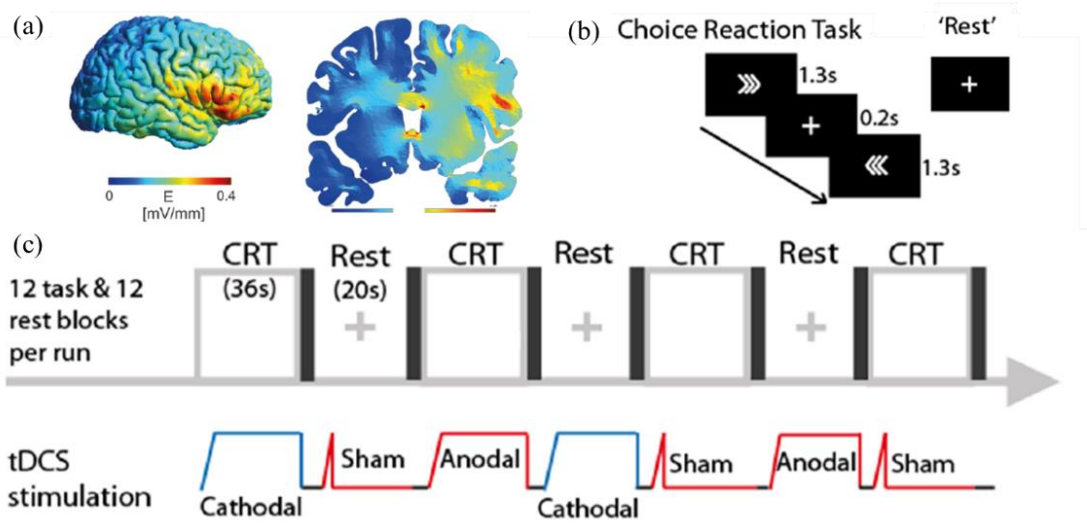

Figure 1 (a) modelling of the peak current density over the rIFG (b) stimuli in the CRT (c) experiment paradigm with concurrent tDCS/fMRI. Each participant performed three runs, each run consisting of four blocks of the six unique combined stimulation and task conditions (CRT + anodal, CRT + cathodal, CRT + sham, "rest" + anodal, "rest" + cathodal, "rest" + sham). Blocks were interspersed by a blank screen and no stimulation. Reproduced with permission from (Li et al 2019a; Li et al 2019b).

2.3 Statistical analysis of behavioral results

Statistical analysis was conducted using MATLAB (MathWorks, Natick, MA), R (www.r-project.org), and SPSS (IBM Corp). Behavioral results were evaluated by accuracy and the percent of correct responses. Reaction time was modelled using an exGaussian distribution (Lacouture & Cousineau, 2008) of the individual overall reaction time and the first reaction time (first reaction time of first trial within each block).

2.4 Delivery of tDCS

The stimulation parameters have been previously described (Li et al 2019a; Violante et al 2017). Stimulation was delivered through the active electrode over the pars triangularis of the

rIFG, with location determined using F8 (using the 10-20 EEG International system). The return electrode was placed over the right shoulder, with the center of the electrode placed over the midpoint between the acromion and base of neck, parallel to the coronal plane. The extracephalic position for the return electrode was selected to remove possibility of unintended, additional brain activation. Dimensions of the active electrode was 4.5 cm diameter circular rubber electrode, and the return electrode was 7 x 5 cm. Prestimulation impedances were below 3 kΩ, and maximum impedance during stimulation was 29 kΩ. To reduce impedance electrodes were affixed with a layer of conductive paste (Ten20, D.O. Weaver, Aurora, CO) and medical tape. Additionally, 1.8 mA current was used as opposed to 2 mA due to the simultaneous tDCS-fMRI setup. Both stimulation polarities (anodal and cathodal) were delivered using a 4.5 ramp up, followed by maintenance of full stimulation intensity, then a 0.5 s ramp-down. Sham stimulation consisted of ramp up and ramp down only. The stimulator was controlled via National Instruments DAQ device (National Instruments, Newbury, UK), receiving output from in-house MATLAB scripts.

Peak electric field was confirmed via computational, finite element method (FEM) head modelling using Simnibs version 2.0.1 (Thielscher, Antunes, & Saturnino, 2015; Windhoff, Opitz, & Thielscher, 2013) with conductivity values for the head, neck and shoulders used the following compartments- WM, grey matter, cerebrospinal fluid, skull, and skin. Tissue conductivity was determined as in (Opitz, Paulus, Will, & Thielscher, 2015). This confirmed peak electric strength was concentrated over the rIFG (Fig 1a).

2.5 Non-diffusion structural and functional MRI acquisition and preprocessing

Image acquisition followed previously published methods (Li et al 2019a). Briefly, T1 and fMRI sequences were acquired using a 3 T Siemens Verio (Siemens, Erlangen, Germany) and 32 channel head coil, using parameters modeled from (Violante et al 2017). Standard T1-weighted structural images were acquired using an MP-RAGE sequence, 1 mm3 isotropic voxel, TR 2.3 s, TE 2.98 ms, inversion time 900 ms, FA 9_, field of view 256 × 256 mm, 256 × 256 matrix, 160 slices, GRAPPA acceleration factor = 2, run time of around 4.5min (Li et al 2019a). Functional images were collected using T2*-weighted gradient-echo, echoplanar echoplanar imaging (EPI) sequence, 3 mm3 isotropic voxel, repetition time (TR) 2 s, echo time (TE) 30 ms, flip angle (FA) 80_, field of view 192 × 192 × 105 mm, 64 × 64 matrix, 35 slices, GRAPPA acceleration factor = 2, run time of 12min 24 s (Li et al 2019a).

fMRI data preprocessing was also performed using FMRI Expert Analysis Tool (FEAT) Version 6.00, from FMRIB's Software Library (FSL; Li et al 2019a; Smith, 2004; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Motion correction was performed using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) in order to remove movement artifacts. FMRIB's Nonlinear Image Registration Tool (FNIRT) was used to conduct removal of low-frequency drifts (high-pass filter of 0.01 Hz ensured retention of frequencies of expected network changes), spatial smoothing to reduce noise and retain valid, biological activation (Gaussian kernel filter with a full width at half maximum of 6 mm), brain extraction to remove non-brain tissue (BET; Smith, 2002), and co-registration. Using the participant's T1-weighted scan and preprocessed data participant's fMRI volumes were registered to Montreal Neurological Institute (MNI) 152 standard space.

Independent component analysis (ICA) analysis was conducted as in (Li et al 2019a). Multivariate Exploratory Linear Optimized Decomposition (MELODIC; Bechmann et al, 2005) was performed on each run. Components were classified using a trained, automatic classification software, FMRIB's ICA-based Xnoiseifier (FIX; Griffanti et al, 2015). Additionally, single-session ICA was conducted manually, with removal of noisy components from the time series.

Manual ICA was conducted to increase signal-to-noise power. Inclusion criteria included DMN or SN-specific activation, regional activation consistent through several time points, and signal contained in grey matter. Exclusion factors included signal located outside the brain, within the cerebral spinal fluid or WM, covers entire hemispheres, demonstrates the "ring effect" (Griffanti et al 2017). Inclusion criteria were based on previous literature (Li et al 2019a; (Griffanti et al 2017; Smith et al 2009; Kelly et al 2010). A conservative approach to the ICA was used to maintain optimal effect size. The initial ICA was manually, independently inspected to maintain a high standard of consistency and between-experimenter validity.

2.6 fMRI analysis: activation

A general linear model (GLM) was used to determine the relationship between activation and the task or rest conditions. Single-session, subject level GLM were first conducted to determine the effects of anodal and cathodal stimulation during the task, with the following regressors of interest: [all task block], [all anodal block], [all cathodal block]. The interactive

regressors [task * anodal] and [task + cathodal] were run to demonstrate the interactive effects of stimulation polarity (anodal or cathodal) and brain state.

The implicit baseline consisted of the ["rest" + sham] blocks. To determine the effects of stimulation in absence of task, the [all anodal blocks] and [all cathodal blocks] regressors were used with the GLM. Subject levels were run again using [all rest block] rather than the [all task block] to demonstrate the effects of anodal and cathodal TDCS during the resting state. To interrogate the effects of stimulation in the absence of task a GLM was constructed substituting "rest" for task, resulting in [all "rest" blocks]. The interactive regressors ["rest" + anodal] and ["rest" + cathodal] then demonstrated the interactive effects of anodal and cathodal stimulation in the absence of task.

All were run using square wave, double-gamma HRF in FSL's FMRI Expert Analysis Tool (FEAT) as described (Li et al 2019a). Six movement regressors were covaried out to account for motion artefact. A regressor of no interest to account for the periods of blank screen was included.

Group-level, mixed effects analysis combined all participant's sessions, then all participants were combined using FLAME 1 + 2 in FSL FEAT. The parameter estimates [task + anodal], [task + cathodal], ["rest" + anodal], ["rest" + cathodal], ["rest" + anodal] > ["rest" + cathodal], and [task + anodal] > [task + cathodal] were run, as were the inverse estimates. Z statistical images were thresholded using Gaussian random field-based cluster inference with threshold of $Z > 3.1$, corrected for cluster significance at a threshold of $p = 0.05$.

Determination of the interaction between state and polarity dependent effects were conducted with a region of interest (ROI) approach. The "task activated" and "task deactivated" network consisted of a binarized mask of the regions of increased (task activated) or decreased (task deactivated) BOLD activation during the shorter, non-stimulated, blocked CRT during the [task > "rest"] contrast.

2.7 Diffusion Tensor Imaging (DTI) acquisition and analysis

DTI image acquisition was the final scan in the session. Diffusion-weighted volumes were acquired using a 64-direction protocol (64 slices, in-plane resolution = 2 x 2 mm, slice thickness = 2 mm, field of view = 25.6 x 25.6 cm, matrix size = 128 x 128, TR = 9500 ms, TE = 103 ms, b-value = 0 mm^2s^{-1}) as previously published protocol (Li et al 2019b). Four images were also acquired without diffusion weighting (b- value = 0 mm^2s^{-1}). DTI data were corrected for head

motion and eddy current distortions, brain mask was extracted and constrained the tensor model using FSL's FMRIB's Diffusion Toolbox (FDT). Application of the tensor model generated voxelwise, individual participant FA maps. The maps were transformed into 1mm-resolution standard space using DTI-TK (Zhang et al 2006). An initial group-based template was generated (Zhang et al 2010), and individual tensor-based images were then registered to the group template using diffeomorphic transformations.

To assess WM structural connectivity in the whole brain and of regions composing the two brain networks of interest (SN and DMN) FA values were extracted for the following structures:

1. Whole Skeleton. This assess whole-brain WM tract integrity.
2. rAI-dACC/pre-SMA tract assessed SN structural integrity in the tract connecting the rAI to the dACC/pre-SMA. This tract partly overlaps the frontal Aslant tract described by Catani (Catani et al 2011).
3. mPFC-PCC/PRE (medial prefrontal cortex to posterior cingulate cortex/precuneus) tract assessed DMN structural integrity within the bilateral cingulum.

FA values were then interrogated in FEAT analysis as both single-group averages with adjusted and continuous covariate interaction.

3 Results

3.1 Behavior

There was a main effect of group on mean reaction time (MRT) between healthy controls and TBI patients (F [1, 0.027] = 7.17, p = 0.008) (Fig 2a). There was not an effect of stimulation type on MRT, and there was not an interaction between group and stimulation type. TBI patients had a greater range in behavioral responses to anodal stimulation (standard deviation (SD) = 0.0696) and cathodal stimulation (SD = 0.0701) than healthy controls (SD = 0.0504, SD = 0.0529, respectively). Percent change in MRT as a result of either stimulation polarity was <1 % in both groups (Fig 2b). There was no relationship between MRT during the shorter, blocked CRT and BOLD activation in the task activated regions in either TBI patients or healthy controls.

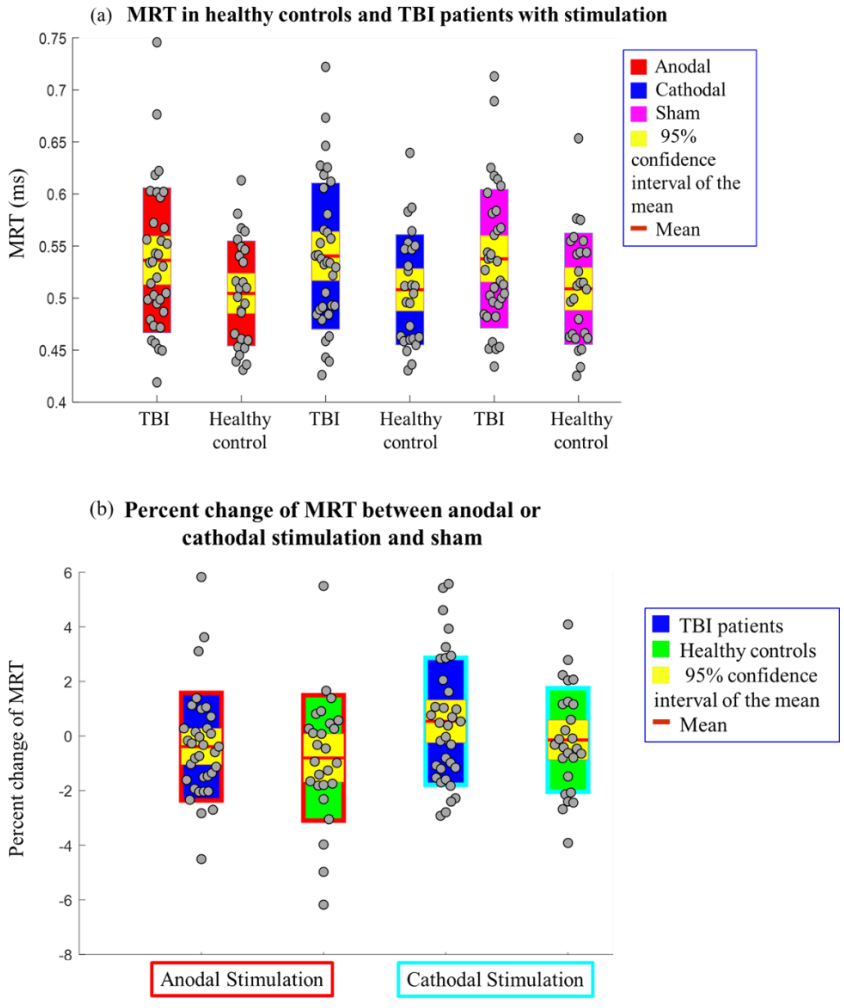

Figure 2 (a) MRT in healthy control and TBI patients with anodal, cathodal, and sham stimulation. (b) Percent change in MRT due to anodal or cathodal stimulation.

3.2 The relationship between WM structure and stimulation influences changes in task performance

Mean FA values in TBI patients for the whole brain (0.305), rAI-dACC/pre-SMA, (0.436), and bilateral cingulum, (0.476) were significantly lower than healthy control FA (0.317, 0.479, 0.512, respectively) (Fig 3). TBI participants had reduced mean FA within the whole skeleton ($t(52) = 2.299$, $p = 0.0256$) in the rAI-dACC/pre-SMA tract representing the SN ($t(52) = 3.137$, $p = 0.0028$) and in the cingulum bundle, representing the DMN ($t(32) = 2.535$, $p = 0.0143$).

Spearman correlations of the relationship between FA and the change in MRT due to either anodal or cathodal stimulation found a very strong correlation after Bonferroni corrections for multiple comparisons between rAI-dACC/pre-SMA FA and the change in MRT due to anodal stimulation in healthy controls ($r_s = 0.57$, $p = 0.0059$) (Fig 4b).

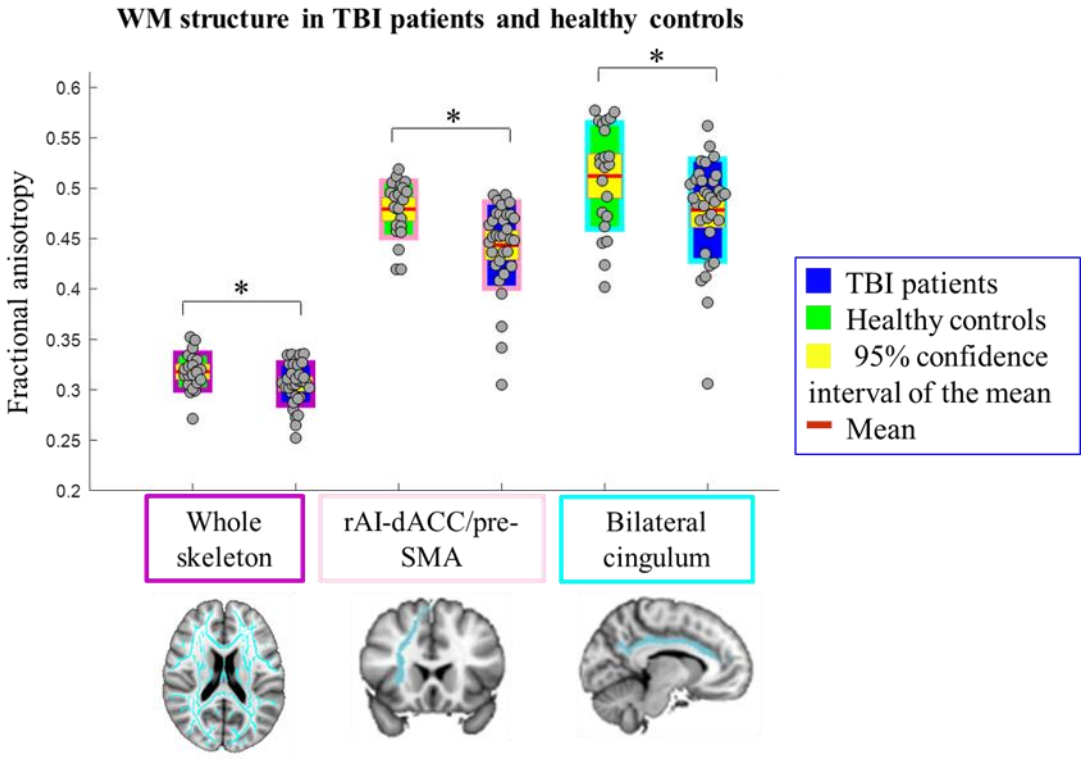

Figure 3 Measures of WM structure in TBI patients are significantly lower than healthy controls. Inset brain pictures show whole skeleton, rAI-dACC/pre-SMA, and bilateral cingulum tracts highlighted in blue. Images of rAI-dACC/pre-SMA and bilateral cingulum reproduced with permission from Li et al 2019 in press. * denotes $p < 0.05$

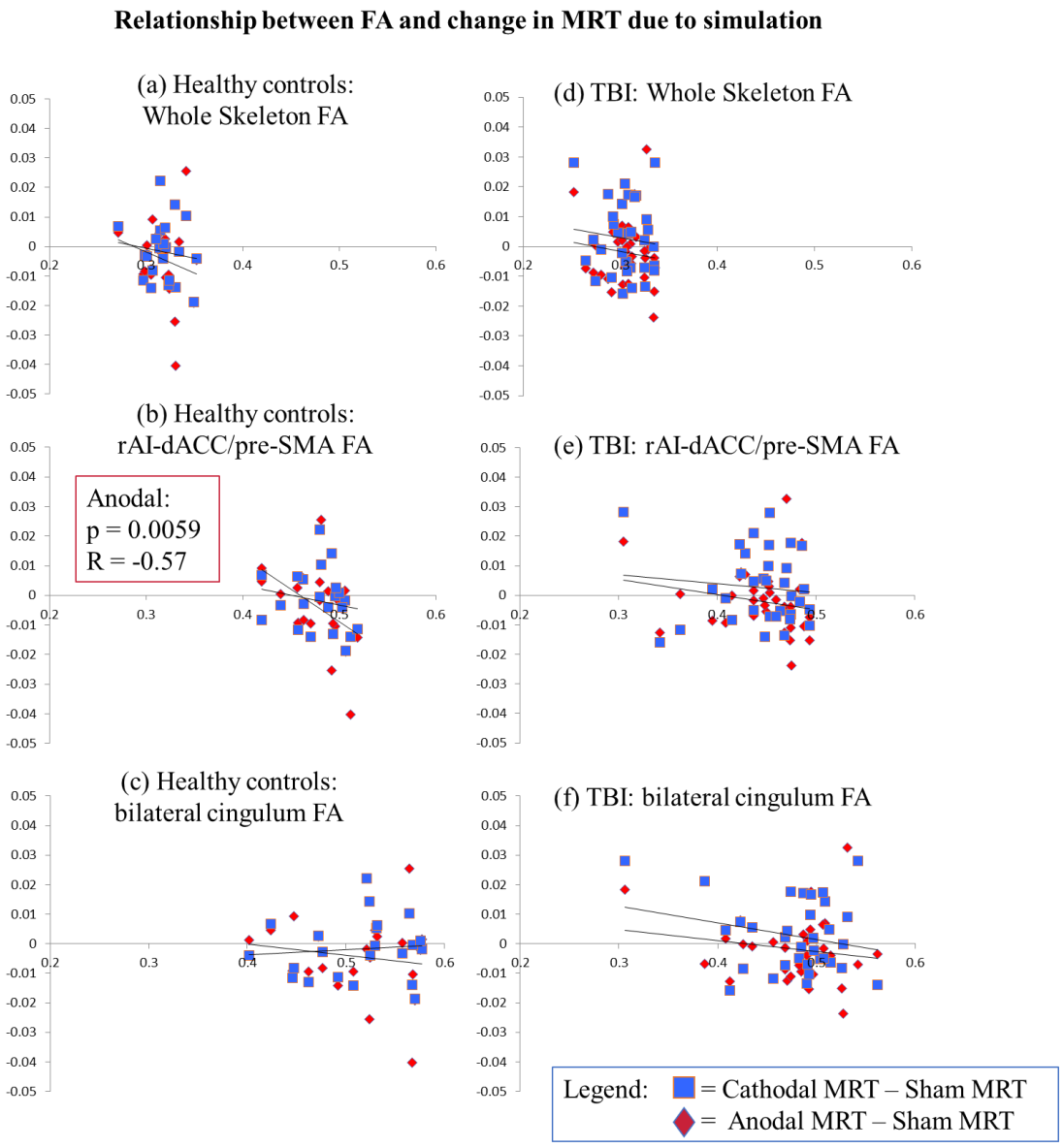

Figure 4 Relationship between FA and change in MRT due to stimulation. (b) There were significant effects of rAI-dACC/pre-SMA FA on the difference in MRT due to anodal stimulation in healthy controls.

3.3 The effects of TDCS on brain activity are dependent on brain state

The shorter, blocked CRT displayed a task activation profile of robust activation of the FPCN, including SN activation (Fig 5a). Task performance also resulted in increased BOLD activation in the primary sensory/motor cortex, basal ganglia, and bilateral thalami, and concurrent deactivation of the PCC, representing the DMN.

Interactive effects of cathodal stimulation and CRT further increased activation of the SN, particularly the dorsal anterior cingulate cortex (Fig 5b). There was no additional activation due to anodal stimulation, and there were not additional decreases in BOLD activity due to interaction of task and stimulation of either polarity.

The main effect of stimulation in the absence of task was to further decrease activity in task activated regions (Fig 5c). Cathodal stimulation further deactivated the SN, and anodal stimulation induced further deactivation of the primary sensory and motor cortices. Cathodal stimulation in the absence of task resulted in further activation of the DMN represented by the PCC. Anodal stimulation in the absence of task increased medial occipital activation.

A GLM contrasting patients and healthy controls reported no differences for either the shorter, blocked CRT or the state dependent effects of tDCS.

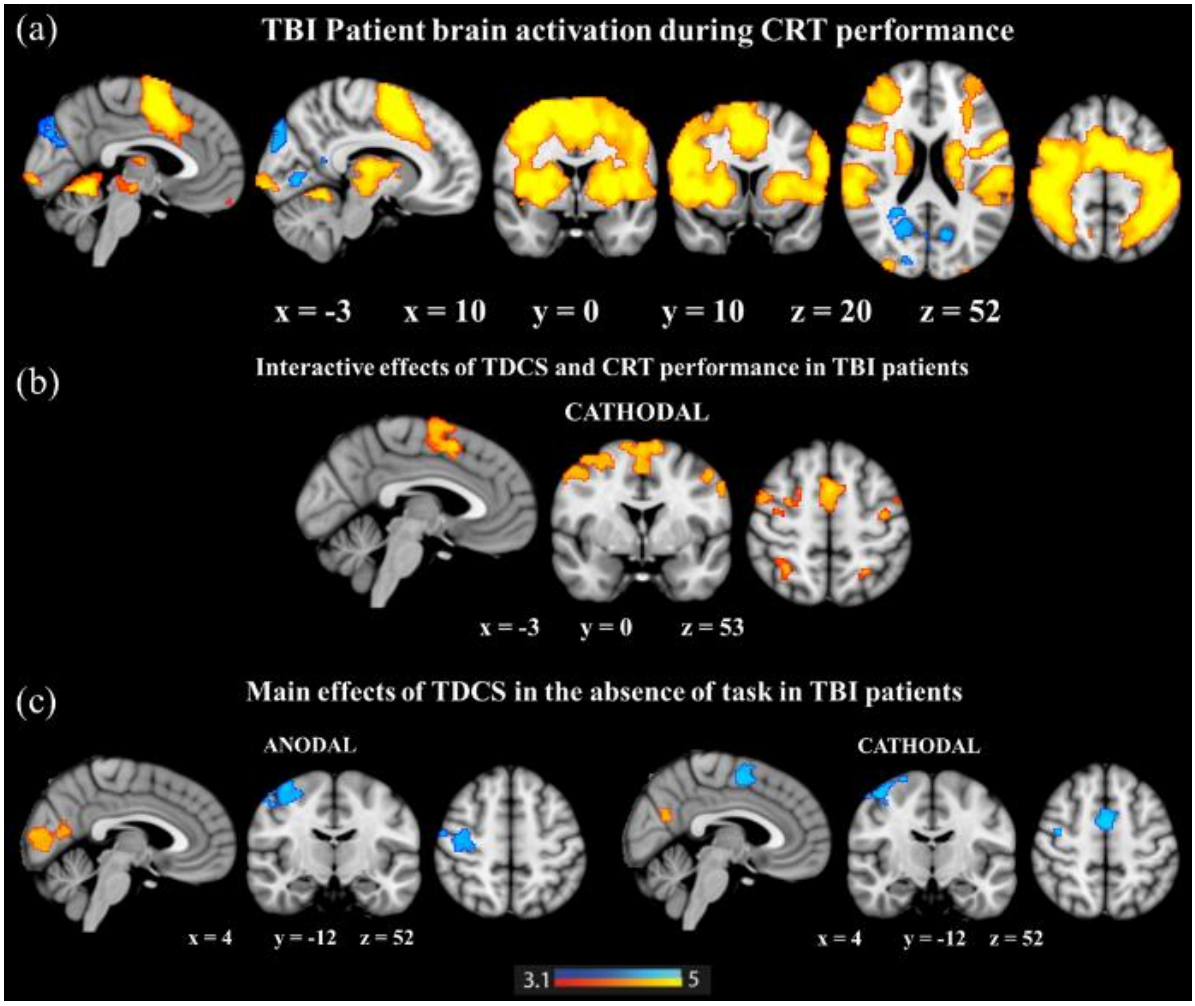

Figure 5 The physiological effects of tDCS during and in the absence of task. (a) Overlay of brain activation (in warm colors) and deactivation (in cool colors) during the short, blocked CRT. (b) Brain areas of further activation due to cathodal stimulation during CRT in TBI patients. (c) Brain areas showing modulated activation due to stimulation in the absence of task. Results are superimposed on a 1mm MNI152 template. Cluster corrected $z = 3.1$, $p < 0.05$.

3.4 The polarity-dependent effects of TDCS interact with underlying brain state

The interactive effects of stimulation polarity and brain state were determined using a ROI approach. We found a significant interaction between brain state and stimulation polarity in both the task activated ROI ($F [1, 213] = 4.23$, $p = 0.042$) and task deactivated ROI ($F [1, 412] = 4.16$, $p = 0.043$) (Fig 6).

During either task or rest both stimulation polarities modulated BOLD activity in the same direction as underlying network activity. Post-hoc t-tests confirmed cathodal stimulation during task produced greater BOLD activity than activity due to anodal ($t(8.65) = 0.782$, $p = 0.020$) and cathodal stimulation ($t(11.84) = 2.384$, $p = 0.004$) during rest. During rest, activity due to cathodal stimulation was less pronounced than anodal stimulation during task ($t(8.56) = 0.448$, $p = 0.031$). There was no difference between the effects of anodal and cathodal stimulation in the task activated regions. The effects of anodal stimulation are less marked than those of cathodal stimulation, which drove the state and polarity dependent effects in the task activated regions. These results highlight that there is an interaction between brain state and stimulation polarity.

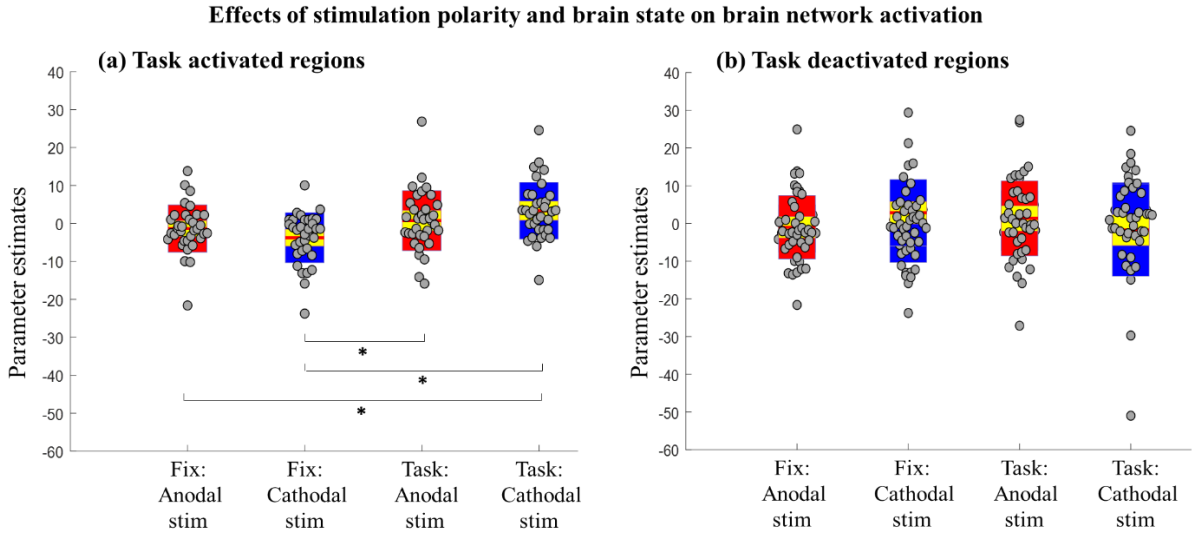

Figure 6 The interaction between brain state and stimulation polarity in the (a) task activated regions and (b) task deactivated regions in the absence of task is (represented by "Fix") and during task. Boxplots display mean values, * denotes $p < 0.05$.

3.5 WM structure influences the effects of stimulation in healthy controls and TBI patients

We investigated the effect WM structure has on physiological effects of tDCS. In healthy controls we found a significant influence of both whole skeleton and bilateral cingulum FA during CRT in the contrast comparing effects of cathodal stimulation to anodal stimulation. Whole skeleton FA was shown to influence greater activation of the superior temporal gyrus and left cerebral cortex (Fig 7a). Bilateral cingulum FA influenced increased activation of the cingulate gyrus, as well as right primary motor and sensory cortices (Fig 7b). In the contrast evaluating the

influence of FA on the interaction between cathodal stimulation and BOLD activity rAI-dACC/pre-SMA FA influenced increasing activation in the left frontal pole in healthy controls (Fig 8).

In TBI patients we found that whole skeleton FA influences the extent to which anodal stimulation increases areas of activation during task as opposed to cathodal stimulation (Fig 9). That is, the higher the FA, the more intact the WM, the greater the activation with anodal stimulation during the task. Regions of increased activation include the precuneus, lingual gyrus, and left lateral visual cortex.

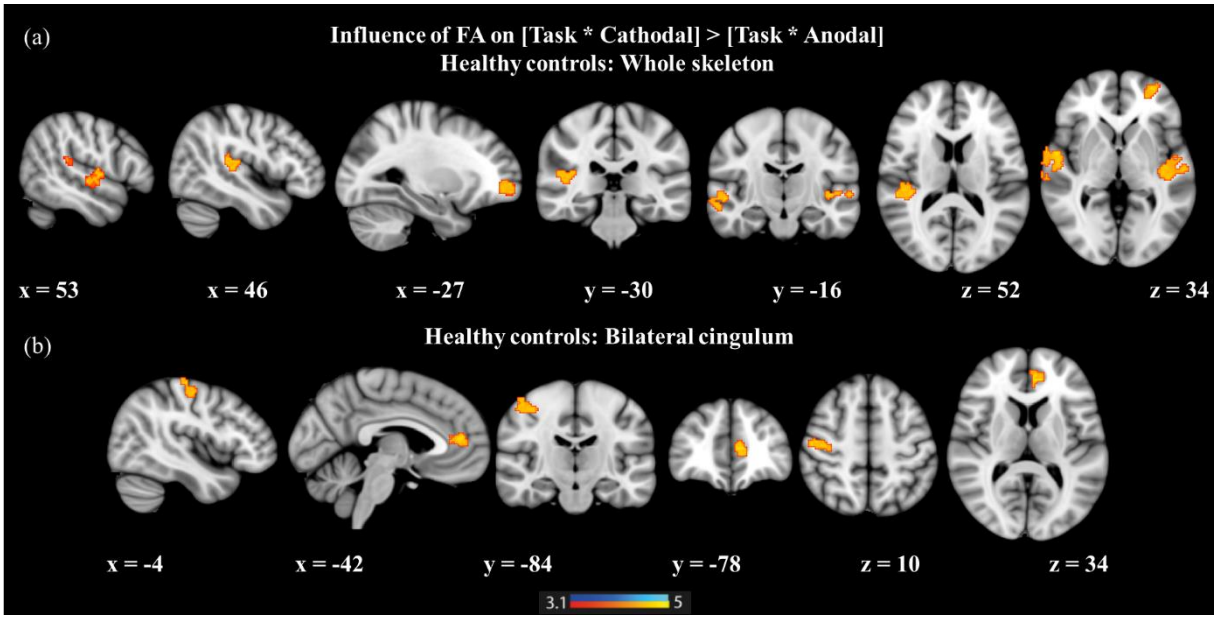

Figure 7 The influence of (a) whole skeleton and (b) bilateral cingulum FA on brain activation due to cathodal stimulation compared to anodal stimulation during the CRT in healthy controls. Results are superimposed on a 1mm MNI152 template. Cluster corrected $z = 3.1$, $p < 0.05$.

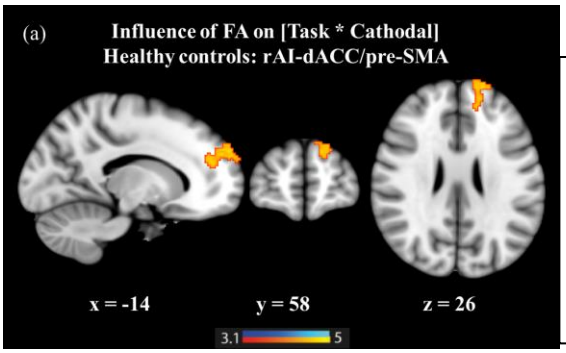

Figure 8 The influence of (a) rAI-dACC/pre-SMA on brain activation due to cathodal during the CRT in healthy controls. Results are superimposed on a 1mm MNI152 template. Cluster corrected $z = 3.1$, $p < 0.05$.

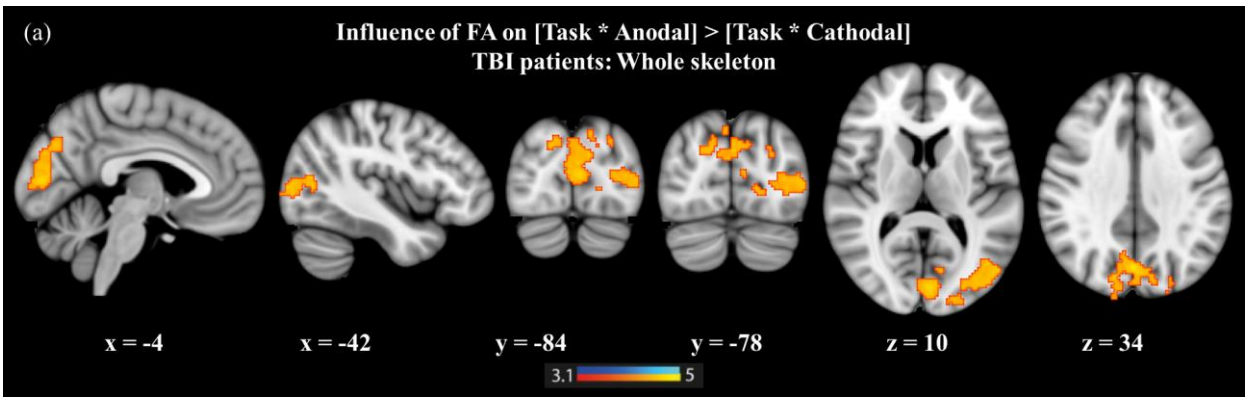

Figure 9 (a) The influence of whole skeleton FA on brain activation due to anodal stimulation as opposed to cathodal stimulation during the CRT in TBI patients. Results are superimposed on a 1mm MNI152 template. Cluster corrected $z = 3.1$, $p < 0.05$.

3.6 The influence of WM structure on the physiological effects of stimulation are different between healthy controls and TBI patients.

The effects of FA on fMRI activation during the CRT are different between TBI patients and healthy controls. Specifically, the influence of whole skeleton structure in response to anodal stimulation, as compared to cathodal stimulation, is stronger in TBI patients than in healthy controls in the anterior cingulate cortex, visual cortex, somatosensory cortex, angular gyrus, middle temporal gyrus, and precentral gyrus (Fig 10a). Additionally, we found tract-specific results for the same contrast. We observed increased activation of the anterior cingulate cortex and frontal/medial cortex due to rAI-dACC/pre-SMA FA (Fig 10b), and bilateral cingulum FA resulted in increased activation of the cingulate gyrus (Fig 10c).

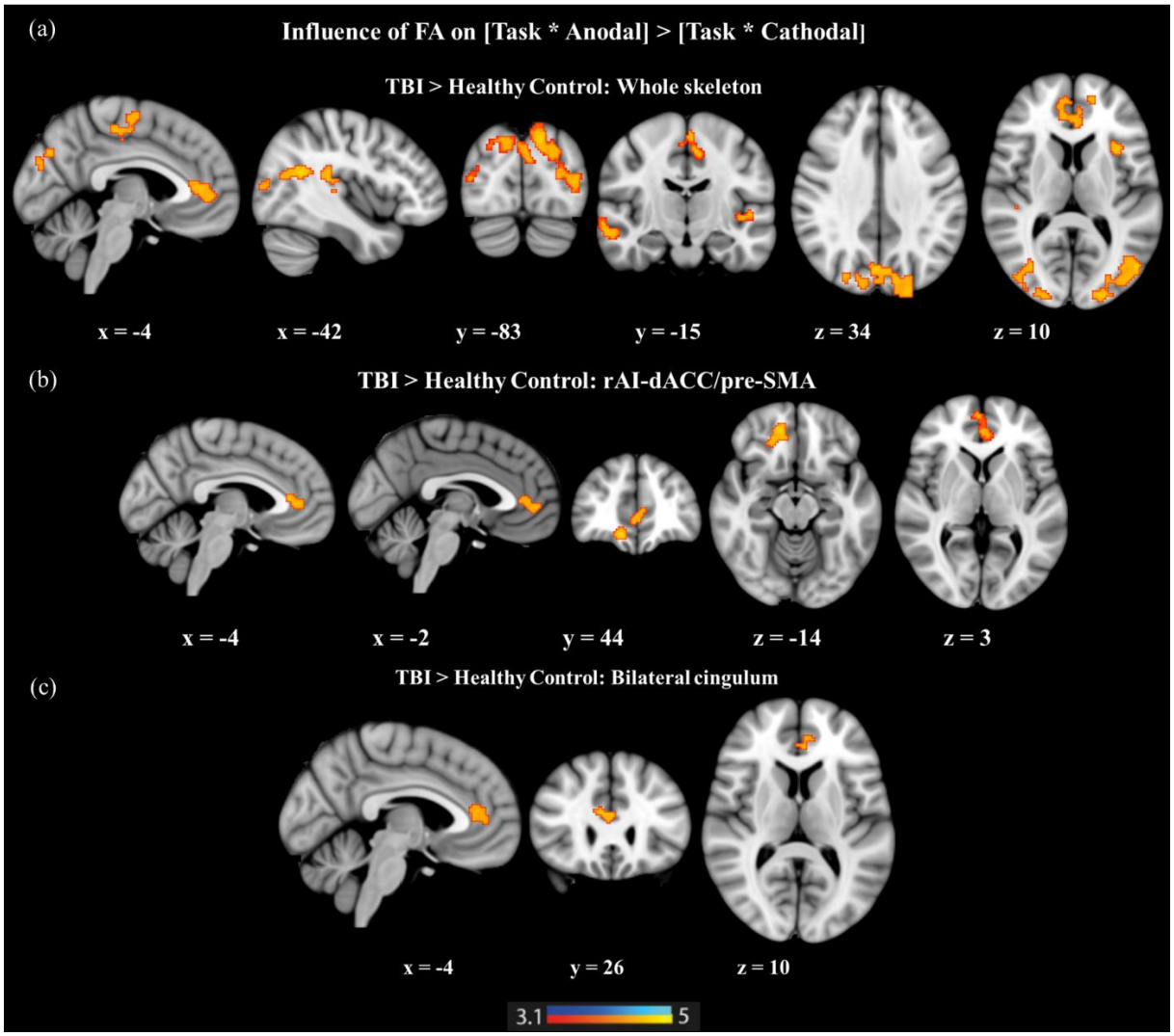

Figure 10 The influence of (a) whole skeleton, (b) rAI-dACC/pre-SMA, and (c) bilateral cingulum FA on anodal stimulation as directly compared to cathodal stimulation is greater in TBI patients compared to healthy controls. Results are superimposed on a 1mm MNI152 template. Cluster corrected $z = 3.1$, $p < 0.05$.

4 Discussion

This study replicated the brain state and polarity dependent effects of stimulation in TBI patients as described in previous literature in healthy controls (Li et al 2019a; Li et al 2019b). We observed the influence of WM structure on the physiological and behavioral effects of stimulation in both TBI patients and healthy controls. Moreover, the influence of WM structure on the physiological and behavioral effects of stimulation were different in TBI patients than in healthy controls.

4.1 Stimulation of the rIFG modulates activity in large-scale cognitive networks

Focal stimulation of the rIFG results in anatomically diverse, network-specific activation. This reaffirms conclusions from previous literature that tDCS operates on a network level (Polania et al 2011; Li et al 2019a) The rIFG has been well-characterized as a crucial node responsible for maintaining attention and cognition, as well as its role in modulating the switch between DMN and SN activity (Jilka et al 2014; Menon and Uddin 2010). Its role in coordinating the activity of multiple networks is well-suited for tDCS's network-modulating effects, particularly for the CRT. The robust, reliable, anticorrelated activity of the SN and DMN offer a well-characterized system of neural dynamics that provide a baseline to observe modulation by tDCS.

The large, physiological effects characterized as network activation are potentially scaled results of the electrophysiological effects of stimulation. In-vitro studies have shown that tDCS modulates the likelihood of producing an action potential in neurons, and the effects of tDCS extend to non-axonal populations, producing excitatory Ca+ waves in astrocytes (Stagg and Nitsche, 2011; Monai et al 2016). Previous literature has suggested the cellular population of the rIFG and neighboring rAI may be particularly sensitive to stimulation, as they contain a large amount of Von Economo neurons (VENs) (Li et al 2019a). VENs are bipolar neurons thought to have the specialized function of generating rapid behavioral responses to changes in the environment (von Economo, 1926; Seely et al 2012). VENs contain large somas, which are thought to be conducive for fast signaling, as the greater surface area may be more easily influenced by currents (Arlotti et al 2012). Therefore, nodes containing high volumes of the VENs (such as the rIFG, rAI, and dACC) may be particularly susceptible to the effects of stimulation.

4.2 The effects of stimulation on brain network activity depends on brain state and stimulation polarity

This study demonstrated that task activated regions, such as those in the SN, are further activated by stimulation, and task deactivated regions are further deactivated due to stimulation, and that these state-dependent effects interact with stimulation polarity (Fig 5; Fig 6). The replication of brain state and polarity dependent effects of tDCS strengthens their role as stimulation parameters, though the interaction between brain state and stimulation polarity is not fully understood. One potential explanation is that stimulation modulates the balance of excitatory and inhibitory neurotransmitters in both neural and glial cells in the cortex (Stagg and Nitsche, 2011). Literature has suggested that the excitatory/inhibitory axis of tDCS's effects are due to inverse relationships between stimulation polarity and GABA/Glutamine concentration: anodal stimulation increases concentration of Glutamine and decreases GABA, whereas cathodal stimulation results in the inverse (Hunter et al 2015; Kim et al 2014; Stagg et al 2009). Local changes in the GABA and Glutamine concentrations due to tDCS could modulate excitatory/inhibitory circuits, thus propagating more widespread effects of tDCS (Stagg and Nitsche, 2011; Sasaki et al 2016; Tazoe et al 2014). However, the multiple cell types and orientations distributed in the cortex increase the complexity and introduce difficulty in interpreting a cellular-level understanding of the effects of stimulation to a circuit or system level. Furthermore, the results that anodal and cathodal stimulation drive brain network effects in the same direction from baseline network activity exceeds the capacity of explanation by the above reasoning.

Additional factors thought to underpin the effects of stimulation are cellular orientation and structure. Studies show the effects of tDCS are influenced by factors such as neuronal morphology, orientation, and layer of axons (Arlotti et al 2012; Lafon et al 2017; Radman et al 2009; Rahman et al 2013). As aforementioned, even localized tDCS will exert effects on the multiple layers and sub-populations of neurons in the cortex, clouding interpretation of the effects of tDCS. Furthermore, the discrete, differing effects of the two polarities of stimulation compound the complexity in the interaction between stimulation and cellular orientation. Each polarity is essentially an opposite direction of current flow, and will induce distinct effects on the heterogeneous cortical tissue (Li et al 2019a).

Despite the difficulty in uniting the cellular, circuit, and system-level mechanisms of tDCS's effects, the replicated results that brain state and stimulation polarity are parameters of stimulation, even in populations as diverse and heterogeneous as TBI patients and healthy controls, reinforce their ubiquity as parameters of tDCS.

4.3 WM structure influences the physiological and behavioral effects of stimulation.

The influence of WM structure was observed in both the physiological and behavioral effects of stimulation. Physiological effects of stimulation influenced by FA were seen in healthy controls (Fig 7; Fig 8) and TBI patients (Fig 9); furthermore, FA influenced stronger effects of anodal stimulation as opposed to cathodal stimulation in a comparison between TBI patients and healthy controls (Fig 10). Interactions between the physiological effects of stimulation and WM structure have been previously observed. For example, impaired WM structure of the dACC-pre/SMA correlated with inappropriate DMN activation during the SST (Bonnelle et al 2012); and stimulation drove increased activity in task activated regions or suppressed the inappropriate activity of the DMN during the SST (Li et al 2019b, Li et al 2019 in press). Similar to these studies, our TBI participants had worse WM structure than healthy controls, and the physiological effects of stimulation were influenced by WM structure. The similar impairments in WM structure in both TBI patient populations are united by TAI incurred as a result of their TBI (Hill et al 2016; Sharp et al 2014). Also, in line with these studies, the damaged WM structure in TBI patients influenced a different physiological response to stimulation. This is likely due to the crucial role of WM in distributing the electrical field of stimulation (Shahid et al 2013; Sadleir et al 2010; Metwally et al 2012; Shahid et al 2014). However, interpretation of the results showing the differing influence of WM structure on the physiological response to stimulation between TBI patients and healthy controls is difficult. Previous literature has shown tDCS works to reinforce underlying network activity (Li et al 2019a; Li et al 2019b; Polania et al 2011) and that these physiological effects of stimulation are influenced by WM structure (Li et al 2019b). In our experiment, though stimulation also reinforced underlying network activity (Fig 5; Fig 6), the influence of WM on the physiological effects of stimulation resulted in further activation of regions separate from the SN or DMN. This may represent the interactions among several parameters of stimulation, which may be different than the overall effect. Further studies to continually characterize the interactions

among the multiple parameters contributing to the physiological effects of stimulation is needed to fully interpret these results.

The influence of WM structure on behavioral effects of stimulation were observed in healthy controls. The strong correlation of rAI-dACC/pre-SMA FA in healthy controls and potential improvement in task performance due to anodal stimulation provides a link between the interaction among parameters of stimulation (brain state, stimulation polarity, and WM structure) and behavioral effects. A study by Li et al have observed an almost identical interaction among WM structure, stimulation, and improvement in their task, the SST. The SST is a response-inhibition task that, similar to the CRT, also exhibits anti-correlated SN/DMN network dynamics (Sridharan et al 2008; Menon et al 2010; Li et al 2019b; Bonnelle et al 2012; Jilka et al 2014). In an experiment that investigated the interactions among FA, stimulation, and SST performance, improvements in task performance due to anodal stimulation were highly correlated with the same tract, the rAI-dACC/pre-SMA (Li et al 2019b). Additionally, 70% of the behavioral variability in response to tDCS was explained by stimulation type and rAI-dACC/pre-SMA FA in a backward, step-wise approach seeking to determine the parameters of the variability in response to tDCS (Li et al 2019b). Applied to our study, this approach may be useful in determining whether TBI patient's increased variability in behavioral response to stimulation is due to their impaired WM structure.

Additional studies evaluating the relationship between WM structure and behavioral response to stimulation have used stroke patients as a model of impaired WM structure. A study by Rosso and colleagues determined that while damage to left Broca's area is necessary to respond to therapy via tDCS, it is not solely sufficient, and WM integrity of the left arcuate fasciculus explains variability in task performance (Rosso et al 2014). Two additional studies corroborated WM structure facilitated behavioral response to stimulation; these studies found a positive relationship between FA of the corticospinal tracts and stimulation-induced task improvement (Bradnam et al 2012; Lindenberg et al 2012). From this we can conclude that in addition to observing direct effects of FA on task performance, FA potentially has an additional, more subtle relationship through modulating the susceptibility to the benefits of stimulation. The inverse correlation between tract damage and potential improvement in response to stimulation implies that the potential lack of a response to tDCS is TBI patients is a result of their damaged WM structure. This is further validated in literature, where median splits of healthy control populations

into high and low FA groups found high FA groups, but not low FA groups, experience significant improvement in task performance due to anodal stimulation (Li et al 2019b). It is possible, then, that since TBI patients have lower FA than the low-FA healthy controls, they have diminished capability to improve in response to stimulation.

4.4 WM structure influences the physiological effects of tDCS differently in healthy controls than in TBI patients

It is difficult to determine a singular cause for the observed differences of the influence of WM structure on the physiological effects of stimulation between TBI patients and healthy controls. Though there are studies that evaluate the influence of WM structure on the *behavioral* effects of stimulation, there are few studies investigating the influence of WM structure on the *physiological* effects of stimulation.

One potential explanation may be that TBI patients exhibit increased activity as a result of compensation. Previous studies have observed increased BOLD activity in TBI patients as compared to healthy controls in networks relevant to cognition, and have posited this increase in activity compensates for deficits due to the impaired WM structure in TBI patients (Levine et al 2002; Rasmussen et al 2008). A study using a PET scanning to evaluate neural activity in moderate-severe TBI patients found that, despite similar task performance, TBI patients show increased activity of frontal, anterior cingulate, and occipital activity. The authors have suggested these increases in activity may be compensatory (Levine et al 2002). In a study of tDCS as a treatment in a stroke population it was hypothesized that tDCS may even have deleterious effects in acute post-stroke patients, as decreased activity due to tDCS may reduce the compensatory activation characterized by stroke patients in the acute phase of recovery (Bradnam et al 2013). This line of reasoning suggests the stronger response during task to anodal stimulation as compared to cathodal stimulation in TBI patients as compared to healthy controls may represent compensatory activation influenced by their decreased FA (Fig 10). However, this does not explain why these compensatory effects are seen in anodal stimulation as directly compared to cathodal stimulation, and continued investigation may clarify the differing influence of anodal and cathodal stimulation on the physiological effects of stimulation in TBI patients and healthy controls.

Though FC was not studied in this experiment, it is worth investigating if the difference in WM structure between TBI patients and healthy controls influences differing FC profiles between

the two groups. This may lend insight to the factors underpinning the differing relationship between FA and the physiological effects of tDCS within TBI patients or healthy controls (Fig 10). A previous study has shown that the impaired WM structure of the rAI-dACC/pre-SMA in TBI populations results in a breakdown of normal DMN FC, and that the worse FA in two separate TBI groups led to decreased FC between the rAI and DMN (Jilka et al 2014; Sharp et al 2014). These deficits in both rAI-dACC/pre-SMA FA and FC in TBI patients resulted in poorer task performance (Jilka et al 2014; Bonnelle et al 2012). A study by Sharp and colleagues showed that though the activation profiles of healthy controls and TBI patients are similar in the CRT, the impaired WM structure in TBI patients affected the FC within the DMN, which in turn predicted worse task performance (Sharp et al 2011). We also determined fMRI activation profiles are similar between TBI patients and healthy controls, and hypothesize that the impaired WM structure in TBI patients interferes with FC. We can also determine whether stimulation works to improve abnormal FC, and if this results in improved performance.

To evaluate the influence of FC on the differing physiological effects of tDCS between TBI patients and healthy controls, we can employ a similar ROI approach as when evaluating the interactions between brain state and stimulation polarity. We could create a mask of the regions displaying stronger activation in TBI patients compared to healthy controls as a result of anodal stimulation opposed to cathodal stimulation (Fig 10). Then, we could interrogate the timecourse of activity in these ROI with the contrast "TBI patients {[Task * Anodal] > [Task * Cathodal]} > healthy controls {[Task * Anodal] > [Task * Cathodal]}" to evaluate the role of changes in functional connectivity on the differing influence of FA on the physiological effects of stimulation. Studies such as this are required to clearly define the mechanisms of the complex relationship of the parameters of tDCS.

4.5 Limitations and future directions

Though well-rationalized, the stimulation of one node within the cognitive networks of interest restricts our interpretation of the effects of stimulation in reference to rIFG stimulation. Targeting additional nodes of the SN (such as the dACC/pre-SMA) may result in similar widespread network effects; additionally, both the rIFG and dACC are well-justified targets for stimulation due to their unique cellular physiology. As previously suggested, a network hierarchy analysis may provide information on other suitable targets for stimulation (Li et al 2019a). An

additional methodological limitation is the inability to explore long-term effects of stimulation. However, unwanted carry-over or lingering effects of stimulation are unlikely due to the pseudorandomized stimulation paradigm, and potential contamination effects are unlikely to cause false positives in the sham block, as analysis measured the effects of [stimulation + task] or [stimulation + "rest"] over and above the effects of [sham + task] and [sham + "rest"]. Though selected for their respective benefits, each imaging technique employed in this study carries their own limitations. For example, using FA as a measure of damaged WM structure may capture other aspects of WM structure, such as orientation, and incorrectly classify them as damage. A final methodological limitation is our limited sample size. Investigation of numerous contrasts resulted in stringent corrections for multiple comparisons and continued investigation with an increased cohort may result in clear exhibition of currently sub-threshold results.

Interpreting the influence of WM structure and stimulation is difficult due to the lack of difference in BOLD activity between TBI patients and healthy controls during the CRT. The similarity of activation profiles prevents us from drawing conclusions concerning the mechanisms by which FA influences the physiological effects of stimulation. Our inability to fully interpret (1) how opposed polarities drive network activity in a similar direction but to a varying extent, or (2) the influence of WM structure and stimulation polarity on the physiological effects of tDCS is a reflection of the current state of understanding of tDCS. This study serves as an intermediary for past tDCS studies that had not begun to characterize the parameters of stimulation, and a potential future where a complete mechanistic understanding of the parameters driving the effects of stimulation enables the informed delivery of TDCS as a therapy. Our findings contribute to the incremental process of untangling the complex interactions influencing stimulation's physiological and behavioral effects.

Conclusions

In our investigation of the interactions among the parameters of tDCS and its behavioral and physiological effects in TBI patients we replicated the brain state and polarity dependent effects of tDCS. We determined the influence WM structure on the physiological effects of stimulation in both TBI patients and healthy controls, as well as the relationship between WM structure and potential improvement in behavior due to tDCS in healthy controls. These results should shape the design and execution of future studies using this promising clinical tool.

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