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The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology

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ABSTRACT

Applying a weak electrical current to the cortex can have effects on a range of behaviours. Techniques such as transcranial direct current stimulation (tDCS) have been widely used in both research and clinical settings. However, there is significant variability across individuals in terms of their responsiveness to stimulation, which poses practical challenges to the application of tDCS, but also provides a unique opportunity to study the link between the brain and behaviour. Here, we assessed the role of individual differences in cortical morphology – specifically in prefrontal cortical regions of interest – for determining the influence of tDCS on decision-making performance. Specifically, we employed magnetic resonance imaging (MRI) and a previously replicated paradigm in which we modulated learning in a simple decision-making task by applying tDCS to the left prefrontal cortex in human subjects of both sexes. Cortical thickness of the left (but not right) prefrontal cortex accounted for almost 35% of the variance in stimulation efficacy across subjects. This is the first demonstration that variations in cortical architecture are associated with reliable differences in the effects of tDCS on cognition. Our findings have important implications for predicting the likely efficacy of different non-invasive brain stimulation treatments on a case by case basis.

1. Introduction

Electrical brain stimulation techniques, like transcranial direct current stimulation (tDCS), can be used to causally study the link between the brain and behaviour (Filmer et al., 2014). This non-invasive approach typically involves passing a current between two electrodes – an anode and a cathode – after one or both are placed on the scalp. Regions of the cortex affected by the current may show an increase or decrease in the likelihood of neural firing depending on the stimulation polarity (Purpura and McMurtry, 1965). tDCS may also modulate concentrations of key neurochemicals, including GABA and glutamate (Stagg et al., 2009). Cortical stimulation with tDCS can affect behaviour in a range of paradigms, including motor learning (Stagg et al., 2011a; Stagg et al., 2011b), decision-making learning (Filmer et al., 2013a; Filmer et al., 2013b), cognitive training (Filmer et al., 2017a,b), and mind wandering (Axelrod et al., 2015; but see Boayue et al., 2019), as well as showing promise in clinical applications such as treating depression (Brunoni et al., 2017).

Many of the above mentioned findings have come from the application of tDCS to the prefrontal cortex, a region associated with a range of executive processes (Roberts et al., 1998), with its dysfunction linked with many psychiatric and neurological conditions including schizophrenia, addiction, and mood disorders (Goto et al., 2010). Investigating the effects of stimulating the prefrontal cortex might therefore plausibly lead to the discovery of new therapeutic targets (e.g. Brunoni et al., 2017) as well as helping to elucidate the mechanisms underlying executive and other high-level functions (Filmer et al., 2014).

Despite its popularity and potential in research and clinical settings, we still have a relatively poor understanding of how tDCS modulates activity within the cortex. Moreover, there is a high-degree of inter-subject variability in the effectiveness of stimulation for modulating behaviour. For example, only around 50% of subjects show what is considered to be a typical polarity-specific modulation in excitability of the motor cortex with tDCS (Wiethoff et al., 2014; although see van der Ruit and Grey, 2018). This variability has been a source of criticism and

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concern for electrical stimulation techniques (Horvath et al., 2014; Parkin et al., 2015). However, individual subject variability is also a useful research tool in itself, as has recently been argued in the context of human neuroimaging (Foulkes and Blakemore, 2018; Kanai and Rees, 2011; Seghier and Price, 2018). Indeed, previous research has linked differences in brain morphology (Frank et al., 2016; Kanai et al., 2010; Schwarzkopf et al., 2011; Verghese et al., 2016) and function (Drew and Vogel, 2008; Garner and Dux, 2015; Vogel and Machizawa, 2004) to variability in behaviour and perception. If responsiveness to tDCS is paired with neuroimaging measures, we may be able to ascertain the sources of variability in tDCS outcomes, which in turn might allow us to predict the efficacy of stimulation at the level of individual subjects.

Previous research has considered variability in induced current from tDCS in the cortex across individuals (Li et al., 2015). There is evidence that the amount of current induced in targeted brain regions for individual subjects may explain some of the variance in stimulation efficacy (e.g. Kim et al., 2014). Similarly, in studies involving transcranial magnetic stimulation (TMS), researchers frequently control for the distance between the stimulating coil and the underlying cortex when deciding upon individual stimulation intensities (e.g. Stokes et al., 2013), with the goal of minimising variability in the induced current across subjects. Measures of cortical architecture, such as cortical thickness, have also been associated with the efficacy of a paired associative stimulation protocol using TMS (Conde et al., 2012). However, no previous research has taken a large-scale approach to assessing the precise role of cortical architecture in tDCS efficacy, or related this to executive processes.

Here, we assessed whether cortical architecture, as measured with structural magnetic resonance imaging (MRI), predicts the efficacy of tDCS in modulating learning. Using a previously replicated paradigm (Filmer et al., 2013a,b), tDCS was applied part way through the learning of a sensory-motor decision-making task. Across three sessions, subjects received anodal, cathodal, or sham stimulation over the left prefrontal cortex. This paradigm typically results in a disruption to learning-related processes (specifically, changes in reaction times) following anodal or cathodal stimulation, and is specific to the left hemisphere prefrontal cortex (Filmer et al., 2013a; Filmer et al., 2013b). To foreshadow the main results, using a region-of-interest (ROI) analysis, we found that the degree of behavioural modulation by tDCS was significantly correlated with cortical thickness of the left (but not right) prefrontal cortex. Thus, inter-subject variability in the effects of left prefrontal tDCS is associated with the underlying morphology of the targeted cortex, and implies a critical role for this region in learning stimulus-response mappings in a simple decision-making task.

2. Method

2.1. Overview

Subjects completed one MRI session and three tDCS sessions, all on separate days (see Fig. 1). During the MRI session, T1 weighted scans were acquired, and four behavioural tasks tapping executive processes were undertaken. For the three tDCS sessions, subjects completed an identical paradigm to that reported in a previously published study by our group (Filmer et al., 2013b), in which they learned stimulus-response mappings for a speeded decision-making task. An offline tDCS protocol was administered part way through the learning process. All of the experimental sessions were completed at approximately the same time of day (±2 h).

2.2. Subjects

Fifty-five subjects completed the study. Datasets from eight subjects were excluded: two due to issues with MRI scans, two due to missing data, and four due to poor performance at baseline (<70% accuracy for the decision-making task and/or exceptionally long (>3SD from mean) reaction times). Exclusion criteria were decided *a priori*. The final sample consisted of 47 subjects (mean age: 22 (SD = 3) years, 26 females). All of the subjects passed safety screening to undergo MRI and receive tDCS, and all gave informed consent. The study was approved by The University of Queensland Human Research Ethics Committee, and the data were collected as part of a larger project assessing predictors of tDCS efficacy.

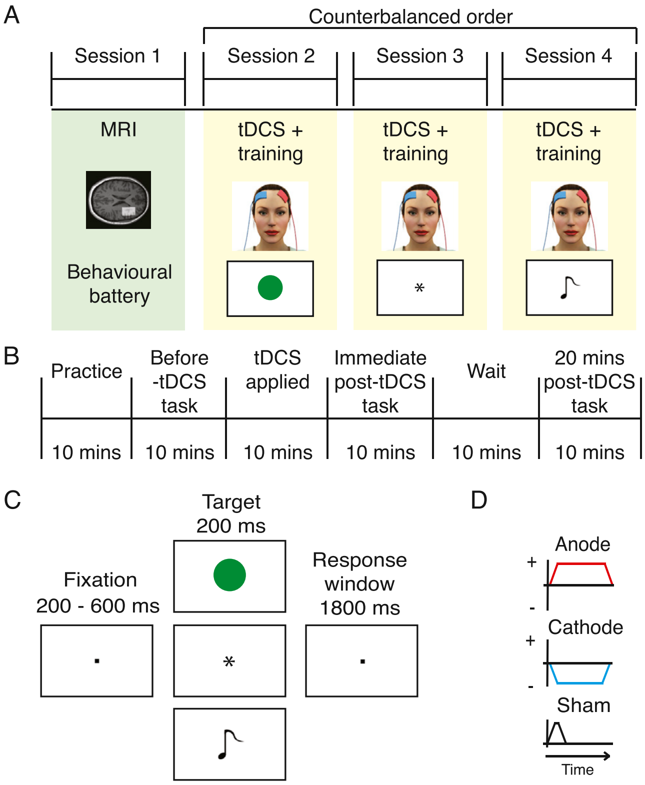

Fig. 1. Experiment overview. (A) Participants each completed four sessions, one with MRI measures and a battery of behavioural tasks, and three with tDCS applied part way through learning a simple decision-making task. (B) For the tDCS sessions, participants completed the task before, immediately after, and 20 min after application of stimulation. (C) The decision-making paradigm consisted of a simple fixation, followed by a stimulus (coloured circle, symbol, or sound), then a response window. (D) In each of the three stimulation sessions, participants were given a different type of tDCS to the left prefrontal cortex: anodal, cathodal, and sham.

2.3. MRI session

T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images were acquired with a 3T Siemens Magnetom PRISMA scanner using a 64-channel head and neck coil and the following parameters: TR: 1900 ms, TE: 2.26 ms, FA: 9°, FOV: 256 mm, voxel size: 1 mm isotropic. Images were captured for the entire head and neck for all participants.

2.4. tDCS sessions

The study consisted of three sessions with tDCS. In each of these sessions, subjects completed a sensory-motor decision-making task, with new stimuli each time (to maximize within-session learning and minimise cross-session learning). The three sets of stimuli consisted of coloured circles (in RGB – red: 237 32 36, dark green: 10 130 65, dark blue: 44 71 151, light green: 109 205 119, light blue: 79 188 220, brown: 167 106 48, pink: 255 57 255, yellow: 255 235 30), typographical symbols (#, %, @, ~,ˆ, *, +, |), and sounds (complex tones, as used by Dux et al., 2006). Subjects registered their responses by pressing a key on the keyboard, with each stimulus associated with a specific response key [A, S,D,F,H,J,K,L]. There were two different decision loads: high load (with six possible stimuli/response keys) and low load (two possible stimuli/response keys). Half of the subjects used the A and L keys (using both little fingers) for the low load task, and the other half used the F and H keys (using both index fingers). After initially learning the response mappings, subjects completed the task over three phases: before stimulation, immediately post stimulation, and 20-mins post stimulation. Each phase consisted of three blocks of 30 trials for each load condition (a total of 180 trials per phase), with the block types interleaved and the starting block type counterbalanced across subjects.

Each session involved a different type of stimulation: anodal, cathodal, and sham. In all cases the target electrode (5 × 5 cm) was placed on the scalp over left prefrontal cortex (1 cm posterior to F3, using the 10–20 EEG system) and the reference electrode (5 × 7 cm) was placed on the scalp over the right prefrontal cortex (1 cm posterior to F4). The current intensity was 0.7 mA (density 0.028 mA/cm^2), applied via a NeuroConn stimulator. The stimulation parameters were chosen to be consistent with a previously published study (Filmer et al., 2013b); they also yielded a comparable current density (0.028 mA/cm^2) to that reported in the motor learning literature (e.g. Nitsche and Paulus, 2000). For the anodal and cathodal sessions, stimulation lasted for 9 min, including 30 s ramping up and down of the current. For the sham session, stimulation lasted for 15 s (plus ramping time). The stimulation condition was single-blinded, and subjects were asked to sit with their eyes open, looking straight ahead, and were instructed not to talk for the full 9 min regardless of stimulation duration. The order of stimulation conditions and the pairing of stimulation condition with the stimulus sets were counterbalanced across subjects.

2.5. Behavioural tasks

In addition to measuring the efficacy of stimulation on learning of arbitrary stimulus-response mappings, we also measured performance on a series of tasks tapping executive functions, to ascertain whether performance on these tasks could be predicted by the morphology of the prefrontal cortex. These tasks were completed during Session 1, immediately after the MRI scan. All of these tasks have been used in previous studies (e.g. Bender et al., 2016; Filmer et al., 2017a,b).

Visual Search. A standard conjunction search task was used as a measure of spatial attention. Subjects were presented with a short fixation (400–800 ms), followed by a single target ('T') displayed amongst distractors ('L's). Subjects were asked to report whether the target was oriented through 90° or 270° by pressing the 'z' or 'm' key on a keyboard. The number of distractor items varied between 8, 12, and 16 to give an index of search time. The task consisted of a short familiarisation phase, then 8 blocks of 30 trials (a total of 80 trials per distractor load). The cost of increasing distractor items was calculated by subtracting the mean search time of the easiest condition (8 items) from the mean search time for the hardest condition (16 items), separately for each subject.

Go No-Go. As a measure of response inhibition (e.g., the suppression of unwanted/inappropriate actions), subjects completed a go no-go task. On each trial, after a short fixation period (200–600 ms), an abstract shape appeared (200 ms), followed by a response window (1800 ms). One shape was a 'go' stimulus (presented on 75% of trials), and subjects were asked to respond as quickly as possible by pressing the 'g' key if they saw this shape. A second shape was a 'no-go' stimulus, and subjects had to try and withhold their response on these trials. The task consisted of a short familiarisation phase, and four blocks of 36 trials.

Raven's Matrices. The short version of the Raven's Progressive Matrices Test (Bilker et al., 2012) was used as a measure of general intelligence. The task involves choosing, from 6 to 8 options, which image completes a presented pattern. There were a total of nine trials, sequentially increasing in complexity. The key measure of interest was accuracy (a score out of 9), and there was no time pressure on subjects to respond.

Psychological Refractory Period. To measure multitasking performance, a classic psychological refractory period (PRP; Welford, 1952) paradigm was used. Subjects initially practiced two different 4-alternative-fored-choice tasks, one visual (symbols) and the other auditory (complex tones). None of these stimuli overlapped with those used in the other tasks. After learning the mappings, subjects practiced multitasking trials in which one visual and one auditory stimulus was presented on each trial, with either a short (200 ms – relatively difficult) or long (1000 ms – relatively easy) interval between the two. After the practice, the task lasted for four blocks of 40 trials. The key measure for this task was the "PRP effect": the difference between the long- and short-interval trial reaction times for the second simulus, given responses to both tasks were correct.

2.6. Statistical analysis

tDCS effects. Analysis of the decision-making task was based on observed effects from our three previous demonstrations of the influence of tDCS on decision making (Filmer et al., 2013a; Filmer et al., 2013b). By design, accuracy was close to ceiling. Thus, the analysis focused upon reaction times (for correct trials; see Table 1 for a summary of accuracy data).

The analysis also focused on reaction times for the six-alternative-forced choice data as these were reliably affected by stimulation in our previous studies (Filmer et al., 2013a,b). The key measures of interest – our indexes of learning – were the change in reaction time from pre-to 20 min post-tDCS for each of the three sessions. The amount of learning was then compared between the sessions using t-tests. In addition, tDCS efficacy was calculated in each individual as the difference between the stimulation sessions in the reaction time measure of learning. Specifically, the calculation was: (sham pre-minus post-tDCS) – (active tDCS pre-minus post-tDCS).

MRI analysis. Image processing was conducted with the Freesurfer 6.0 standard processing pipeline Recon-All (Fischl et al., 2002). Due to multiple skull strip errors in mri_watershed, we performed a simultaneous skull-strip using ROBEX (Iglesias et al., 2011) and replaced Freesurfer's brain mask with the ROBEX output before autorecon2. We employed Freesurfer's 3T bias correction and MPRAGE signal-to-noise ratio parameters. Cortical thickness measures were extracted for each subject and each ROI in the Destrieux Atlas (Destrieux et al., 2010). We selected ROIs in proximity to the tDCS target location (the posterior portion of the left inferior frontal gyrus) for further analysis. These consisted of the left opercular and triangular regions of the inferior frontal gyrus, middle frontal gryus, inferior frontal sulcus, middle frontal sulcus, and the inferior portion of the precentral sulcus (see Fig. 2). In a separate control analysis, to ascertain hemispheric specificity, an identical analysis was conducted for the right hemisphere homologues.

Skull thickness. Skull thickness was assessed at the approximate locations of the tDCS electrodes, as this parameter may account for some individual differences in the amount of current that reaches the cortex (Opitz et al., 2015). These estimates were produced by manually locating

Table 1
Mean accuracy (% correct) for each of the sessions and conditions of the decision-making task.

	High-load			Low-load		
	Pre	Immediate- post	Delayed- post	Pre	Immediate- post	Delayed- post
Anode	95.6	95	95.8	98.4	96.7	96.8
Cathode	94.8	94.3	95.7	98	97.6	96.5
Sham	94.3	95.4	95.9	97.7	97.8	97.8

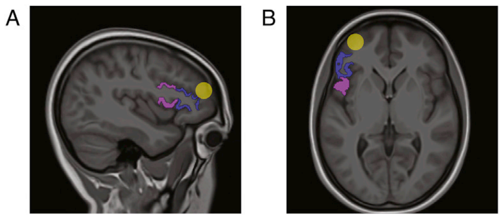

Fig. 2. Illustration of the location of the three key ROIs. Minimum deformation average template of all subjects in the study with cortical grey matter labels for the triangular (blue) and opercular (pink) portions of the inferior frontal gyrus, and the approximate location of the middle frontal sulcus (yellow). Shown for the (A) sagittal and (B) axial views.

the inferior frontal junction on each subject's T1 scan, and measuring the skull thickness at the nearest point of the skull. Three researchers independently calculated these measures in both hemispheres. The final skull thickness estimates were the average of the three researchers' measurements, calculated separately for the two hemispheres.

Modelling the electrical field. We used the realistic volumetric approach to simulate transcranial electric stimulation (ROAST; Huang et al., 2018) to estimate the induced current in the cortex both in an average head (see Fig. 3A) and for individual subjects. The induced current (V/m) for each subject was extracted for a 5 x 5 × 5 mm volume in the opercular and triangular regions of the inferior frontal gyrus. The median value for this volume was then calculated, giving an indication of the model's estimated induced current in these regions.

Behavioural data. Key measures for each of the behavioural tasks were extracted, as described above.

Individual differences. To assess the relationship between the measures of cortical thickness and tDCS efficacy (the dependent variable), several Bayesian linear regressions were run using JASP (Team, 2017). These regressions included a null model with the factors of left and right hemisphere skull thickness, sex, age, and task pairing (the allocation of stimulus set to tDCS condition). Independent variables of cortical thickness for the included ROIs were used (see above), with separate regressions run for the left and right hemisphere data. Regressions were run in turn with the following dependent variables: active tDCS efficacy (averaged across anode and cathode stimulation), anodal tDCS efficacy, and cathodal tDCS efficacy. A summary of the key analyses is shown in Table 2.

It was not the focus of the study to consider the relationship between the behavioural tasks and cortical thickness. However, we ran further regression models with key measures from the behavioural tasks as dependent variables. These analyses were exploratory. The regressions used the same cortical regions as outlined above, and included age and sex, and, in the case of the PRP analysis, mean Task 1 reaction time.

In our analyses, $BF_{10} > 3$ was taken as substantial evidence for the alternative hypothesis, In contrast, $BF_{10} < 0.33$ (or $BF_{01} > 3$) was considered as substantial evidence for the null, with BF_{10} between 0.33 and 1 providing anecdotal evidence for.

2.7. Data availability

The task scripts, data extraction scripts, behavioural data, and MRI data are publicly available (Filmer et al., 2019b).

3. Results

3.1. Blinding

At the end of the experiment we explained to subjects that one of the three tDCS sessions had involved a sham/placebo stimulation protocol. Subjects were then asked to indicate which of the three sessions they thought had been the sham condition. Overall, subjects' accuracy was at 47%. Given how the question was posed, if subjects were guessing we would expect 33% accuracy. Indeed, a Chi Squared test results in a borderline significance value (χ^2 (1) = 2.87, p = 0.09). Whilst it is arguable whether the blinding was complete, subjects were generally poor at determining which stimulation condition they had been assigned to in each session.

3.2. tDCS

In line with our previous findings (Filmer et al., 2013a; Filmer et al., 2013b), there was a significant effect of active tDCS (relative to sham) on the change in reaction times with learning (t(46) = 2.23, p = 0.03; Fig. 3C). This result confirmed our replication was successful.

3.3. Individual differences

3.3.1. Active stimulation efficacy

Left hemisphere. Bayesian linear regressions revealed that the effect of active tDCS on learning was associated with the morphology of both the opercular and triangular regions of the left inferior frontal gyrus ($BF_{10} = 4.016$, $R^2 = 0.224$). Neither of these two portions of the inferior frontal gyrus held anything greater than anecdotal evidence on their own (opercular: $BF_{10} = 0.626$ $R^2 = 0.079$, triangular: $BF_{10} = 1.688$, $R^2 = 0.141$), and they yielded opposing relationships with tDCS efficacy: greater disruption with active tDCS was associated with a relatively thicker opercular portion, in contrast to the triangular portion, of the inferior frontal gyrus. To test this relationship directly, we calculated the relative thickness of these two regions (using a ratio – opercular/triangular thickness), and found this ratio was correlated with the magnitude of the tDCS effect ($BF_{10} = 6.933$, $R^2 = 0.22$), such that higher ratios (i.e., relatively thicker cortex in the opercular than triangular region) were associated with greater disruption by tDCS.

Right hemisphere. There was no evidence to support cortical morphology in the right hemisphere correlating with active tDCS efficacy ($BF_{10} < 1$); in fact, the right hemisphere model with the opercular and triangular regions of the inferior frontal gyrus provided anecdotal evidence in support the *null hypothesis* ($BF_{01} = 2.747$, $R^2 = 0.077$).

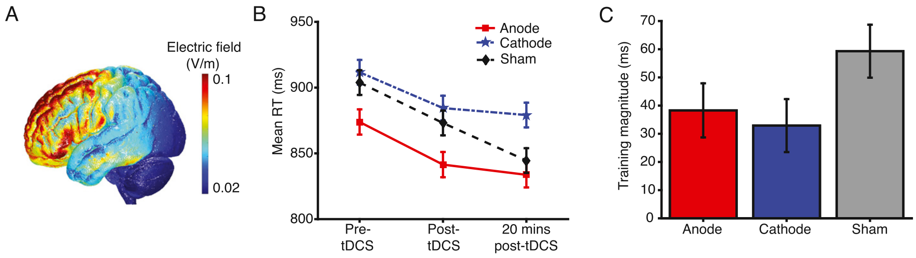

Fig. 3. Stimulation field and group-level effects on behaviour. The induced current, as modelled in ROAST (A). The mean reaction times (RT) for the three phases of each session, and the three stimulation conditions (B). The magnitude of training benefits for the stimulation sessions, calculated as the difference from pre-to 20 min after tDCS (C). Error bars reflect the SEM for the change in reaction time from pre-to delayed post-tDCS.

Table 2

A summary of the key individual differences analyses (linear regressions). All include sex, age, task pairing with tDCS session, and left and right skull thickness in the null model unless otherwise stated. ROIs included as independent variables (unless otherwise stated) were: opercular and triangular regions of the inferior frontal gyrus, middle frontal gryus, inferior frontal sulcus, middle frontal sulcus, and the inferior portion of the precentral sulcus.

Stimulation polarity	ROI Hemispheres	Independent variables	Winning model	BF_{10}
Active tDCS	Left hemisphere	All ROIs	Opercular and triangular portions of inferior frontal gyrus	4.016
		Opercular/ triangular ratio	Opercular/ triangular ratio	6.933
	Right hemisphere	All ROIs	NA	All <1
Anodal tDCS	Left hemisphere	All ROIs	Opercular and triangular portions of the inferior frontal gyrus, and the middle frontal sulcus	22.39
		Opercular/ triangular ratio, with middle frontal sulcus in null model	Opercular/ triangular ratio	49.73
		All ROIs, modelled current in null model	Opercular and triangular portions of inferior frontal gyrus	18.779
		All ROIs, skull thickness removed from the null model	Opercular and triangular portions of the inferior frontal gyrus, and the middle frontal sulcus	33.266
		All ROIs, subject session time of day in null model	Opercular and triangular portions of the inferior frontal gyrus, and the middle frontal sulcus	40.414
	Right hemisphere	All ROIs	NA	All <1
Cathodal tDCS	Either hemisphere	All ROIs	NA	All <1.78

3.3.2. Anodal stimulation efficacy

Left hemisphere. The relationship between disruption of performance with anodal tDCS and cortical morphology in the left and right hemispheres is shown in Fig. 4. Modulations of behaviour with anodal tDCS were associated with the left opercular and triangular portions of the inferior frontal gyrus, and also the middle frontal sulcus ($BF_{10} = 22.39$, $R^2 = 0.349$). Specifically, greater anodal tDCS disruption was associated with thicker cortex in the middle frontal sulcus (see Fig. 4C) and operular region, and thinner cortex in the triangular region (see Fig. 4A) of the inferior frontal gyrus. Again, not one of the three regions alone was reliably associated with effects of tDCS (opercular $BF_{10} = 0.679$ $R^2 = 0.079$, triangular $BF_{10} = 2.134$, $R^2 = 0.141$, middle sulcus $BF_{10} = 0.813$ $R^2 = 0.106$). The relative thickness of the inferior frontal opercular and triangular gyri (as a ratio, and accounting for middle sulcus in the null model) gave a strong account of the variance in terms of anodal tDCS efficacy ($BF_{10} = 49.73$, $R^2 = 0.345$).

Right hemisphere. Cortical morphology in the right hemisphere homologues held no associated value for anodal tDCS efficacy ($BF_{10} < 1$; see Fig. 4B and D).

3.3.3. Cathodal tDCS efficacy

There was at best anecdotal evidence for an association between left or right hemisphere cortical thickness and cathodal tDCS effects ($BF_{10} < 1.78$ for all morphology models tested).

3.3.4. Current modelling

We checked whether the amount of induced current in the cortex was correlated with the extent to which stimulation modulated behaviour. For this analysis, we included sex, age, and the counterbalanced factor of task pairing into the null model, entered stimulation efficacy (for anodal and cathodal separately) as dependent variables, and the modelled current (median value) for the left opercular and triangular regions as independent variables. There was no evidence for either of the modelled current values relating to the efficacy of anodal or cathodal stimulation ($BF_{10} < 0.9$ for all models).

Despite not showing an association with stimulation efficacy alone, we also ran our key analysis correlating anodal tDCS efficacy and cortical thickness with the modelled current included in the null model. We again included skull thickness, age, sex, and task pairing in the null model, along with median induced current for the opercular and triangular portions of the inferior frontal gyrus (left hemisphere). There was no substantive effect of adding these variables to the regression, with the greatest evidential value again for the model that included cortical thickness in the opercular and triangular gryi and middle frontal sulcus ($BF_{10} = 18.779$, $R^2 = 0.35$).

3.4. Control analyses

Time of day. Time of day can influence neural functioning (Colquhoun, 1981) and cognitive performance (Wong et al., 2018), and has been suggested as an important contributor to the behavioural effects of tDCS (Filmer et al., 2013b). We therefore ran a control analysis with cortical thickness data in the left hemisphere in which time of day was included in the null model. This analysis yielded the same key findings as reported above. Of central importance, we again observed that the relative thickness of the left opercular and triangular portions of the inferior frontal gyrus, and the middle frontal sulcus, best described the anodal tDCS data ($BF_{10} = 40.414$, $R^2 = 0.345$). To test whether the correlation between cortical thickness for anodal tDCS efficacy was robust, we also ran a split-half analysis in which odd and even numbered subjects were analysed separately. Despite the considerable reduction in power for this analysis, both halves of the data showed support for the model that included relative cortical thickness in the opercular and triangular regions, and the middle frontal sulcus ($BF_{10} = 4.309$, $R^2 = 0.449$; $BF_{10} = 1.861$, $R^2 = 0.524$).

Importance of skull thickness. We included measures of skull thickness in the null model as these may have contributed variance to the sample by modulating the amount of current that reached the cortex. We also ran a variant of the analysis in which left and right hemisphere skull thickness was instead included as an independent variable, to test whether they accounted for substantial variance in the winning model. In this case, the model that best described anodal tDCS efficacy was still the model containing the relative thickness of the left opercular and triangular portions of the inferior frontal gyrus, and the left middle frontal sulcus ($BF_{10} = 33.266$, $R^2 = 0.324$), with only slightly reduced evidence and slightly less data explained than the model reported above in which skull thickness was accounted for in the null. In addition, neither of the two measures of skull thickness, either independently or paired, were related to the effect of anodal stimulation ($BF_{10} < 1$ for all). In other words, although including skull thickness in the null model improved the model fits slightly, these measures were not critical in predicting stimulation efficacy.

Training magnitudes. When the sham training effect was considered independently of active stimulation effects, performance was associated with the ratio of the left opercular and triangular portions of the inferior frontal gyrus ($BF_{10} = 3.273$, $R^2 = 0.159$), although it explained a

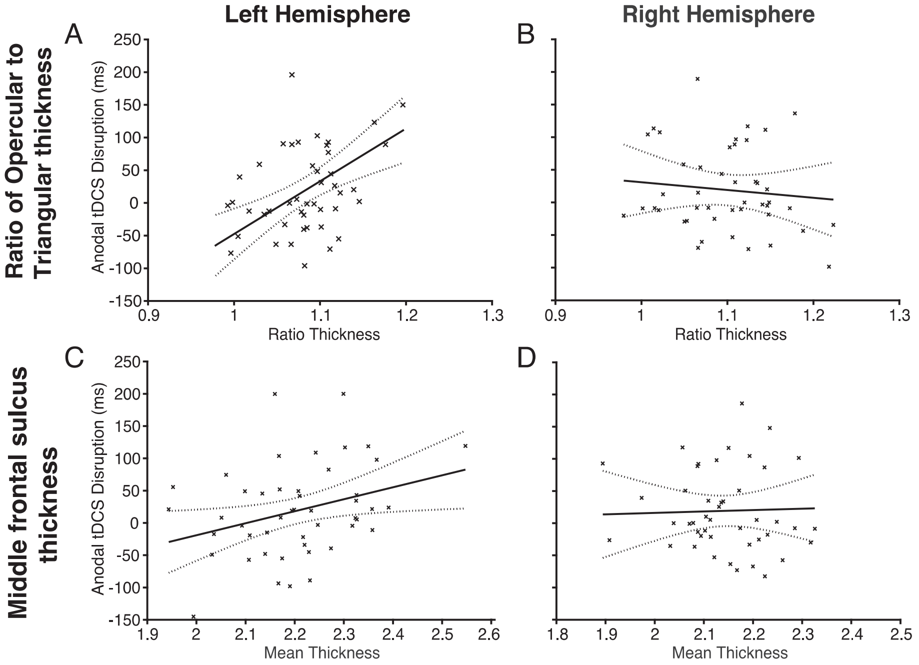

Fig. 4. Scatter plots depicting the relationship between disruption to decision-making training from anodal tDCS and measures of cortical thickness. Specifically, (A) the ratio of the opercular to triangular portions of the inferior frontal gyrus in the (A) left and (B) right hemispheres, and cortical thickness in the middle frontal sulcus for the (A) left and (B) right hemispheres. Plotted data are corrected for the nuisance variables of sex, age, and tDCS-decision-making task pairing. Plots depicting the ratio of opercular to triangular cortical thickness are corrected for the middle sulcus thickness, and plots depicting the middle sulcus are corrected for the ratio of opercular to triangular thickness. The solid line reflects the best fit to the data, the dotted lines 95% confidence intervals.

relatively small portion of the variance. In contrast, there was no evidence that cortical thickness in the left hemisphere (the ratio between the opercular and triangular portions, and the middle frontal sulcus) was related to learning in the anodal session, independent of sham ($BF_{10} = 1.828$, $R^2 = 0.205$), and no evidence cortical thickness was related to learning when cathodal stimulation was applied, independent of sham ($BF_{10} > 1$). Hence, although cortical thickness is related to the extent to which subjects improved their performance in the absence of stimulation, the relationship seems to be substantially stronger when considering the efficacy of stimulation in disrupting performance.

Low load performance. Our analysis focused upon reaction times for the high-load condition only, rather than the low-low condition, as we previously found group-level effects exclusively for the more challenging high-load condition (Filmer et al., 2013b). However, we also analysed the low-load RTs. At a group level, there was no evidence that stimulation modulated low-load performance for anodal or cathodal stimulation conditions (relative to sham; $BF_{10} < 1.4$ for both analyses). Further, we assessed whether the extent to which stimulation modulated low-load RTs related to cortical thickness in the selected left hemisphere ROIs. Using the same approach as for the high-load data, we ran three regressions: one on the combined effect of anodal and cathodal tDCS, one on the anodal effect alone, and one on the cathodal effect alone (all relative to sham). The null model again contained the variables of left and right skull thickness, sex, age, and task-pairing. None of the regressions supported the alternative hypotheses ($BF_{10} < 1.14$ for all).

Behaviour tasks. Although it was not the focus of the study, we also ran a series of regression analyses to assess whether performance on any of the four behavioural tasks was predicted by cortical thickness in the left or right prefrontal cortex. Both the visual search and the go no-go task had anecdotal evidence linking them to cortical thickness in either hemisphere ($BF_{10} < 2.11$ for all). The PRP effect, an index of multitasking performance, was associated with the left opercular and triangular portions of the inferifor frontal gyrus, the left middle frontal sulcus, and the left inferior precentral sulcus ($BF_{10} = 3.616$, $R^2 = 0.504$). There was only weak evidence that right hemisphere cortical thickness was correlated with multitasking ($BF_{10} < 1.55$). Scores on the Raven's Matrices Test was not associated with cortical thickness in the left hemisphere ($BF_{10} < 1$), but was in the right hemisphere, including regions of the middle frontal gyrus, inferior frontal sulcus, middle frontal sulcus, and inferior precentral sulcus ($BF_{10} = 5.454$, $R^2 = 0.26$).

4. Discussion

We asked whether cortical thickness is associated with the effects of anodal and cathodal tDCS on cognitive function. Using a previously replicated approach designed to measure the effects of learning arbitrary stimulus-response mappings in a simple decision-making task (Filmer et al., 2013a,b), we applied tDCS to the left prefrontal cortex as subjects were exposed to a six-alternative forced choice paradigm. Our findings replicated those from our previous studies by showing that active stimulation (anodal and cathodal) disrupted learning. Critically, we accounted for a significant proportion of the variance in explaining the effectiveness of anodal tDCS by including in the model the cortical thickness of regions within the left (but not right) prefrontal cortex. Specifically, we found that individuals with a thicker cortex in the middle frontal sulcus and opercular portion of the inferior frontal gyrus, and thinner cortex in the inferior frontal triangular gyrus, showed more disruption of learning with anodal stimulation. The precise ratio of cortical thickness in the opercular and triangular portions of the inferior frontal gyrus seems to be particularly important in accounting for stimulation efficacy. Hence, differences in morphology of the prefrontal frontal cortex can to some extent explain individual variability in behavioural responses to anodal tDCS over this region. This is the first demonstration that the morphology of an individual's cortex can predict the extent to which tDCS can alter behaviour. Variation in the efficacy of cathodal tDCS could not be accounted for by cortical thickness, indicating that despite similarities in the behavioural effects of anodal and cathodal tDCS, sources of variance for the two stimulation polarities may vary.

We previously showed that the effect of prefrontal tDCS on decision-making learning is specific to the left hemisphere. Targeting the right hemisphere homologue (with a left orbitofrontal reference location) did not modulate performance (Filmer et al., 2013a,b). Also, when targeting the left prefrontal cortex, performance was equally affected whether the reference electrode was placed over the right orbitofrontal or prefrontal (1 cm posterior to F4) regions ((Filmer et al., 2013a,b)). Finally, our results indicate that cortical thickness only in the left PFC related to the efficacy of tDCS to modulate learning showing no role for the right hemisphere homologues. Thus, although we used a bilateral electrode montage in the current study, we believe it is most likely that the tDCS effect was predominantly due to functional modulation of the left prefrontal cortex alone. However, a role for stimulation to the right hemisphere cannot be entirely ruled out. The present findings corroborate our previously published experiments (Filmer et al., 2013a,b) by showing that cortical thickness in the left prefrontal region accounts at least in part for tDCS efficacy. Furthermore, we used a relatively large sample size (47 subjects), included two separate stimulation conditions (anodal and cathodal, compared with sham), and ran analyses on control brain regions (in addition to our *a priori* regions of interest).

Previous fMRI studies have highlighted an important role of the left prefrontal cortex in decision-making. In particular, activity in posterior portions of the inferior frontal gyrus, and parts of the middle frontal cortex, have been correlated with performance in speeded decision-making tasks similar to the one we used in this study (Dux et al., 2006). The benefits of training decision-making tasks, in a multitasking context, have also been linked to the same region (Dux et al., 2006). The target area of stimulation we used, 1 cm posterior to F3, was intended to target this same region of the cortex, thus providing causal evidence for the involvement of this region in decision-making learning. We now have evidence that the individual-specific morphology of the cortex in this region of the prefrontal cortex is important for learning in a simple decision-making task. It is important to note that not all sources of variation in stimulation efficacy have accounted in our model. Many other factors are likely to play a role in the effects of tDCS on cognitive performance, including experimental factors (e.g., precision/consistency of electrode placement), neurochemical concentrations (e.g. Filmer et al., 2019; Li et al., 2015), white matter (connectivity) properties, and state-based factors such as fatigue and motivation. It is also possible that other brain regions, outside of the ROIs we selected here, contribute to stimulation efficacy. The latter could arise from the direct effects of stimulation, or indirectly from connectivity with areas directly influenced by stimulation.

We cannot say with certainty what is at the core of the relationship between disruption to learning via stimulation and cortical thickness. It is possible that variation in cortical thickness affects the path of the applied electrical current, and that variability in the location or magnitude of the current across regions of the cortex gives rise to individual variation in tDCS efficacy. Indeed, the role of individual anatomy in modulating current flow has been highlighted in recent work (Dux et al., 2006). However, when we directly modelled the induced current in the cortex the results remained substantively unchanged, suggesting that the relationship between anodal tDCS efficacy and cortical thickness is unlikely to be explained simply by the field of the induced current. Alternatively, variation in cortical thickness may reflect underlying neural properties of how the decision-making task is learned, with stimulation differentially modulating behaviour based on these specific properties. We propose that the latter is perhaps more plausible (or, at least, part of the answer) as we found that cortical thickness can predict decision-making learning in the absence of effective stimulation (in the sham session), i.e., cortical thickness has at least some relevance to variability in learning magnitude irrespective of inducing a current with tDCS.

Although it was not a focus of our study, we also looked at whether cortical morphology was correlated with performance on a range of behavioural tasks. Our findings linked performance with cortical thickness for two of the four paradigms: the PRP task and Raven's Matrices. For the PRP task, multitasking costs were associated with cortical thickness in the region around the left inferior frontal junction, in line with previous fMRI findings (Hearne et al., 2016). Raven's scores, on the other hand, were associated with the right middle frontal gyrus. This is in line with recent resting-state connectivity analyses implicating this region in general intelligence (Horvath et al., 2014).

In sum, we have provided the first demonstration that cortical morphology is related to an individual's behavioural response to tDCS. Variability in responsiveness to stimulation has been cited as a concern for the field (Parkin et al., 2015), and has been suggested to limit the potential usefulness of the approach (Filmer et al., 2013a,b). Studies such as ours will be important for developing models to predict tDCS efficacy, and also to provide insights into how stimulation can modulate the brain and behaviour. Both of these points are important for future clinical applications of tDCS, and may assist in optimising paradigms aimed at investigating the effects of tDCS on behaviour.

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