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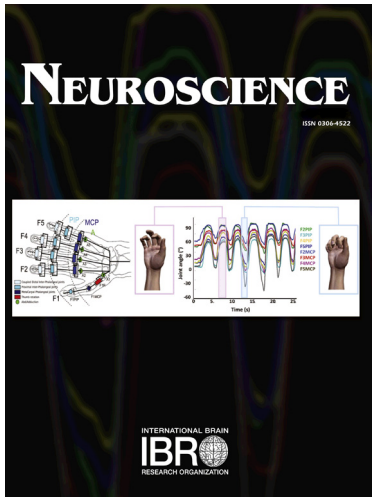

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PII: S0306-4522(17)30724-8
DOI: https://doi.org/10.1016/j.neuroscience.2017.10.005
Reference: NSC 18070

To appear in: *Neuroscience*

Received Date: 31 May 2017
Accepted Date: 4 October 2017

Please cite this article as: A.K. Martin, J. Huang, A. Hunold, M. Meinzer, Sex mediates the effects of high-definition transcranial direct current stimulation on "mind-reading", *Neuroscience* (2017), doi: https://doi.org/10.1016/j.neuroscience.2017.10.005

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Sex mediates the effects of high-definition transcranial direct current stimulation on "mind-reading"

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Sex differences in social cognitive ability are well established, including measures of Theory of Mind (ToM). The aim of this study was to investigate if sex mediates the effects of high definition transcranial direct current stimulation (HD-tDCS) administered to a key hub of the social brain (i.e., the dorsomedial prefrontal cortex, dmPFC) on the Reading the Mind in the Eyes Test (RMET). 40 healthy young adults (18-35 years) were randomly allocated to receive either anodal or cathodal HD-tDCS in sham HD-tDCS controlled, double blind designs. In each of the two sessions, subjects completed the RMET. Anodal stimulation to the dmPFC increased accuracy on the RMET in females and impaired performance in males. To assure regional specificity we performed a follow up study stimulating the right temporoparietal junction and found no effect in either sex. The current study is the first to show improved performance on the RMET after tDCS to the dmPFC in females only. The polarity specific effects and use of focal HD-tDCS provide evidence for sex dependent differences in dmPFC function in relation to the RMET. Future studies using tDCS to study or improve ToM, need to consider sex.

Dorsomedial prefrontal cortex; Theory of Mind; Social cognition; Sex differences; Brain stimulation; Temporoparietal junction

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Introduction

Theory of mind (ToM) refers to the ability to ascribe mental states to others that differ from those of our own. For example, we are able to attribute the actions of others (e.g. reaching for food) to underlying, unobservable mental states (e.g. they *want* food) that often differ from one's own (Decety & Sommerville, 2003). Although this ability is considered fundamental for what makes us human, ToM ability has been shown to vary across the lifespan, between different cultural groups, and between sexes (Adams et al., 2010; Baron-Cohen et al., 2006; Moran, 2013). Females often outperform their male counterparts on measures of ToM, with the greatest differences observed on measures of affective ToM, or the ability to understand the emotions of others (McClure, 2000). As ToM deficits are apparent in neuropsychiatric disorders associated with sex ratios in favour of males, such as autistic spectrum disorders and schizophrenia (Diflorio & Jones, 2010; McGrath, 2006; Newschaffer et al., 2007), understanding the sex-dependent effects of tDCS on social cognition has both the potential to improve our understanding of the social brain and improve our ability to intervene.

ToM has conceptualized as two largely independent systems or components, i.e., cognitive and affective ToM (Baron-Cohen & Wheelwright, 2004; Kalbe et al., 2010). Cognitive ToM refers to the ability to understand the beliefs and intentions of others as different to our own while affective ToM refers to the ability to understand the emotions or feelings of others as different to our own. Importantly, sex differences have been highlighted for both cognitive (Russell, Tchanturia, Rahman, & Schmidt, 2007) and affective ToM, including the Reading the Mind in the Eyes Task (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb,

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2001; Rutherford et al., 2012; Schiffer, Pawliczek, Muller, Gizewski, & Walter, 2013). Whereas Russell et al (2007) showed a male advantage on a measure of cognitive ToM, females consistently outperform males on measures of emotion recognition or affective tasks (McClure, 2000), including the RMET (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, et al., 2001).

The neural networks subserving human social cognition have predominantly been investigated using functional magnetic resonance imaging (fMRI). These studies have identified a set of regions that are consistently activated across social tasks are often referred to as the 'social brain' (Adolphs, 2009). A region often described is the medial prefrontal cortex (mPFC) and within the mPFC, the dorsal region has been implicated with tasks requiring the consideration of others (such as ToM task and trait attributions; Amodio & Frith, 2006; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Although the dmPFC is often associated with cognitive ToM tasks, it is also implicated in affective ToM (Sebastian et al., 2012; Vollm et al., 2006). Sex mediated differences in dmPFC activity during ToM tasks have been identified using fMRI. For example, Frank *et al* (2015), identified greater activity in females during a false-belief task. Other studies have identified sex mediated differences in connectivity during rest in networks thought to subserve ToM functioning, including the default mode network (DMN; Takeuchi et al., 2014) which includes the dmPFC. Sex mediated differences have also been identified in structural connectivity within the DMN (Ritchie et al, 2017).

Recently, transcranial direct current stimulation (tDCS) has been employed to study the social brain (for review see Sellaro, Nitsche, & Colzato, 2016), including ToM (Adenzato et

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al., 2017; Martin, Dzafic, Ramdave, & Meinzer, 2017; Santiesteban, Banissy, Catmur, & Bird, 2015). TDCS is a safe, non-invasive technique that modulates neural activity through the application of a weak current to the skull. Generally, it is thought that excitatory "anodal" tDCS increases and inhibitory "cathodal" stimulation reduces the likelihood of neuronal firing, although polarity specific effects may not always be present (Fertonani & Miniussi, 2016) and cathodal stimulation often results in weaker effects (Jacobson, Koslowsky, & Lavidor, 2012; Lafon, Rahman, Biksom, & Parra, 2016). Anodal stimulation is thought to increase the resting potential of the neuronal population underneath the anode. Although this does not result in action potentials and neuronal firing, it reduces the neuronal input necessary to reach threshold and fire. Cathodal stimulation may result in weaker effects due to the antagonistic effects on the neuron at the soma and axon (for details see Lafon *et al,* 2016). Sex differences in tDCS response have rarely been explored in social cognition (Conson et al., 2015; Fumagalli et al., 2010). Only one study has explored sex differences in tDCS response on ToM functioning, (Adenzato et al., 2017) with an interaction identified between sex and response to anodal tDCS to the mPFC on a cognitive ToM measure, with improved performance in females only.

The current study is the first to explore whether sex mediates the effect of tDCS to the dmPFC during affective ToM, using the RMET. We used high-definition tDCS (HD-tDCS) which allows for more focal current delivery to the target region and used both anodal and cathodal sham-controlled studies to investigate polarity specific effects. Stimulation of a control site within the "social brain" network (right temporoparietal junction, rTPJ) addressed site specificity.

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Experimental Procedures

Participants

All subjects were tDCS-naive, were not currently taking psychoactive medication, and had no diagnosis of neurological or psychiatric disorder. They provided written consent prior to inclusion, completed a safety-screening questionnaire and were compensated with AUD$50.

40 healthy young adults aged between 18 and 35 were recruited for the study. 20 each were stratified by sex and assigned to either anodal or cathodal HD-tDCS, double-blinded, sham HD-tDCS controlled, crossover studies. Each group contained equal male and females counterbalanced for stimulation order. The cohort in the anodal and cathodal studies were matched for age, M±SD, 22.9±4.4 v 24.0±4.1 years, p=0.42. There were no differences in age between males and females in either study, (M±SD F/M, anodal study: = 21.6±2.7/ 24.1±5.5 years, p=0.21; cathodal study: 23.9±3.4/ 24.0±4.9 years, p=0.96).

In order to assess regional specificity, we conducted a follow-up study and stimulated the right temporoparietal junction, a region within the social brain not previously associated with RMET performance (Schurz et al., 2014). Only anodal stimulation was used as the cathodal stimulation was not significant in the initial dmPFC study. 20 healthy young adults (10 male/10 female) aged beteen 18 and 35 were recruited. A double-blinded, sham HD-tDCS controlled, crossover design was employed with stimulation order randomized equally for males and females.

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Baseline Testing

In order to control for differences between sexes, or polarity of stimulation, being as a result of underlying depression, anxiety, or autistic spectrum scores, questionnaires were completed prior to testing. Baseline depression and anxiety scores were collected using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Autism quotient scales were collected using the Autism Spectrum Quotient (ASQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001).

In order to control for differences between sexes or the two independent samples (anodal and cathodal studies), being as a result of underlying cognitive differences, a number of baseline cognitive measures were collected. We used the following tests: Stroop Test, National Adult Reading Test (NART), Boston Naming Test, phonemic and semantic verbal fluency, and the following tests from CogState® computerized test battery (https://cogstate.com/): International shopping list, Identification test, One-back, Two-back, Set-shifting test, Continuous paired associates learning test, social-emotional cognition test, and the International shopping list - delayed recall.

Any differences identified were subsequently entered into the models to assess the association with sex or polarity mediated effects. Subjects were randomly assigned either active or sham stimulation first, with order of stimulation balanced across sex.

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Transcranial direct current stimulation

The stimulation was administered using a one-channel direct current stimulator (DC-Stimulator Plus®, NeuroConn) and two concentric rubber electrodes (Bortoletto, Rodella, Salvador, Miranda, & Miniussi, 2016; Gbadeyan, Steinhauser, McMahon, & Meinzer, 2016). A small centre electrode (diameter: 2.5 cm) and a ring-shaped return electrode (diameter inner/outer: 9.2/11.5cm) were used (see Figure 1). The set-up is a variation of the "4x1" HD-tDCS set-up, which constrains the current by using four return electrodes that are arranged in a circle around the centre electrode (Alam, Truong, Khadka, & Bikson, 2016; Hogeveen et al., 2016; Kuo et al., 2013). Safety, effective behavioural modulation and focal current delivery have been demonstrated for both montages, but the concentric set-up was chosen because it does not require an expensive multi-channel stimulator (Bortoletto et al., 2016; Gbadeyan, Steinhauser, et al., 2016). Electrodes were attached over the target region using an adhesive conductive gel (Weaver Ten20® conductive paste) and held in place with an EEG cap to ensure a stable conductive adhesion with the skin. The position of the centre electrode was determined using the 10-20 international EEG system. In study 1, the dmPFC was located by first locating FPz and Fz and measuring the distance between. The scalp region overlying the dmPFC was located by locating 15% of the distance from the Fz towards the FPz. This approximated the MNI coordinates (0/54/33), which corresponds to the peak activity in the ToM meta-analysis conducted by Schurz *et al* (2014). The ring electrode was positioned symmetrically around the centre electrode. In the follow up study, the right TPJ was located by locating CP6 of the 10-20 international EEG system. In order to fit the HD-tDCS electrodes without overlapping the right ear, a slightly smaller return electrode

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(diameter inner/outer: 7.5/9.8cm). The small centre electrode was identical to the dmPFC stimulation.

In all stimulation conditions, the current was ramped up to 1mA over 8 seconds prior to 40 seconds direct current prior to commencement of the experiment. In the "sham" condition the direct current then ramped down over 5 seconds. Following this, no stimulation was delivered. In the active stimulation conditions (anodal & cathodal) HD-tDCS was administered for 20 minutes before ramping down over 5 seconds. In the anodal HD-tDCS condition, the centre electrode was the anode and the ring electrode was the cathode. The polarities were switched for the cathodal HD-tDCS condition. During sham HD-tDCS, the current was ramped down after 15 seconds, which elicits a physical sensation on the scalp, mimicking that of the active stimulation, to assure participants were blinded to the experimental condition, without modulating neural function. Researchers were blinded to the experimental condition by using the "study-mode" of the DC-stimulator (i.e. a pre-assigned code triggered the respective stimulation conditions). Adverse effects and mood were assessed following each stimulation session.

To avoid carryover effects of stimulation, stimulation sessions were conducted with at least 72 hours (3 days) in between. Neurophysiological studies that employed conventional set-ups have confirmed that the effects of single stimulation sessions are short lived (depending on the stimulation parameters approx. 30-60 min). Consequently, typical wash-out times in cross-over studies range from 1 - 7 days (for reviews see Sarkis, Kaur, & Camprodon, 2014; Stagg & Nitsche, 2011). While HD-tDCS effects on motor evoked potentials may be stronger and slightly delayed compared with conventional tDCS (Kuo et al. 2013), no significant neurophysiological effects were found beyond 120 min after the end of the

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stimulation for HD-tDCS as well. Therefore, it is safe to assume that three days are sufficient to prevent carry-over effects of the stimulation.

Reading the Mind in the Eyes Test (RMET)

The RMET (Baron-Cohen, Wheelwright, Hill, et al., 2001) is considered a measure of affective ToM functioning, although recently conceptualized as a measure of emotion recognition (Oakley, Brewer, Bird, & Catmur, 2016). Subjects completed the Reading the Mind in the Eyes test (RMET) as part of a larger battery of social cognitive tests described in detail in a previous study of our group (Martin, Dzafic, Ramdave, & Meinzer, 2017). Subjects completed the same test in session two, although the order of stimuli were randomized to prevent simple memory effects. We modified the task to include a greater variety of female eyes, especially older females. We also amended the responses so that each option only occurred once throughout the test. A set of eyes were presented with four mental attribution words surrounding. Subjects were instructed to choose the mental attribution that was best represented in the eyes. Subjects were then asked to judge the age and sex of the person in the picture, again on a four-point scale (1= young male, 2= young female, 3= old man, 4= old woman). Old was considered greater than 50 years of age. There was no time limit on responding and the next stimulus was presented as soon as a response was recorded. The age/sex question occurred directly after the mental state attribution question, with both conditions during online (active or sham) stimulation. Accuracy scores were computed for the mental attributions and age and sex judgments (each with a total correct out of 38).

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Statistical analysis

Repeated measures analysis of variance (RM-ANOVA) with stimulation (active or sham) as a within-subjects factor and study (anodal and cathodal) and sex (male or female) as between-subject factor was conducted. Baseline cognitive, HADS, and ASQ scores were assessed using independent groups t-tests. Significant results were entered into the above models as covariates. Paired t-tests were used for follow-up analyses. All measures were checked for the relevant assumptions for the statistical model used.

Current modelling

Current modelling for both the dmPFC and right TPJ is provided in figure 1.

*** Figure 1 here ***

Figure 1. Current modelling for both the dmPFC and rTPJ. Left: FEM volume conductor elements of the scalp surface (gray) and the stimulation electrodes, anode (red) and cathode (blue). Center: current density vectors in sagittal (top) and coronal (bottom) slices of the models, color-coded by their amplitude in logarithmic scale. Right: current density amplitude in the gray matter surface elements color-coded in linear scale.

Modeling of current flow was based on a realistic head model and structural T1-weighted magnetic resonance imaging dataset of a healthy young volunteer (standard T1-sequence, 3T MAGNETOM Trio, Siemens, Erlangen, Germany). The MRI data was segmented using the

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FreeSurfer (FS) software (Martinos Center for Biomedical Imaging, Charlestown, MA, USA, www.surfer.nmr.mgh.harvard.edu, (Fischl, 2012)). Afterwards, binary masks for white and gray matter, cerebrospinal fluid, skull and scalp using a segmentation approach were created (Perdue & Diamond, 2014) using the iso2mesh toolbox (Fang & Boas, 2009). The combined binary masks were meshed with the freely available SimBio-Vgrid software (www.vgrid.simbio.de) to hexahedral elements with an isotropic resolution of 1 mm allowing a node shift with a constraint of 0.33 (Camacho, Hopper, Lin, & Myers, 1997; Wolters, Anwander, Berti, & Hartmann, 2007). The finite element method (FEM) model comprised 4.3 million hexahedral elements with 4.4 million nodes in a right - anterior - superior (RAS) coordinate system. We assigned the following tissue compartment conductivity values: 0.14 S/m (white matter), 0.33 S/m (gray matter), 1.79 S/m (cerebrospinal fluid, CSF), 0.014 S/m (skull) and 0.33 S/m (scalp), (Baumann, Wozny, Kelly, & Meno, 1997; Baysal & Haueisen, 2004; Geddes & Baker, 1967)

For the simulation of stimulation effects, we extended our volume conductor model of the head with stimulation electrodes. Similar to Wagner et al. (2014), we dilated the scalp layer 4 mm. This layer represented the compartments of rubber electrodes and conductive paste. According to the electrode geometry used in our present study, we used a central disk and a concentric cylinder ring centered at positions derived from the international 10-20-system. Electrode dimensions and positions matched the ones previously described. For the frontal stimulation site, we centered the electrodes on the midline 15% from Fz towards the Fpz with a diameter of 25 mm for the central disk; the cylinder ring had an inner diameter of 92 mm and outer diameter of 115 mm. For the parietal stimulation site, we centered the

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electrodes on the position CP6 with a diameter of 25 mm for the central disk; the cylinder ring had an inner diameter of 75 mm and outer diameter of 98 mm.

The HD-tDCS simulations were performed in the SimBio software, applying the adjoint approach (Wagner et al., 2014). We obtained the vectorial current density in each finite element generated by HD-tDCS. The current strength was set to 1 mA at the central disk electrode and to -1 mA at the concentric ring electrode-. The electrode conductivity was set to 1.4 S/m (Datta, Baker, Bikson, & Fridriksson, 2011).

RESULTS

There were no significant differences between performance on the RMET nor the age/sex attributions between the first and second sessions across the entire sample or in each sample independently (all $p>0.15$). This shows that learning did not influence the results in the current study. There was no difference between the order of stimulation for males (5 active first) or females (6 active first) in either the anodal-tDCS study ($X^2= 0.37$) or for males (5 active first) or females (5 active first) in the cathodal-tDCS study ($X^2=1$). Baseline cognitive performance was comparable between the anodal and cathodal groups (see Table 1). Females outperformed males on the International shopping list – delayed response (10.9 v 9.8, $p=0.02$) and males reported more depressive symptoms on the HADS (3.2 v 1.9, $p=0.04$) (see Table 2). Therefore, these were entered as covariates in follow-up analyses for those with significant interaction with sex. No differences between females and males were noted on other baseline variables.

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Adverse Effects and Blinding

All participants tolerated the stimulation well with only minor physical sensations. Self-reported mild adverse effects and mood (Brunoni et al., 2011; Folstein & Luria, 1973) were comparable between the stimulation conditions (see Table 3). Subjects guessed the stimulation order at chance level in both the anodal dmPFC (number of correct guesses: 11/20, p=0.65), cathodal dmPFC HD-tDCS studies (number of correct guesses: 7/20 p=0.18). There was no difference in self-reported blinding between males and females in the anodal study (M=7/10, F=4/10, p=0.18) nor in the cathodal study (M=4/10, F=3/10, p=0.22). This demonstrates that the behavioural effects of stimulation were not affected by non-related side-effects of the stimulation or the participants' ability to recognize active stimulation.

Reading the Mind in the Eyes (RMET)

RMET performance did not correlate with ASQ nor with any of the baseline measures (all p's >0.1). During sham-tDCS (baseline performance), females (M=28.00±3.08) and males (M=27.00±3.11), had comparable performance on the RMET, t(38)=1.02, p=0.31. A significant interaction was identified between stimulation (sham & active), study (anodal & cathodal), and sex (male & female), such that anodal improved performance in females (M=29.6 ±0.9) compared to sham (M=28.0 ±1.0) and impaired performance in males (M=26.4±0.9) compared to sham (M=27.9 ±1.0), F(1, 36)= 6.98, p=0.01, η_2=0.16 (see Figure 2). Follow-up analysis in the anodal and cathodal studies separately identified a significant effect for the stimulation by sex interaction for the anodal study, F(1,18)= 6.05, p=0.02, η_2=0.25 but not for the cathodal study, F(1, 18)=1.36, p=0.26, η_2=0.07. Paired t-test

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identified a significant improvement in females after anodal stimulation, t(9)=-2.39, p=0.04, cohen's d=0.82. However, the decline in males was not significant, t(9)=1.41, p=0.19, cohen's d=0.45. There was no overall effect (combined male and female) of stimulation on the RMET for either anodal (M=28.0 ±0.6) compared to sham (M=28.0 ±0.7), or cathodal (M=27.1 ±0.7) compared to sham (M=26.7 ±0.6) (see Table 4). As performance on the delayed recall section of the International Shopping List and depression symptoms on the HADS were significantly different between males and females (see Table 2), we entered these into the general linear model as covariates. The significant interaction between stimulation, study, and sex remained significant, F(1, 31)= 7.85, p=0.009, η_2=0.20. The significant interaction between stimulation and sex in the anodal study only, also remained significant, F(1, 16)= 8.06, p=0.01, η_2=0.34. Therefore, the sex mediated effects of stimulation were not due to baseline cognitive or depression differences between males and females.

***** Figure 2 here *****

Figure 2. Effect of anodal and cathodal HD-tDCS to the dmPFC and anodal HD-tDCS to the rTPJ on performance on the RMET. Positive scores indicate increase in correct responses after active stimulation. Error bars represent standard error of the mean.

Age and Sex Attribution

Overall, males (M=32.58) and females (32.30) performed comparably on the age and sex attribution test, F(1, 36)= 0.17, p=0.68, η_2=0.005. No interaction was identified between

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stimulation (active v sham), study (anodal v cathodal), or sex (male v female) for the age and sex control task, $F(1, 36)= 0.12$, $p=0.73$, $\eta_2=0.003$.

RESULTS – Follow up study (rTPJ stimulation)

Performance on the baseline cognitive measures was comparable between the dmPFC and rTPJ studies, with all subjects performing within normal age-corrected norms. All participants tolerated the rTPJ stimulation well with only minor physical sensations (see Table 3). Subjects guessed the active rTPJ stimulation at chance level, (number of correct guesses: 11/20 $p=0.65$).

There were no significant differences between performance for either the RMET or the age/sex attributions between the first and second sessions (all $p>0.2$). Therefore, learning did not influence the results in the current study. There was no difference between the order of stimulation for males (5 active first) or females (5 active first) ($X^2=1$).

No effect of anodal stimulation was identified on the RMET in the combined (male & female) sample, $F(1, 18)= 2.08$, $p=0.17$, $\eta_2=0.10$, nor was an interaction with stimulation and sex identified, $F(1, 18)= 0.03$, $p=0.88$, $\eta_2=0.001$. No effect of anodal stimulation was identified on the age/sex judgements in the combined sample, $F(1, 18)= 1.03$, $p=0.33$, $\eta_2=0.05$, nor was an interaction with stimulation and sex identified, $F(1, 18)= 0.66$, $p=0.43$, $\eta_2=0.04$ (see Table 4). As anxiety was significantly greater in females (see Table 5), we entered this into the model with no effect.

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Table 1. Baseline cognitive characteristics of subjects in the anodal and cathodal sham-controlled studies. Mean and standard deviations are reported. Cognitive data for subjects included in the right TPJ study is provided.

Task	dmPFC Anodal X±sd	dmPFC Cathodal X±sd	Between groups comparison	rTPJ Anodal X±sd
Questionnaires				
HADS - depression	2.6±1.9	2.5±6.3	p=0.82	3.9±2.8
HADS - anxiety	7.1±4.4	6.4±2.6	p=0.51	7.8±4.6
ASQ	14.7±5.7	13.9±5.7	p=0.66	14.8±6.4
Cognitive screening				
Stroop - colour naming	27.2±4.3	25.2±4.0	p=0.12	28.3±6.8
Stroop - word reading	21.0±3.8	19.3±3.2	p=0.14	21.8±4.3
Stroop – inhibition	45.8±7.5	41.7±9.0	p=0.13	45.2±10.5
NART FSIQ	110.1±3.7	111.6±4.0	p=0.24	103.3±4.0
Boston Naming Test (out of 15)	14.1±0.9	14.0±1.1	p=0.75	14.8±0.4
Verbal Fluency - phonemic	17.2±4.5	17.7±4.5	p=0.70	18.1±6.2
Verbal Fluency - semantic	25.1±4.3	24.8±5.8	p=0.85	25.6±6.0
ISL (number correct out of 36)	29.5±3.6	29.6±2.9	p=0.86	29.0±2.9
IDN - acc	1.6±0.3	1.5±0.1	p=0.20	1.5±0.1
ONB - acc	1.4±0.1	1.4±0.1	p=0.84	1.3±0.2
TWOB - acc	1.3±0.1	1.3±0.1	p=0.79	1.2±0.2
SETS (number of errors out of 120)	13.8±3.3	15.7±5.2	p=0.18	18.2±7.5
CPAL (number of errors)	47.0±42.9	32.9±31.2	p=0.24	51.7±33.1
SEC - acc	1.2±0.1	1.1±0.1	p=0.48	1.1±0.1
ISL- delayed recall (out of 12)	10.3±1.4	10.5±1.2	p=0.60	10.3±1.0

NART FSIQ= National Adult Reading Test Full-scale Intelligence Quotient, HADS= Hospital anxiety and depression scale, ASQ= Autism Spectrum Quotient, ISL= International Shopping List Test, IDN= Identification Test, ONB= One Back Test, TWOB= Two Back Test, SETS= Set-Shifting Test, CPAL= Continuous Paired Associates Learning Test, SEC= Social-Emotional Cognition test, acc= Accuracy (arcsin sqrt proportion).

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Table 2. Baseline cognitive characteristics of males and females across the anodal and cathodal sham-controlled dmPFC stimulation studies. Mean and standard deviations are reported.

Task	Female Mean**±sd**	Male Mean**±sd**	Between groups comparison
Questionnaire			
HADS - depression	1.9±1.6	3.2±2.4	*p=0.04*
HADS - anxiety	7.3±3.6	6.2±3.5	p=0.36
ASQ	14.1±6.2	14.6±5.1	p=0.78
Cognitive screening			
Stroop - colour naming	27.0±4.6	25.4±3.6	p=0.21
Stroop - word reading	21.0±3.6	19.3±3.4	p=0.14
Stroop - inhibition	44.8±9.3	42.8±7.5	p=0.44
NART FSIQ	111.2±2.7	110.6±4.9	p=0.65
Boston Naming Test (out of 15)	14.1±1.0	13.9±1.0	p=0.53
Verbal Fluency - phonemic	16.5±4.4	18.4±4.4	p=0.19
Verbal Fluency - semantic	25.7±5.2	24.3±4.9	p=0.39
ISL (number correct out of 36)	30.3±2.6	28.9±3.5	p=0.18
IDN - acc	1.5±0.1	1.6±0.3	p=0.37
ONB - acc	1.4±0.1	1.4±0.1	p=0.28
TWOB - acc	1.3±0.1	1.3±0.1	p=0.86
SETS (number of errors out of 120)	13.6±3.9	15.9±4.8	p=0.12
CPAL (number of errors)	37.2±35.9	45.7±40.2	p=0.50
SEC - acc	1.1±0.1	1.2±0.1	p=0.67
ISL- delayed recall (out of 12)	10.9±1.1	9.8±1.4	*p=0.02*

NART FSIQ= National Adult Reading Test Full-scale Intelligence Quotient, HADS= Hospital anxiety and depression scale, ASQ= Autism Spectrum Quotient, ISL= International Shopping List Test, IDN= Identification Test, ONB= One Back Test, TWOB= Two Back Test, SETS= Set-Shifting Test, CPAL= Continuous Paired Associates Learning Test, SECT= Social-Emotional Cognition Test, acc= Accuracy (arcsin sqrt proportion).

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Table 3. Summary of positive and negative mood ratings assessed pre and post stimulation and adverse effects ratings as assessed after the end of each stimulation session for both stimulation conditions (active-, sham- dmPFC and rTPJ HD-tDCS) for both anodal and cathodal stimulation studies; means and standard deviation are reported.

Symptom	dmPFC anodal Stimulation		Within group comparison	dmPFC cathodal Stimulation		Within group comparison	rTPJ anodal stimulation		Within group comparison
	Active	Sham		Active	Sham		Active	Sham	
Headache	1.2±0.4	1.4±0.7	p=0.21	1.3±0.4	1.2±0.4	p=0.16	1.4±0.5	1.5±0.7	p=0.80
Neck pain	1.1±0.2	1.1±0.2	p=1.00	1.0±0.0	1.1±0.2	p=0.33	1.2±0.4	1.2±0.5	p=0.75
Scalp pain	1.3±0.6	1.1±0.2	p=0.06	1.1±0.2	1.2±0.4	p=0.16	1.2±0.5	1.3±0.7	p=0.58
Tingling	1.8±0.6	1.6±0.6	p=0.26	1.7±0.7	1.6±0.6	p=0.49	1.8±0.7	1.7±0.6	p=0.61
Itching	1.3±0.4	1.2±0.4	p=0.67	1.1±0.2	1.0±0.0	p=0.33	1.2±0.4	1.3±0.4	p=0.67
Burning	1.4±0.6	1.2±0.4	p=0.33	1.4±0.7	1.3±0.5	p=0.49	1.5±0.7	1.3±0.4	p=0.16
Sleepiness	1.8±1.0	1.7±1.0	p=0.69	1.8±0.8	1.7±0.8	p=0.61	1.8±0.8	1.8±0.6	p=1.00
Concentration	2.1±0.9	1.7±0.9	p=0.14	1.5±0.7	1.6±0.6	p=0.75	1.8±0.9	1.9±0.8	p=0.48
Mood changes	1.2±0.5	1.2±0.4	p=1.00	1.1±0.3	1.1±0.3	p=1.00	1.3±0.6	1.2±0.4	p=0.67
VAMS									
Positive	-5.8±23.5	-4.5±32.5	p=0.89	-4.6±12.7	-12.5±23.9	p=0.12	-0.5±1.7	-1.1±1.8	p=0.38
Negative	5.3±6.7	-0.5±13.4	p=0.13	2.1±6.1	1.2±5.5	p=0.56	0.2±0.7	0.2±0.8	p=0.81

VAMS=Visual analogue mood scale

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Table 4. Performance on the Reading the Mind in the Eyes Test (RMET) during sham and active stimulation across the dmPFC anodal, cathodal, and rTPJ anodal studies for males and females separately.

	Sham condition			Active stimulation				
	Mean	sd	Range	Mean	sd	Range	p-value	Effect size (cohen's d)
dmPFC anodal study								
Males	27.9	2.4	25-32	26.4	3.2	22-32	.19	0.45
Females	28.0	2.4	24-32	29.6	1.4	28-32	*.04**	0.82
dmPFC cathodal study								
Males	26.1	3.6	21-33	26.3	2.7	23-30	0.79	0.10
Females	28.0	3.8	21-34	27.0	3.3	24-32	0.21	0.43
rTPJ anodal study								
Males	26.8	3.8	21-32	25.6	5.1	17-32	0.35	0.33
Females	29.2	3.8	21-33	27.7	4.1	21-35	0.32	0.33

dmPFC = dorsomedial prefrontal cortex; rTPJ= right temporoparietal junction

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Table 5. Baseline cognitive characteristics of males and females across the anodal rTPJ stimulation study. Mean and standard deviations are reported.

Task	Female Mean**±sd**	Male Mean**±sd**	Between groups comparison
Questionnaire			
HADS - depression	3.8±3.3	3.9±2.3	p=0.94
HADS - anxiety	9.9±4.8	5.7±3.5	*p=0.04*
ASQ	15.2±4.4	14.4±8.1	p=0.79
Cognitive screening			
Stroop - colour naming	29.9±8.4	26.7±4.6	p=0.30
Stroop - word reading	21.8±4.3	21.8±4.5	p=1.00
Stroop - inhibition	42.1±7.5	48.2±12.6	p=0.20
NART FSIQ	103.0±2.4	103.6±5.2	p=0.75
Boston Naming Test (out of 15)	14.8±0.4	14.8±0.4	p=1.0
Verbal Fluency - phonemic	18.7±8.4	17.4±3.2	p=0.65
Verbal Fluency - semantic	25.6±7.2	25.6±4.9	p=1.0
ISL (number correct out of 36)	29.5±2.7	28.4±3.1	p=0.41
IDN - acc	1.5±0.1	1.5±0.1	p=0.59
ONB - acc	1.2±0.3	1.3±0.1	p=0.32
TWOB - acc	1.1±0.2	1.3±0.1	p=0.12
SETS (number of errors out of 120)	16.6±7.4	19.7±7.6	p=0.37
CPAL (number of errors)	39.0±26.6	64.4±35.3	p=0.09
SEC - acc	1.1±0.2	1.1±0.1	p=0.75
ISL- delayed recall (out of 12)	10.6±1.2	10.0±0.7	p=0.18

NART FSIQ= National Adult Reading Test Full-scale Intelligence Quotient, HADS= Hospital anxiety and depression scale, ASQ= Autism Spectrum Quotient, ISL= International Shopping List Test, IDN= Identification Test, ONB= One Back Test, TWOB= Two Back Test, SETS= Set-Shifting Test, CPAL= Continuous Paired Associates Learning Test, SECT= Social-Emotional Cognition Test, acc= Accuracy (arcsin sqrt proportion).

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DISCUSSION

In this study, we provide the first evidence that HD-tDCS can improve affective ToM performance in females only in a region specific manner. The sex mediated effects of HD-tDCS provide the first causal evidence for sex differences in dmPFC functioning and its association with affective ToM.

Variability in response to non-invasive brain stimulation has been of increased interest (Fertonani & Miniussi, 2016). Understanding the variability in tDSC response and the underlying mechanisms responsible is of paramount importance, with several lines of research addressing the issue. For example, a recent study found that current flow to frontal regions was sex-dependent (Russell et al., 2017) and may partially explain sex-dependent differences in cognitive response to tDCS, especially considering sex has been shown to moderate the effects of DLPFC stimulation dose, with greater effect sizes associated with greater number of females within a study (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). Previous studies have highlighted the variable effects of stimulation in the motor and cognitive domains (Dyke, Kim, Jackson, & Jackson, 2016; Lindenberg, Sieg, Meinzer, Nachtigall, & Floel, 2016; Martin, Meinzer, Lindenberg, Sieg, & Floel, 2017; Sarkar, Dowker, & Cohen Kadosh, 2014) with sex mediated effects previously identified in studies into auditory and visual processing using tDCS (Chaieb, Antal, & Paulus, 2008; Ladeira et al., 2011). In the social cognitive domain, sex mediated effects have previously been identified for mPFC stimulation on a cognitive ToM task, such that anodal stimulation improved performance for females only (Adenzato et al., 2017). In the current study we used a more

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focal stimulation to identify sex specific effects of stimulation to the dmPFC and extended the findings of Adenzato *et al* (2017) to affective ToM as well as cognitive ToM.

Sex effects on social cognition have been identified across a number of tasks, including the RMET (Baron-Cohen et al., 1997; Baron-Cohen, Wheelwright, Hill, et al., 2001). Although not significant, females performed slightly better on the RMET at baseline (28.0 v 27.0). A female advantage on measures of emotion recognition or affective ToM has been suggested to reflect differences in cognitive style or underlying neuroanatomical or functional differences. To date, sex differences in affective ToM have received little attention and evidence for brain-level differences remain scarce.

One possible explanation for sex differences in tDCS response could be underlying neuroanatomical differences. A recent large study (N= 5216) identified greater connectivity in females in the default mode network (DMN) which includes the mPFC (Ritchie, 2017). A large meta-analysis also identified greater grey-matter volume or density in females in several prefrontal regions including the middle frontal gyrus and frontal pole (Ruigrok et al., 2014). The greater neural tissue may result in an enhanced effect of tDCS in females. Likewise, the greater connectivity may result in greater excitability of downstream regions enhancing the network-level recruitment of neural resources, consequently improving performance in females.

Another possibility is that females have functional differences in the dmPFC in regards to ToM. Although the majority of fMRI studies into ToM recruit all male or all female samples to remove the issue of sex differences, few studies have directly compared ToM related

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activation differences between the sexes. Using the RMET, Baron-Cohen (2006) identified greater activation in the DLPFC in males with greater recruitment of the inferior frontal gyri bilaterally in females, but no differences in the dmPFC. In the two studies to identify dmPFC recruitment for affective ToM, both only included males. Therefore, the current study suggests that functional differences in the dmPFC may underlie sex-mediated effects in affective ToM performance.

Integration of other into self is considered to be a key component underlying empathic or ToM ability (Cialdini, Brown, Lewis, Luce, & Neuberg, 1997). The dmPFC may have a considerable role in our ability to integrate social information from external sources into the self (Martin, Dzafic, et al., 2017). One possibility supported by previous studies (Baron-Cohen, 2002) is that females may rely on a more integrative or empathic cognitive approach to attributing mental states that requires a greater mergence between self and other. Therefore, females may recruit the dmPFC to a greater extent for tasks requiring mental state attribution. On the other hand, males may approach the same task with a more systematic cognitive style for attributing mental states that may rely on networks or regions not involving the dmPFC, such as DLPFC as identified by Baron-Cohen *et al* (2006). If increasing excitability in the dmPFC reduces excitability in the DLPFC due to network level antagonism (Anticevic et al., 2012), this may explain the reduction in performance in males after stimulation to the dmPFC. The empathizing-systemizing theory has been extended to the extreme male brain theory of autism (Baron-Cohen, 2002) and sex related differences in tDCS response may have implications for understanding autism and the greater prevalence in males (Chakrabarti & Fombonne, 2005).

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Biophysical models of current flow suggest that HD- compared to conventional tDCS set-ups results in more focal current flow (Bortoletto et al., 2016; Kuo et al., 2013) and may allow inducing regionally specific effects on cognition (Gbadeyan, McMahon, Steinhauser, & Meinzer, 2016). However, aside from current modelling studies, the extent of HD-tDCS effects on brain physiology remains unknown. However, HD-tDCS may impact on functionally connected distant brain regions in a similar manner to conventional tDCS (Meinzer et al., 2012; Stagg et al., 2013). In addition, the dmPFC refers to a large frontal region with both cortical and deeper midline components and the extent to which HD-tDCS influences this region is currently unknown. As HD-tDCS is suitable for use simultaneously with fMRI (Gbadeyan, Steinhauser, et al., 2016), future studies using this method may provide insight into the mechanisms underlying the sex mediated cognitive effects demonstrated in the current study.

The study is limited by the single measure of affective ToM used, with recent evidence suggesting the task may better capture emotion recognition ability (Oakley et al., 2016). Although the study builds on previous evidence for sex dependent variability for tDCS to the mPFC on ToM (Adenzato et al., 2017), replication in larger samples is required. As the RMET was designed to assess affective ToM deficits in clinical groups with severe impairments, future studies may benefit from increasing the difficult of the stimuli. Additionally, looking at performance on the more challenging stimuli within the RMET may also be beneficial (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Recruiting clinical cohorts with associated ToM deficits may also provide evidence for sex related stimulation differences and potential implications for the clinical use of tDCS across a broad range of disorders associated with social cognitive deficits. Considerable work is required to understand the

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variability in tDCS response and the underlying mechanisms that result in varied efficacy for improving cognition.

Conclusion

The current study provides the first evidence for sex-mediated effects of tDCS to the dmPFC for affective ToM performance. Future research using non-invasive brain stimulation to study ToM and social cognition more broadly, should consider sex as a mediating factor. The current results are also relevant for the potential clinical use of tDCS, alongside cognitive training programmes to improve ToM in disorders associated with reduced ToM functioning.

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Acknowledgements

We would like to acknowledge all participants for their time and commitment. We would also like to acknowledge Swathi Ramdave who assisted with data collection and scoring and Ilvana Dzafic, who assisted with the coding of the initial test battery.

Funding

This work was supported by a Future Fellowship grant [FT120100608] and a strategic seed-funding grant from the University of Queensland, awarded to Marcus Meinzer.

Author Contributions

A.K.M & M.M conceived and designed the experiment. A.K.M collected the data, performed the analyses, and wrote the manuscript. J. H assisted with data collection and analysis. A. H. conducted the current modelling. M.M edited the manuscript and supervised all aspects of the project.

Conflicts of Interest

None declared

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REFERENCES

Adams, R. B., Jr., Rule, N. O., Franklin, R. G., Jr., Wang, E., Stevenson, M. T., Yoshikawa, S., . . . Ambady, N. (2010). Cross-cultural reading the mind in the eyes: an fMRI investigation. *J Cogn Neurosci, 22*(1), 97-108. doi:10.1162/jocn.2009.21187

Adenzato, M., Brambilla, M., Manenti, R., De Lucia, L., Trojano, L., Garofalo, S., . . . Cotelli, M. (2017). Gender differences in cognitive Theory of Mind revealed by transcranial direct current stimulation on medial prefrontal cortex. *Sci Rep, 7*, 41219. doi:10.1038/srep41219

Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annu Rev Psychol, 60*, 693-716. doi:10.1146/annurev.psych.60.110707.163514

Alam, M., Truong, D. Q., Khadka, N., & Bikson, M. (2016). Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). *Phys Med Biol, 61*(12), 4506-4521. doi:10.1088/0031-9155/61/12/4506

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci, 7*(4), 268-277. doi:10.1038/nrn1884

Anticevic, A., Cole, M. W., Murray, J. D., Corlett, P. R., Wang, X. J., & Krystal, J. H. (2012). The role of default network deactivation in cognition and disease. *Trends Cogn Sci, 16*(12), 584-592. doi:10.1016/j.tics.2012.10.008

Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends Cogn Sci, 6*(6), 248-254.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). Another advanced test of theory of mind: evidence from very high functioning adults with autism or asperger syndrome. *J Child Psychol Psychiatry, 38*(7), 813-822.

Baron-Cohen, S., Ring, H., Chitnis, X., Wheelwright, S., Gregory, L., Williams, S., . . . Bullmore, E. (2006). fMRI of parents of children with Asperger Syndrome: a pilot study. *Brain Cogn, 61*(1), 122-130. doi:10.1016/j.bandc.2005.12.011

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *J Autism Dev Disord, 34*(2), 163-175.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry, 42*(2), 241-251.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord, 31*(1), 5-17.

Baumann, S., Wozny, D., Kelly, S., & Meno, F. (1997). The electrical conductivity of human cerebrospinal fluid at body temperature. *IEEE Trans Biomed Eng, 44*(3), 220-223.

Baysal, U., & Haueisen, J. (2004). Use of a priori information in estimating tissue resistivities--application to human data in vivo. *Physiol Meas, 25*(3), 737-748.

ACCEPTED MANUSCRIPT

Bortoletto, M., Rodella, C., Salvador, R., Miranda, P. C., & Miniussi, C. (2016). Reduced Current Spread by Concentric Electrodes in Transcranial Electrical Stimulation (tES). *Brain Stimul, 9*(4), 525-528. doi:10.1016/j.brs.2016.03.001

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol, 14*(8), 1133-1145. doi:10.1017/S1461145710001690

Camacho, D. L., Hopper, R. H., Lin, G. M., & Myers, B. S. (1997). An improved method for finite element mesh generation of geometrically complex structures with application to the skullbase *Journal of Biomechanics, 30*(10), 1067-1070.

Chaieb, L., Antal, A., & Paulus, W. (2008). Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. *Vis Neurosci, 25*(1), 77-81. doi:10.1017/S0952523808080097

Chakrabarti, S., & Fombonne, E. (2005). Pervasive developmental disorders in preschool children: confirmation of high prevalence. *The American journal of psychiatry, 162*(6), 1133-1141. doi:10.1176/appi.ajp.162.6.1133

Cialdini, R. B., Brown, S. L., Lewis, B. P., Luce, C., & Neuberg, S. L. (1997). Reinterpreting the empathy-altruism relationship: when one into one equals oneness. *J Pers Soc Psychol, 73*(3), 481-494.

Conson, M., Errico, D., Mazzarella, E., Giordano, M., Grossi, D., & Trojano, L. (2015). Transcranial Electrical Stimulation over Dorsolateral Prefrontal Cortex Modulates Processing of Social Cognitive and Affective Information. *PLoS One, 10*(5), e0126448. doi:10.1371/journal.pone.0126448

Datta, A., Baker, J. M., Bikson, M., & Fridriksson, J. (2011). Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimul, 4*(3), 169-174. doi:10.1016/j.brs.2010.11.001

Decety, J., & Sommerville, J. A. (2003). Shared representations between self and other: a social cognitive neuroscience view. *Trends Cogn Sci, 7*(12), 527-533.

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain Stimul, 9*(4), 501-517. doi:10.1016/j.brs.2016.04.006

Diflorio, A., & Jones, I. (2010). Is sex important? Gender differences in bipolar disorder. *Int Rev Psychiatry, 22*(5), 437-452. doi:10.3109/09540261.2010.514601

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves "mind-reading" in humans. *Biol Psychiatry, 61*(6), 731-733. doi:10.1016/j.biopsych.2006.07.015

Dyke, K., Kim, S., Jackson, G. M., & Jackson, S. R. (2016). Intra-Subject Consistency and Reliability of Response Following 2 mA Transcranial Direct Current Stimulation. *Brain Stimul, 9*(6), 819-825. doi:10.1016/j.brs.2016.06.052

Fang, Q. Q., & Boas, D. A. (2009). Tetrahedral Mesh Generation from Volumetric Binary and Gray-Scale Images. *2009 Ieee International Symposium on Biomedical Imaging: From Nano to Macro, Vols 1 and 2*, 1142-1145. doi:Doi 10.1109/Isbi.2009.5193259

Fertonani, A., & Miniussi, C. (2016). Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. *Neuroscientist*. doi:10.1177/1073858416631966

ACCEPTED MANUSCRIPT

Fischl, B. (2012). FreeSurfer. *NeuroImage, 62*(2), 774-781. doi:10.1016/j.neuroimage.2012.01.021

Folstein, M. F., & Luria, R. (1973). Reliability, validity, and clinical application of the Visual Analogue Mood Scale. *Psychol Med, 3*(4), 479-486.

Frank, C. K., Baron-Cohen, S., & Ganzel, B. L. (2015). Sex differences in the neural basis of false-belief and pragmatic language comprehension. *NeuroImage, 105*, 300-311. doi:10.1016/j.neuroimage.2014.09.041

Fumagalli, M., Vergari, M., Pasqualetti, P., Marceglia, S., Mameli, F., Ferrucci, R., . . . Priori, A. (2010). Brain switches utilitarian behavior: does gender make the difference? *PLoS One, 5*(1), e8865. doi:10.1371/journal.pone.0008865

Gbadeyan, O., McMahon, K., Steinhauser, M., & Meinzer, M. (2016). Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: A High-Definition Transcranial Direct Current Stimulation Study. *J Neurosci, 36*(50), 12530-12536. doi:10.1523/JNEUROSCI.2450-16.2016

Gbadeyan, O., Steinhauser, M., McMahon, K., & Meinzer, M. (2016). Safety, Tolerability, Blinding Efficacy and Behavioural Effects of a Novel MRI-Compatible, High-Definition tDCS Set-Up. *Brain Stimul, 9*(4), 545-552. doi:10.1016/j.brs.2016.03.018

Geddes, L. A., & Baker, L. E. (1967). The specific resistance of biological material - A compendium of data for the biomedical engineer and physiologist. *Medical and Biological Engineering, 5*(3), 271-293.

Hogeveen, J., Grafman, J., Aboseria, M., David, A., Bikson, M., & Hauner, K. K. (2016). Effects of High-Definition and Conventional tDCS on Response Inhibition. *Brain Stimul*. doi:10.1016/j.brs.2016.04.015

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Exp Brain Res, 216*(1), 1-10. doi:10.1007/s00221-011-2891-9

Kalbe, E., Schlegel, M., Sack, A. T., Nowak, D. A., Dafotakis, M., Bangard, C., . . . Kessler, J. (2010). Dissociating cognitive from affective theory of mind: a TMS study. *Cortex, 46*(6), 769-780. doi:10.1016/j.cortex.2009.07.010

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. *Brain Stimul, 6*(4), 644-648. doi:10.1016/j.brs.2012.09.010

Ladeira, A., Fregni, F., Campanha, C., Valasek, C. A., De Ridder, D., Brunoni, A. R., & Boggio, P. S. (2011). Polarity-dependent transcranial direct current stimulation effects on central auditory processing. *PLoS One, 6*(9), e25399. doi:10.1371/journal.pone.0025399

Lafon, B., Rahman, A., Biksom, M., & Parra, L. C. (2016). Direct current stimulation alters neuronal input/output. *Brain Stimulation, (in press)*.

Lindenberg, R., Sieg, M. M., Meinzer, M., Nachtigall, L., & Floel, A. (2016). Neural correlates of unihemispheric and bihemispheric motor cortex stimulation in healthy young adults. *NeuroImage*. doi:10.1016/j.neuroimage.2016.01.057

Martin, A. K., Dzafic, I., Ramdave, S., & Meinzer, M. (2017). Causal evidence for the task-specific involvement of the dorsomedial prefrontal cortex in social cognition. *Soc Cogn Affect Neurosci*.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Martin, A. K., Ilvana Dzafic, I., Ramdave, S., & Meinzer, M. (2017). Causal evidence for task-specific involvement of the dorsomedial prefrontal cortex in human social cognition. *Soc Cogn Affect Neurosci*. doi:10.1093/scan/nsx063

Martin, A. K., Meinzer, M., Lindenberg, R., Sieg, M. M., & Floel, A. (2017). Effects of transcranial direct current stimulation on neural network structure in young and older adults. *Journal of Cognitive Neuroscience*.

McClure, E. B. (2000). A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol Bull, 126*(3), 424-453.

McGrath, J. J. (2006). Variations in the incidence of schizophrenia: data versus dogma. *Schizophrenia bulletin, 32*(1), 195-197. doi:10.1093/schbul/sbi052

Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., . . . Floel, A. (2012). Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. *J Neurosci, 32*(5), 1859-1866. doi:10.1523/JNEUROSCI.4812-11.2012

Moran, J. M. (2013). Lifespan development: the effects of typical aging on theory of mind. *Behav Brain Res, 237*, 32-40. doi:10.1016/j.bbr.2012.09.020

Newschaffer, C. J., Croen, L. A., Daniels, J., Giarelli, E., Grether, J. K., Levy, S. E., . . . Windham, G. C. (2007). The epidemiology of autism spectrum disorders. *Annu Rev Public Health, 28*, 235-258. doi:10.1146/annurev.publhealth.28.021406.144007

Oakley, B. F., Brewer, R., Bird, G., & Catmur, C. (2016). Theory of mind is not theory of emotion: A cautionary note on the Reading the Mind in the Eyes Test. *J Abnorm Psychol, 125*(6), 818-823. doi:10.1037/abn0000182

Perdue, K. L., & Diamond, S. G. (2014). T1 magnetic resonance imaging head segmentation for diffuse optical tomography and electroencephalography. *J Biomed Opt, 19*(2), 026011. doi:10.1117/1.JBO.19.2.026011

Ruigrok, A. N., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev, 39*, 34-50. doi:10.1016/j.neubiorev.2013.12.004

Russell, M. J., Goodman, T. A., Visse, J. M., Beckett, L., Saito, N., Lyeth, B. G., & Recanzone, G. H. (2017). Sex and electrode configuration in transcranial electrical stimulation. *Front Psychol, 8*(147).

Russell, T. A., Tchanturia, K., Rahman, Q., & Schmidt, U. (2007). Sex differences in theory of mind: A male advantage on Happé's "cartoon" task. *Cognition and Emotion*.

Rutherford, H. J., Wareham, J. D., Vrouva, I., Mayes, L. C., Fonagy, P., & Potenza, M. N. (2012). Sex differences moderate the relationship between adolescent language and mentalization. *Personal Disord, 3*(4), 393-405. doi:10.1037/a0028938

Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2015). Functional lateralization of temporoparietal junction - imitation inhibition, visual perspective-taking and theory of mind. *Eur J Neurosci*. doi:10.1111/ejn.13036

Sarkar, A., Dowker, A., & Cohen Kadosh, R. (2014). Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. *J Neurosci, 34*(50), 16605-16610. doi:10.1523/JNEUROSCI.3129-14.2014

Sarkis, R. A., Kaur, N., & Camprodon, J. A. (2014). Transcranial direct current stimulation (tDCS): Modulation of executive function in health and disease. *Current Behavioural Neuroscience Reports, 1*(2), 74-85.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Schiffer, B., Pawliczek, C., Muller, B. W., Gizewski, E. R., & Walter, H. (2013). Why don't men understand women? Altered neural networks for reading the language of male and female eyes. *PLoS One, 8*(4), e60278. doi:10.1371/journal.pone.0060278

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neurosci Biobehav Rev, 42*, 9-34. doi:10.1016/j.neubiorev.2014.01.009

Sebastian, C. L., Fontaine, N. M., Bird, G., Blakemore, S. J., Brito, S. A., McCrory, E. J., & Viding, E. (2012). Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Soc Cogn Affect Neurosci, 7*(1), 53-63. doi:10.1093/scan/nsr023

Sellaro, R., Nitsche, M. A., & Colzato, L. S. (2016). The stimulated social brain: effects of transcranial direct current stimulation on social cognition. *Ann N Y Acad Sci, 1369*(1), 218-239. doi:10.1111/nyas.13098

Stagg, C. J., Lin, R. L., Mezue, M., Segerdahl, A., Kong, Y., Xie, J., & Tracey, I. (2013). Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. *J Neurosci, 33*(28), 11425-11431. doi:10.1523/JNEUROSCI.3887-12.2013

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist, 17*(1), 37-53. doi:10.1177/1073858410386614

Takeuchi, H., Taki, Y., Nouchi, R., Sekiguchi, A., Hashizume, H., Sassa, Y., . . . Kawashima, R. (2014). Association between resting-state functional connectivity and empathizing/systemizing. *NeuroImage, 99*, 312-322. doi:10.1016/j.neuroimage.2014.05.031

Vollm, B. A., Taylor, A. N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., . . . Elliott, R. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *NeuroImage, 29*(1), 90-98. doi:10.1016/j.neuroimage.2005.07.022

Wagner, S., Rampersad, S. M., Aydin, U., Vorwerk, J., Oostendorp, T. F., Neuling, T., . . . Wolters, C. H. (2014). Investigation of tDCS volume conduction effects in a highly realistic head model. *J Neural Eng, 11*(1), 016002. doi:10.1088/1741-2560/11/1/016002

Wolters, C. H., Anwander, A., Berti, G., & Hartmann, U. (2007). Geometry-adapted hexahedral meshes improve accuracy of finite-element-method-based EEG source analysis. *IEEE Trans Biomed Eng, 54*(8), 1446-1453.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand, 67*(6), 361-370.

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- Sex mediates HD-tDCS response on the Reading the Mind in the Eyes test
- Sex mediated differences in the dorsomedial prefrontal cortex for ToM
- Future tDCS studies using ToM need to consider sex

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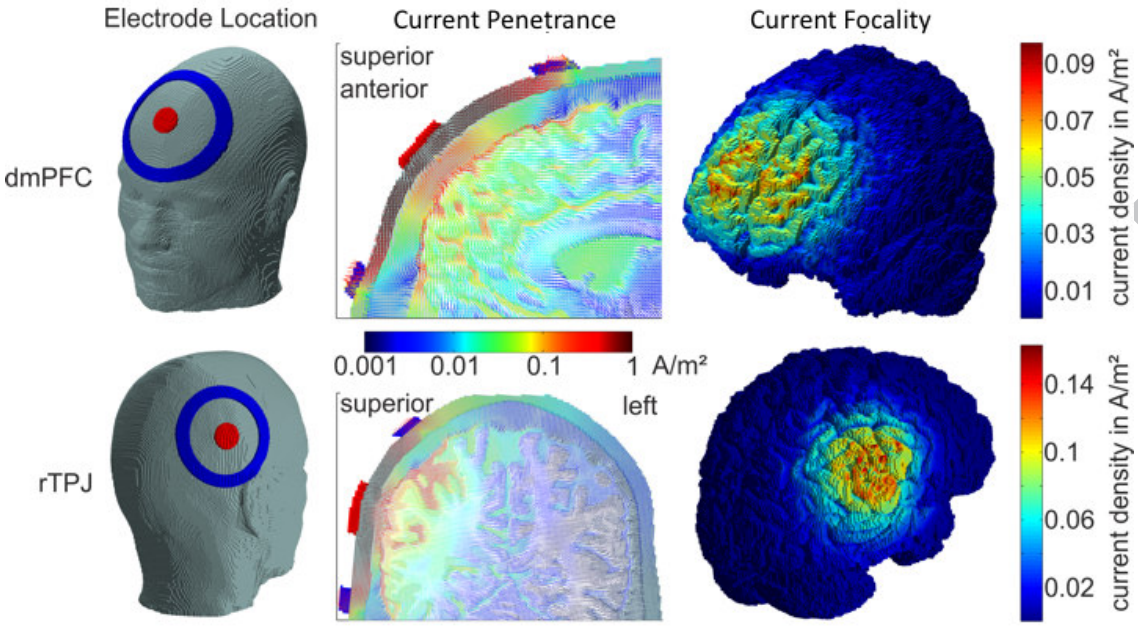

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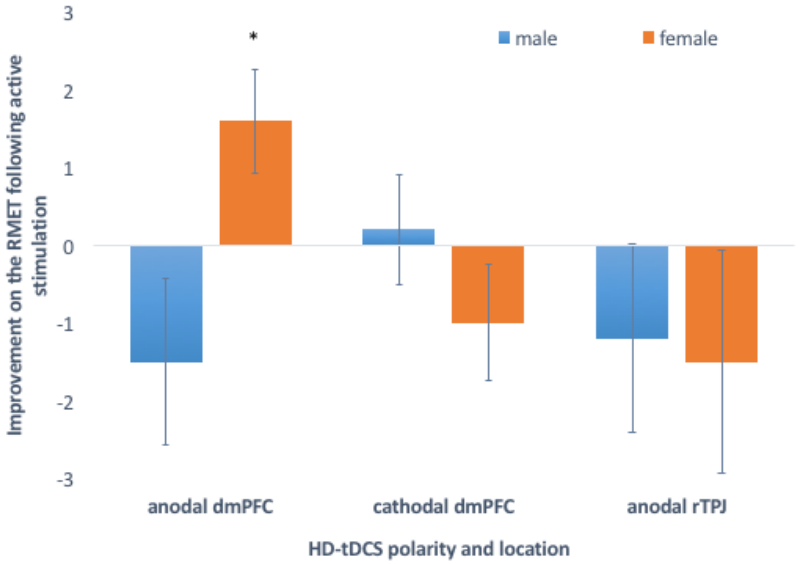

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