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O papel da junção temporoparietal direita no controlo de imitação em sujeitos com esquizofrenia: um estudo através de estimulação transcraniana de corrente contínua

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DISSERTAÇÃO DE MESTRADO

Orientador: Sérgio Eduardo de Carvalho Machado

Coorientador: Nuno Albertino Barbosa Ferreira da Rocha

RIO DE JANEIRO

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Dissertação de Mestrado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental - PROPSAM do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Mestre em Saúde Mental.

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O PAPEL DA JUNÇÃO TEMPOROPARIETAL DIREITA NO CONTROLO DE IMITAÇÃO EM SUJEITOS COM ESQUIZOFRENIA: UM ESTUDO ATRAVÉS DE ESTIMULAÇÃO TRANSCRANIANA DE CORRENTE CONTÍNUA

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RESUMO

Introdução: As alterações no controle das representações do *self* e do outro têm sido destacadas como o mecanismo subjacente aos défices de cognição social da esquizofrenia. A junção temporoparietal (JTP) apresenta um papel crucial no cérebro social, estando associada, segundo estudos com estimulação transcraniana de corrente contínua, ao controle das representações do *self* e do outro em sujeitos sadios. O funcionamento atípico da TPJ em pacientes com esquizofrenia está relacionado com alterações na cognição social, apesar de não existir evidência específica em relação ao controle das representações do *self* e do outro.

Objetivo: Avaliar o papel da TPJ direita no controle das representações do *self* e do outro de pacientes com esquizofrenia em comparação com sujeitos sadios.

Métodos: Dezoito pacientes com esquizofrenia e 18 sujeitos sadios foram recrutados e completaram a avaliação inicial (dados sociodemográficos e clínicos, questionário de segurança de neuroestimulação, IQ). Cada participante completou 3 sessões de 20 minutos de tDCS (anódica, catódica e *sham*), separadas por 5 a 7 dias e com ordem randomizada (desenho *cross-over*). A estimulação foi aplicada com elétrodos de 7 x 5 cm posicionados em CP6 (TPJ direita) e Cz. O ânodo foi colocado em CP6 para a tDCS anódica e em Cz para a estimulação catódica. Após a estimulação os participantes realizaram as tarefas de controle de imitação e controle inibitório não-imitativo bem como o questionário de efeitos adversos.

Resultados: Como os tempos de reação de base nos dois grupos foram diferentes, a análise de dados foi realizada separadamente para cada grupo. Não existiu interação significativa entre condição e tarefa em nenhum dos grupos. A ANOVA a um fator indicou que não existiram efeitos significativos do tipo de estimulação nos pacientes com esquizofrenia. Nos sujeitos sadios, verificaram-se efeitos significativos da estimulação no controle de imitação, com a tDCS anódica a promover uma capacidade de controle de imitação superior às restantes condições.

Conclusão: Estes resultados sugerem que a modulação da excitabilidade cortical da TPJ direita não modifica o controle da imitação em pacientes com esquizofrenia. A inexistência de resultados da estimulação sugere que as alterações neurobiológicas e neurofisiológicas intrínsecas aos pacientes afetam os efeitos neuroplásticos potencialmente induzidos pela tDCS. O uso de medicação pode também ter condicionado os efeitos da estimulação. Estudos futuros devem explorar os efeitos da tDCS em tarefas alternativas que avaliem o controle das representações do

self e do outro, utilizando também sujeitos com alto risco para a psicose ou pacientes de primeiro episódio não medicados também poderá ajudar a perceber melhor estes resultados.

Palavras-chave: esquizofrenia; controle das representações do *self* e do outro; junção temporoparietal

ABSTRACT

Introduction: Self-other control is the ability to manipulate the extent to which the neural representations attributed to the self or the other are activated. Self-other control impairment has been explored as a putative mechanism underlying social cognitive deficits observed in schizophrenia. The temporoparietal junction (TPJ) plays a key role in the social brain and transcranial direct current stimulation (tDCS) studies reported that the right TPJ is associated with self-other control in healthy subjects. Abnormal functioning of TPJ in patients with schizophrenia has been related to impaired social cognition, although there is no specific evidence regarding self-other control.

Objetive: The goal of this study was to assess the role of the right TPJ on self-other control of participants with schizophrenia in comparison to healthy subjects.

Methods: Eighteen patients with schizophrenia and 18 healthy subjects were recruited and completed an initial assessment for study eligibility (sociodemographic and clinical information, brain stimulation safety questionnaire, IQ). Then, each participant completed three 20 minute tDCS conditions (anodal, cathodal, or sham), 5 to 7 days apart in a randomized order (cross-over design). Stimulation was delivered with 7 x 5 cm with electrodes positioned at CP6 (right TPJ) and Cz. The anodal electrode was placed at CP6 for anodal tDCS and at Cz in the cathodal condition. After stimulation participants completed the control of imitation and non-imitative inhibitory control tasks as well a questionnaire regarding adverse effects of tDCS. **Results:** As baseline reaction times were different between healthy subjects and patients with schizophrenia, data analysis was completed separately for each group. There was no significant condition x task interaction in either group. One-way ANOVA's revealed no stimulation effects in either task for patients with schizophrenia. In healthy subjects, there were significant effects of stimulation on the control of imitation task, with anodal tDCS inducing superior imitative-control performance in comparison to the other conditions.

Conclusion: These findings suggest that right TPJ modulation of cortical excitability does not change imitative-control in patients with schizophrenia. The lack of modifications of self-other control after stimulation may suggest that intrinsic brain-related biological and electrophysiological dysfunction in patients with schizophrenia hinders tDCS induced plasticity changes. Medication intake by patients with schizophrenia might have interacted with tDCS

stimulation effects. Future studies should explore tDCS effects on alternative behavioral task to assess self-other control. The effects of tDCS on ultra-risk individuals or first-episode drug-naïve patients will also allow to further understand the reported findings.

Key-words: schizophrenia; self-other control; temporoparietal junction

LISTA DA ILUSTRAÇÕES E TABELAS

ABREVIATURAS

ANOVA = Analysis of Variance

DSM = Diagnostic Statistic Manual

EEG = Electroencephalography

fMRI = Functional Magnetic Resonance Imaging

GABA = Gamma-Aminobutyric Acid

IQ = Intelligence Quotient

M = Mean

mA = milliamps

MINI = Mini International Neuropsychiatric Interview

ms = milliseconds

NMDA = N-methyl-D-aspartate

PANSS = Positive and Negative Syndrome Scale

SD = Standard Deviation

SSRI's = Selective Serotonin Reuptake Inhibitors

tDCS = Transcranial Direct Current Stimulation

TMS = Transcranial Magnetic Stimulation

TPJ = Temporoparietal Junction

WAIS = Wechsler Adult Intelligence Scale

SUMÁRIO

INTRODUCTION

Social cognition dysfunction is a major hallmark of schizophrenia and it's intrinsically associated with the difficulties these patients display on social interaction and overall functioning (Fett et al., 2011; Kern, Glynn, Horan, & Marder, 2009; Savla, Vella, Armstrong, Penn, & Twamley, 2013). People with schizophrenia typically present impairments in several social cognitive domains, namely facial affect recognition, social perception, attributional styles and theory of mind (Farkas & Anthony, 2010; Kurtz & Richardson, 2012; Savla et al., 2013). Another key aspect of social cognition essential to guide social behavior is self-other processing. Current evidence suggests that people with schizophrenia usually experience difficulties in distinguishing their own emotions, intentions, and actions from those of others (Asai, Mao, Sugimori, & Tanno, 2011; Jardri et al., 2009; Jardri et al., 2011). However, research regarding social cognition and schizophrenia has mainly explored the patient´s ability to understand and/or integrate their own and other's intentions and emotions, with, little attention been devoted to problems in self–other control (van der Weiden, Prikken, & van Haren, 2015).

Key symptoms typically experienced by patients with schizophrenia can be related to impaired self-other control, that is, difficulty in managing representations of self and others. For instance, reality disturbances such as hallucinations, persecutory delusions and thought insertion represent the misattribution of self-generated representation to others (Allen et al., 2004; Jeannerod, 2009). Moreover, people with schizophrenia display impaired motor predictions (Raveendran & Kumari, 2007), which can hinder the process of distinguishing self of the other (Blakemore, Smith, Steel, Johnstone, & Frith, 2000; Johns et al., 2001; Renes et al., 2015). Biased cognitive expectations associated with patients symptoms can also lead to misattributions of agency (Maeda et al., 2012). Thereby, it has been recently suggested that social cognition impairments experienced by patients with schizophrenia are closely related to atypical modulation of self and other representations (Ferri et al., 2012; Sowden & Shah, 2014).

The basic neurocognitive mechanisms that underlie complex social behavior are still widely unknown, but self-other control (control of neural representations of the self and of other people) has been highlighted as a valuable candidate (Brass, Ruby, & Spengler, 2009; Spengler, von Cramon, & Brass, 2009a). It has been suggested that the mechanisms mediating the control of representations of the self and the other play a crucial role in higher-order socio-cognitive abilities like theory of mind (Brass et al., 2009). Although social interaction appears to be facilitated by

shared information between representations of the self and other, social situations often require individuals to engage more with the representations of other or, inversely, to distance themselves from other people (Sowden & Shah, 2014). Self-other control is the ability to manipulate the extent to which the neural representations attributed to the self or the other are activated, allowing people to inhibit or enhance representation of other self or the other in order to achieve successful social interactions (Brass & Heyes, 2005; Decety & Sommerville, 2003; Spengler et al., 2009a). For example, while empathizing with other people requires to put aside or inhibit one's own mental and/or affective state, to generate our independent actions we must inhibit the motor representations of the people we are interacting with (Sowden & Shah, 2014).

A task now readily used as a behavioral index of self-other control is that of the control of imitation (e.g. Brass, Bekkering, & Prinz, 2001; Brass, Derrfuss, & von Cramon, 2005; Brass et al., 2009; Spengler et al., 2009a). In this task participants respond to a symbolic cue (usually a number) that instructs them to lift either their index finger or their middle finger. The symbolic cue is overlaid on a video showing another individual lifting their index or middle finger. When the cue and the video are incongruent, participants are required to inhibit the motor representation of the other person's action and to excite my self-generated motor representation in order to perform the task successfully. Thereby, control of imitation requires self-other control processes, namely the ability to distinguish between one's own motor plan and that of the other. More specifically, the task requires the ability to inhibit the other-representation and imitative response tendencies, while enhancing self-representation in order to carry out their own motor actions. Numerous control studies and conditions have been employed to demonstrate that this task really does seem to isolate automatic imitative tendencies (see *Heyes, 2011* for a review).

Researchers have also tried to understand the brain circuitry that underlies effective-self-other control. The TPJ is a brain region located at the intersection of the superior temporal sulcus and inferior parietal lobule (Mars et al., 2012) that has been highlighted by several authors as a key part of the ''social brain'' (Eddy, 2016; Sperduti, Delaveau, Fossati, & Nadel, 2011; Van Overwalle, 2009). Nowadays, there is a growing body of evidence implicating the right TPJ in low-level and high-level sociocognitive processes, including self-other control (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; Farrer & Frith, 2002; Vollm et al., 2006). Evidence from functional magnetic resonance imaging (fMRI) studies suggests that the ability to inhibit imitative responses is closely associated with right TPJ activity (Brass et al., 2005; Brass et al., 2009;

Spengler et al., 2009a; Spengler, von Cramon, & Brass, 2009b). Furthermore, acquired temporoparietal lesions have been associated with asomatognosia (misidentification of part of one's own body as belonging to another; Feinberg, Venneri, Simone, Fan, & Northoff, 2010) and to impaired control of imitation (Brass, Derrfuss, Matthes-von Cramon, & von Cramon, 2003; Spengler, von Cramon, & Brass, 2010).

Studies using brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have also provided insight into the role of the TPJ in self-other control. Brain stimulation methods can complement neuroimaging data as they allow the direct manipulation of cortical excitability and allow us to infer causal involvement of a specific brain region in the cognitive process under investigation (Nitsche et al., 2008; Santiesteban, Banissy, Catmur, & Bird, 2015). Sowden & Catmur (2015) found that disruptive rTMS over right TPJ led to a domain specific decrease in the ability to control the tendency to imitate in comparison to a control site stimulation condition, suggesting that this region is implicated in self-other control. There are also several studies that found that anodal tDCS improved the on-line control of self-other representations elicited by the control of imitation task, enhanced online-control of self and other representations. Hogeveen et al. (2015) actually found that right TPJ tDCS had specific effects on self-other control, as there were no stimulation effects on a non-imitative inhibitory control task. These findings has led researchers to postulate that the core neurocognitive function of TPJ is to control the degree to which the self or another is represented.

There have reports highlighting structural and functional abnormalities in the TPJ of patients with schizophrenia relative to healthy controls (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Lee, Quintana, Nori, & Green, 2011; Plaze et al., 2015; Walter et al., 2009; Zhang et al., 2014). There is also evidence suggesting that TPJ activation during a theory of mind task is not only reduced in patients with schizophrenia, but it's also abnormally higher in individuals at high risk of psychosis (Brune et al., 2011). This suggests that elevated right TPJ activity may be a biomarker of risk for psychosis, which ultimately turns to reduced activation after disease onset due to the effects of neural atrophy, compensatory brain response, and medication. Finally, there are also reports of right TPJ hypoactivation in unaffected siblings of people with schizophrenia (Goldschmidt et al., 2014). Thereby, although it´s safe to state that patients with schizophrenia display changes in TPJ activity, current evidence does not allow to assume whether reduced TPJ activation is a marker of vulnerability or resilience (Eddy, 2016).

It is also important to notice that diminished activation in the TPJ has been associated with impaired social cognitive performance, in particular theory of mind and emotion processing domains in patients with schizophrenia (Benedetti et al., 2009; Das et al., 2012; Lee et al., 2011). Furthermore, current models highlight the importance of the TPJ in psychotic symptoms related to self-other processing mechanisms (Wible, 2012). Right TPJ dysfunction can lead to a poor integration of the self, which can be closely related with psychotic symptoms such as misperceptions and hallucinations (Eddy, 2016). There is evidence that right TPJ duration of activation during an own-body processing task is positively related to abnormal self-processing (Arzy, Mohr, Michel, & Blanke, 2007). Furthermore, Walter et al. (2009) found that patients with paranoid schizophrenia present reduced bilateral TPJ activity during a theory of mind task which included conditions involving physical causality and intended human actions. More recently, another research group also found structural abnormalities (sulcus morphology) in the right TPJ of patients with schizophrenia, that were associated with auditory hallucinations self-other attribution (Plaze et al., 2015).

In conclusion, the is a significant amount of evidence describing functional and structural changes in the right TPJ of patients with schizophrenia as well as their relationship with impaired social cognition and self-other processing. However, there are no clear efforts exploring the role of this brain region in self-other control mechanisms in schizophrenia.

JUSTIFICATION

In the last decades there have been numerous studies reporting social cognitive deficits in patients with schizophrenia, including impaired self-other processing. More recently, there is a growing amount of evidence suggesting that impaired self-other control is associated with social cognitive deficits and other key symptoms experienced by patients with schizophrenia. Self-other control may play a critical role in successful social behavior as several social situation often require individuals to engage more with the representations of other or, inversely, to distance themselves from other people.

The TPJ is widely considered as a critical "brain hub" for social cognition. There is clear evidence reporting TPJ functional impairments in patients with schizophrenia as well as in their siblings and individuals with high-risk for psychosis. Furthermore, abnormal functioning of TPJ in patients with schizophrenia has been related to impaired social performance in tasks related to self-other processing.

However, there is no evidence exploring the brain regions that directly support self-other control in patients in schizophrenia. As previous evidence suggests that the right TPJ is closely related to self-other control in healthy subjects, it is important to explore if this brain region has the same functional role in patients with schizophrenia. Modulating right TPJ cortical excitability in patients with schizophrenia vs healthy subjects using tDCS followed by performance behavioral task assessing self-other control can provide the initial breakthroughs regarding this topic.

tDCS was selected to explore this research question as it provide an easy, inexpensive, and non-invasive method to manipulate cortical excitability and understand the causal relationship between the right TPJ and self-other control in schizophrenia. Moreover, the control of imitation task was selected to assess self-other control as previous tDCS studies with healthy subjects reported improved imitative-control after anodic stimulation targeting the right TPJ.

OBJETIVES

The main goal of this study was to understand the role of the right TPJ on self-other control of participants with schizophrenia. More specifically, this study aimed to assess if self-other control assessed by the control of imitation task could be modulated in patients with schizophrenia using several tDCS conditions targeting the right TPJ (cross-over design). Furthermore, this trial also intended to evaluate if tDCS effects targeting the right TPJ on control of imitation were similar between patients with schizophrenia and healthy subjects. Finally, this trial also aimed to assess the effects of right TPJ stimulation on the control of imitation task in comparison to the non-imitative control task.

HYPOTHESIS

In order to investigate the role of the right TPJ on self-other control in subjects with schizophrenia, we used tDCS to enhance or diminish cortical excitability in this brain region before the performance of the control of imitation task. Our hypothesis is that if the cortical excitability changes in the right TPJ play a role in self-other control performance in both subjects with schizophrenia and healthy participants, active tDCS targeting this brain region will have an effect on the control of imitation task, but not on the non-imitative inhibitory control task in both groups. If tDCS effects on the behavioral tasks are different between patients with schizophrenia and healthy subjects, this suggests that the right TPJ contributes differently to self-other control in patients with schizophrenia.

METHODS

Participants

Subjects with schizophrenia were recruited from the day's hospital and outpatients unit of the Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB-UFRJ). Participants had to be diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders IV criteria (APA, 2000), screened using the Mini International Psychiatric Interview (MINI; Sheehan et al., 1998) applied by trained psychologist from the research team. Information from each patient psychiatrist, family and clinical records were obtained whenever necessary in order to validate diagnosis. Healthy subjects were employees and students from IPUB-UFRJ. Both healthy controls and patients with schizophrenia had to be aged between 18 and 60 years, display an estimated IQ over 80, and have the ability to read in order to participate in this study. Participants were excluded if they had an history of neurologic problems or disorders (e.g. epilepsy, seizures, head trauma), substance abuse or dependence in the last 6 months, or any sort of contraindication to perform brain stimulation techniques (electronic implants, metal in the brain/skull, neurostimulator, cardiac pacemaker, intracardiac lines or metal, medication infusion device, pregnancy, etc). Patients with schizophrenia were also excluded if they had significant medication changes in the previous month (new medications added to regimen), a psychiatric hospitalization in the previous 3 months or a comorbid Axis II disorder (based on MINI interview). Furthermore, healthy controls could not participate in this study if they had an history of mental illness or used any kind of psychiatric medication in the previous 2 years, and if they had

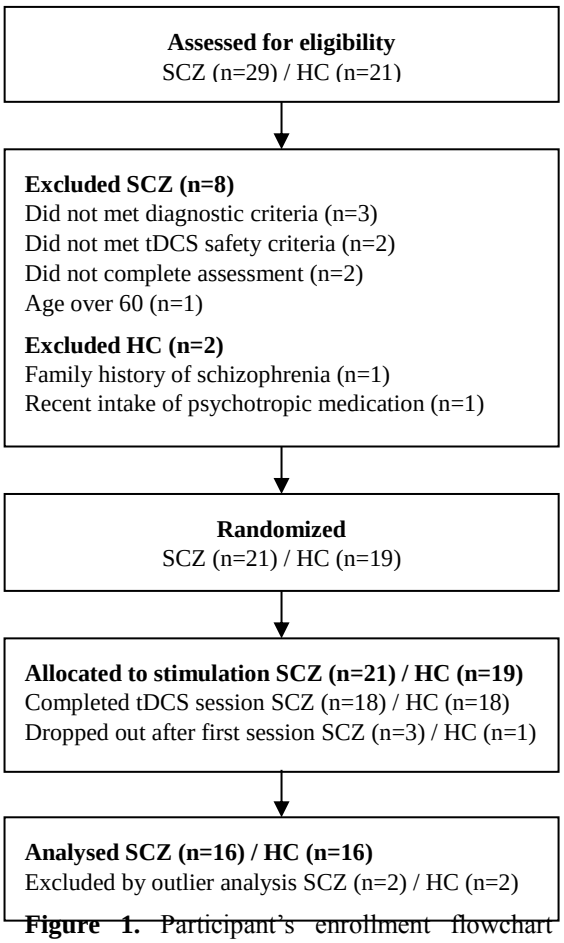

Figure 1. Participant's enrollment flowchart (SCZ = schizophrenia; HC = healthy controls)

any first degree relative with an history of severe mental illness.

The flowchart presented at Figure 1 displays detailed information regarding participants' enrollment. Twenty-nine patients and 21 healthy volunteers were assessed for eligibility. Six patients are not eligible for the study, as well as 2 healthy controls. Two patients did not complete assessment procedures and 3 patients and 1 healthy control dropped out after the first stimulation session. Finally, 2 participants from the schizophrenia group and 2 healthy subjects were also removed from further analysis as they performed 2.5 standard deviation below the mean performance across at least one condition. Thereby, the final sample for analysis was composed of 32 subjects (16 for each group).

Each participant signed a written consent form and the ethics committee of the Institute of Psychiatry of the Federal University of Rio de Janeiro (CAAE 59056716.7.0000.5263) approved all experimental procedures, according to the Norms of Conduct in Human Research (CNS resolution 466/2012). Participants travel expenses to the laboratory were reimbursed by the research team whenever required.

Experimental Design

Before starting the experimental procedures, all participants received information about the study and signed a written informed consent form. The tDCS procedures as well as the associated risks and safety concerns were also fully explained. On the first visit to the laboratory, participants firstly completed a survey to gather sociodemographic data and clinical information as well as a brain stimulation safety questionnaire (Antal et al., 2017; Nitsche, Liebetanz, et al., 2003; Poreisz, Boros, Antal, & Paulus, 2007) in order to assure their eligibility for this study. Secondly, participants completed the MINI interview (Sheehan et al., 1998) and the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). This scale was used to assess schizophrenia-related symptom severity through a semi structured interview as well as the reports from family members or health professionals which have contact with the patient. This scale encompasses a total of 30 items, rated from 1 (absence of symptoms) to 7 (extreme severe symptoms), that are divided into three domains: positive symptoms, negative symptoms and general psychopathology. Finally, participants completed the Matrix Reasoning and Vocabulary sub-scales of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III – Wechsler, 1997)

in order to estimate global IQ according to Ringe, Saine, Lacritz, Hynan, & Cullum (2002). Composite score of Matrix Reasoning and Vocabulary sub-scales has highly significant correlation with full scale IQ ($r = 0.93$) and can be used as a fast and reliable measure to screen global IQ. Furthermore, the Vocabulary subtest has been highlighted as a reliable measure of premorbid intelligence for patients with schizophrenia (Reichenberg et al., 2005).

Following the previously described procedures, each participant completed three tDCS conditions (anodal, cathodal, or sham) that were completed 5 to 7 days apart (cross-over-design). Session order was randomly assigned and counterbalanced across each group using a web-based tool (www.randomization.com). In order to avoid potential confounding effects of medication intake time in patients, sessions were scheduled approximately at the same period of the day for each participant (e.g. every morning). After completing stimulation, participants completed the control of imitation and non-imitative inhibitory control tasks, followed by a questionnaire regarding potential adverse effects of tDCS (Fertonani, Ferrari, & Miniussi, 2015). Each stimulation session lasted around 45 minutes. Participants were not tested before and after stimulation due to the considerable likelihood of ceiling effects as a result of repetition of the control of imitation and non-imitative inhibitory control tasks (Santiesteban et al., 2012).

Stimulation Procedures

Stimulation was delivered using a battery-driven direct current stimulation device (TCT, China) connected with two 35 cm2 surface sponge electrodes soaked in saline (140 mMol NaCl dissolved in Milli-Q water). Stimulation sites were identified according to the international 10-20 system for EEG (Jasper, 1958), using a landmark cap (Neurosoft, Russia) modified according to standard 10% landmarks. The experimenter marked the electrode positioning sites at CP6 (targeting the right TPJ) and Cz (50% of the distance between the periauricular points, crossing a point 50% of the distance between inion and nasion). In the anodic condition, the anodal electrode was placed at CP6, while the cathodal electrode at the vertex. In the cathodic condition, the anode and cathode positioning was inverted. Each stimulation session lasted 20 minutes and current intensity was set at 1 mA. Stimulation started with a 10 second ramp-up and finished with a 10 s ramp-down period in order to reduce cutaneous sensation and other transient phenomena (Nitsche et al., 2008). For sham stimulation, electrodes were placed as in the anodal tDCS condition and the

ramping procedure was similar, but the stimulation device automatically turned off after 30 seconds of stimulation. Thereby, participants usually fell the initial itching sensation associated with tDCS and remain 20 minutes in the room without any stimulation effects, allowing to mimic the experience of real stimulation (Gandiga, Hummel, & Cohen, 2006). Before beginning the stimulation procedures, a standardized instruction was given in order to reduce attention to environmental stimuli during stimulation (Damoiseaux et al., 2006). Participants were directed to "sit quietly with your eyes closed, think of nothing in particular and let the experimenter know if you experience any discomfort" (Hogeveen et al., 2015).

There are a few considerations to support the previously described stimulation procedures. In our study, the behavioral task was only performed after the stimulation period, as there is evidence suggesting that "offline" stimulation (stimulation preceding the task) achieves more robust effects in comparison to on-line stimulation (concurrent to task performance) at least for anodic stimulation (Pirulli, Fertonani, & Miniussi, 2013). Furthermore, the behavioral task was immediately performed after stimulation as there is evidence from corticospinal excitability studies suggesting that the neuromodulatory effects of tDCS are mainly observed 90 minutes after stimulation (Nitsche & Paulus, 2001).

Control of imitation and non-imitative inhibitory control tasks

The control of imitation and non-imitative inhibitory control tasks were performed concurrently immediately after each stimulation condition using similar settings as (Hogeveen et al., 2015). The tasks were performed using a *MSI GP70 PE Leopard laptop*, with participants seated at approximately 50 cm of the screen. To perform both these tasks participants have to lift the index or middle finder from a computer keyboard in response to numerical cues (1 and 2, respectively). At cue onset, an onscreen hand was manipulated in several ways (Figure 2):

- **Control of imitation task:** a congruent or incongruent hand movement is displayed on the screen. In the congruent trials the action performed by the hand on the screen is the same as the action the participants are required to perform. In the incongruent trials, the hand movement displayed on the screen is opposite to the required action (Brass, Bekkering, Wohlschlager, & Prinz, 2000; Brass et al., 2009). During this task participants must inhibit

the tendency to imitate on incongruent trials by enhancing their own motor plan and suppressing the representation of the other.

- **Non-imitative inhibitory control task:** congruent or incongruent effector is highlighted in green. In the congruent trials, the finger highlighted in green on the present stimulus is the same as the finger the participant is required to move. In incongruent trials, the participant has to move a finger which is opposite to the finger heighted on the screen (Cook & Bird, 2011; Cook & Bird, 2012). Thereby, participants are required to inhibit the tendency to move the highlighted finger on incongruent trials, without the need to control self- and other-related motor plans.
- **Low-level baseline trials:** the image with the onscreen hand becomes pixelated as the cue is presented. These trials aim to gather information about baseline reaction times. The same number of cues for the index and middle finger were presented (Sowden & Catmur, 2015).

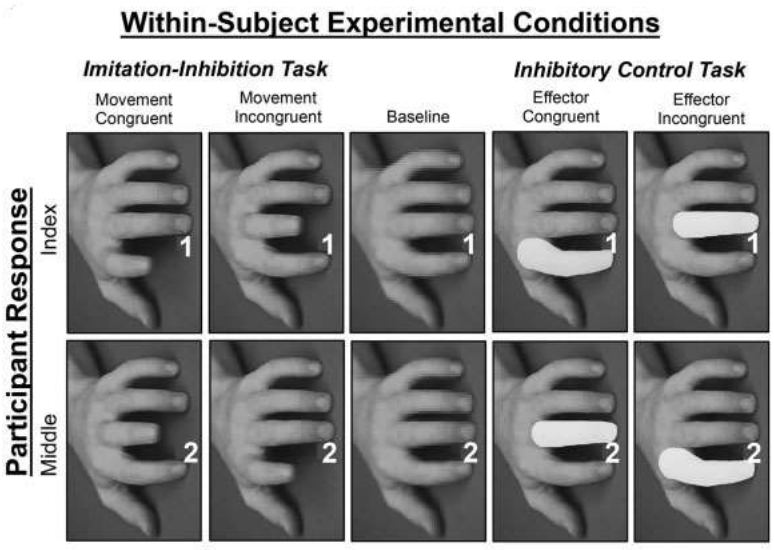

Figure 2. Control of Imitation and Non-Imitative Control Tasks Stimulus

Participants completed 30 trials of each type, split into randomized blocks of 50 trials. In both the control of imitation and non-imitative inhibitory control tasks, participants completed the same number of congruent and incongruent trials. The non-imitative inhibitory control task was designed so that it matched the control of imitation task in terms of the irrelevant stimulus dimension's spatial information and action affordances (Cook & Bird, 2011; Cook & Bird, 2012). The duration of both tasks together was approximately 15 min.

Data Analysis

Prior to the statistical analysis, incorrect and extreme reaction times (2.5 s.d. above or below the mean) from the control of imitation and non-imitative control tasks were identified and removed within each task domain (e.g. non-imitative congruent, imitation inhibition incongruent, etc) and stimulation condition (Hogeveen et al., 2015). Difference scores between incongruent and congruent trials for each task were computed in order to measure inhibition effects, namely "imitation inhibition" and "non-imitative inhibitory control" (Cook & Bird, 2011; Cook & Bird, 2012). Thereby, our outcome measures were imitation inhibition and non-imitative inhibitory control measure by reaction times on valid trials.

Statistical procedures were performed using IBM SPSS Statistics 24.0 (Statistics Package for Social Sciences) software, with all statistic procedures (e.g. assumptions) completed according to the work of Marôco (2011). Descriptive statistics were used to characterize both groups regarding sociodemographic and clinical characteristics and to report outcome measures after each stimulation condition and adverse effects of tDCS. Mean and standard deviation were calculated for the continuous variables and absolute/relative frequencies were presented for nominal variables.

Inferential statistics were performed with a significant level of 0.05. Inferential statistics were used to compare sociodemographic characteristics and IQ measures between patients with schizophrenia and healthy control subjects. Independent samples t-student tests were used for continuous variables (e.g. age and IQ) and Fisher's Exact test and Chi-Square Likelihood Ratio were used for categorical and ordinal variables (e.g gender, education level). Furthermore, as average baseline reaction times across conditions were statistically different between healthy subjects and patients with schizophrenia ($t = 3.533$; $p = 0.002$), the stimulation effects on the control of imitation and non-imitative control tasks were analyzed separately for each group.

Thereby, our main analysis were 2 x 3 repeated measures ANOVA's performed for each group in order to assess the interaction between task and stimulation condition in inhibition effects (measures by congruent and incongruent difference scores). The sphericity assumption was tested using the Mauchly's test and the Greenhouse-Geisser correction was used whenever data sphericity was violated. Post-hoc comparisons were performed using the Bonferroni correction. Following

the main analysis, one-way ANOVA's for each task was performed in order to assess stimulation effects on imitation inhibition and non-imitative inhibitory control.

Effect sizes comparing the active stimulation conditions (anodal and cathodal) with sham tDCS were also computed for each group and each outcome measure. Effect sizes were computed using the equation proposed by Morris & DeShon (2002), on the software G*Power (version 3.1). Effect sizes were classified according with Rosenthal (1996) as trivial (d <0.19), small (d = 0.20-0.49), moderate (d = 0.50-0.79), large (d = 0.80-1.29) and very large (> 1.30).

RESULTS

I. Sample Characteristics

Participant's sociodemographic and clinical information is presented at Table 1. There were no significant differences between the schizophrenia and the healthy control group in gender, age, education, IQ measures and handedness ($p > 0.05$).

Table 1. Participant's sociodemographic and clinical information

Sociodemographic Information	***Schizophrenia (n=16)***	***Healthy Subjects (n=16)***	***p***
Gender (M / F)	8 / 8	8 / 8	1.000 *
Age (years)	40.50 ± 13.86	38.06 ± 13.29	0.615 **
Education			0.190 ***
Middle School	1	1	
High School	12	7	
College	3	8	
Self-reported handedness (R/L)	14 / 2	16 / 0	0.484 *
EHI score	32.13 ± 7.45	34.25 ± 1.73	0.282 **
IQ Assessment			
Global IQ Estimate	99.75 ± 9.69	103.13 ± 12.76	0.406 **
Vocabulary subtest	10.81 ± 2.14	11.19 ± 2.43	0.646 **
Matrix Reasoning subtest	11.44 ± 2.45	12.38 ± 2.99	0.339 **
Clinical Information			
Duration of Illness (years)	14.31 ± 10.47		
Number of hospitalizations	5.19 ± 6.21		
Antipsychotic Mediation (CPZ equivalent dosage)	653.13 ± 456.44		
Other medication	Benzodiazepines (5) SSRI's (4) Biperiden (3) Carbamazepine (1) Levodopa (1) Lithium (1) Topiramate (1)		
PANNS Positive	14.50 ± 4.26		
PANSS Negative	16.69 ± 4.05		
PANSS General Psychopathology	30.88 ± 5.49		
PANNS Total	62.06 ± 8.91		

M = Male; F = Female; R = Right; L = Left; EHI = Edinburgh Handedness Inventory; CPZ = chlorpromazine; SSRI = selective serotonin reuptake inhibitors

*Fisher's Exact Test
**Independent t-test
***Chi-Square Likelihood Ratio

II. Effects of tDCS on non-imitative and imitative control

As previously described, average baseline reaction times across conditions were statistically different between healthy subjects and patients with schizophrenia, which lead to separate analysis for each group. Descriptive statistics and one-way ANOVA results for non-imitative and imitative control for both groups are reported at Table 2.

Table 2. Non-Imitative and Imitative Control Outcome Measures (ms)

		Anodal	*Cathodal*	*Sham*	*F*	*p*	η^2_p
Schizophrenia	*Non-Imitative Control*	30.12 ± 40.48	30.29 ± 46.94	24.64 ± 37.06	0.190	0.828	0.012
	Imitative-Control	31.53 ± 40.08	35.56 ± 63.84	50.59 ± 42.67	0.065	0.357	0.06
Healthy Controls	*Non-Imitative Control*	21.69 ± 33.66	31.53 ± 25.84	38.18 ± 40.27	2.282	0.120	0.132
	Imitative-Control	32.97 ± 34.02	52.23 ± 35.09	47.17 ± 33.78	3.771	0.035	0.201

In the schizophrenia group, two-way repeated measures ANOVA revealed no significant condition x task interaction [$F(2,30) = 1.245$, $p = 0.302$, $\eta^2_p = 0.077$] and main effect of condition [$F(2,30) = 0.305$, $p = 0.740$, $\eta^2_p = 0.020$]. There were significant main effects of task [$F(1,30) = 4.899$, $p = 0.043$, $\eta^2_p = 0.246$], as patients with schizophrenia displayed more non-imitative inhibitory control (M = 28.348) in comparison to imitation inhibition (M = 39.226). Further analysis using one-way ANOVA for each task found no significant effects of stimulation condition on both non-imitative task performance [$F(2,15) = 0.190$, $p = 0.828$, $\eta^2_p = 0.012$] and control of imitation task [$F(2,15) = 1.065$, $p = 0.357$, $\eta^2_p = 0.066$]. However, it is important to highlight that on the control of imitation task, performance in the anodal and cathodal condition was quite similar (M = 31.53; SD = 40.08 vs M = 35.56; SD = 63.84, respectively) in comparison to sham tDCS (M = 50.59; SD = 42.67; Figure 4). Effect size analysis indicates that regarding the non-imitative control task stimulation effects were trivial in the anodal and cathodal conditions in comparison to

sham tDCS (*d* = -0.12 and -0.15, respectively). In the control of imitation task, there was a moderate effect size of anodal tDCS (*d* = 0.52) and a small effect of cathodal stimulation (*d* = 0.23).

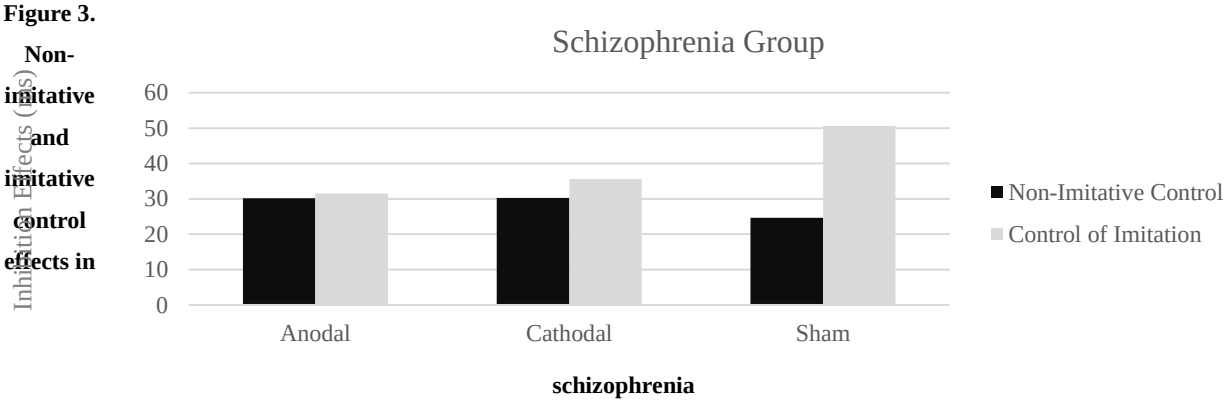

Figure 3. Non-imitative and imitative control effects in schizophrenia

In the healthy controls group, two-way repeated measures ANOVA revealed no significant condition x task interaction [F (2,30) = 0.511, p = 0.605, η^2_p = 0.033]. There were significant main effects of condition [F (2,30) = 7.902, p = 0.002, η^2_p = 0.345] and task [F(1,30) = 5.557, p = 0.032, η^2_p = 0.270]. Post-hoc analysis revealed that average inhibition effects regardless of task in the anodal condition (M = 27.331) were significantly higher in comparison to both cathodal stimulation (p = 0.001; M = 41.882) and sham (p = 0.029; M = 42.672). Furthermore, differences between tasks were only explained by performance in the cathodal condition (p = 0.021), as healthy subjects displayed a far much worse imitative control (M = 52.234) in comparison to non-imitative inhibitory control (M = 31.529).

Further analysis using one-way ANOVA for each task found no significant effects of stimulation condition on non-imitative task performance [F (2,15) = 2.282, p = 0.120, η^2_p = 0.132]. However, there were significant differences between conditions on imitative inhibitory control performance [F (2,15) = 3.771, p = 0.035, η^2_p = 0.201]. Although post-hoc analysis did not reveal any statistically significant difference between conditions, descriptive statistics clearly show that healthy subjects displayed improved imitative control in the anodal condition (M = 32.973; SD = 34.02) in comparison to the cathodal (M = 52.234; SS = 35.09) and sham conditions (M = 47.166; SS = 33.78). Effect size analysis revealed moderate and small effects of anodal and cathodal tDCS (*d* = 0.47 and 0.21, respectively) on non-imitative control. In the control of imitation task, there were small effects of anodal (*d* = 0.48) and cathodal tDCS (*d* = -0.21), but effects were on different directions.

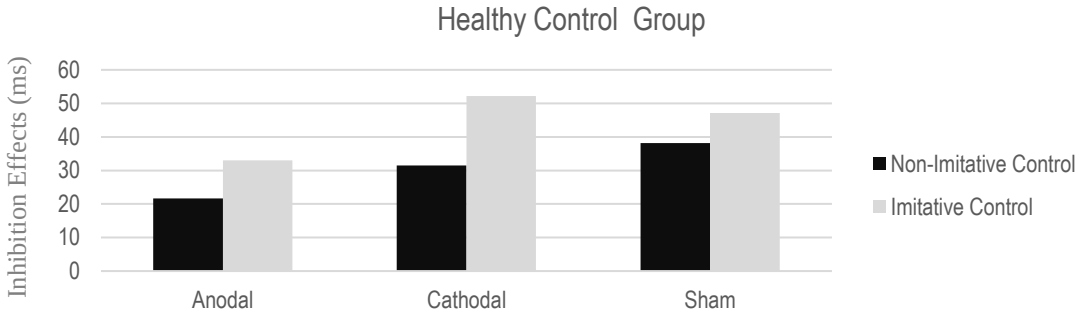

Figure 4. Non-imitative and imitative control effects in healthy controls

III. Adverse Effects of tDCS

Data regarding adverse effects experienced by patients with schizophrenia and healthy subjects is presented at Table 3. Overall, schizophrenia experience any kind of adverse effect in 62.96% of the stimulation session in comparison to 27.78% in healthy subjects. The most common adverse effects were itching and fatigue for schizophrenia (25.93% and 18.52%, respectively) and pinching and itching sensation for healthy subjects (13.21% and 7.55%, respectively.

Table 3. Adverse effects of tDCS

Sensations	Schizophrenia	Healthy Controls
Itching	25.93%	7.55%
Fatigue	18.52%	0%
Pinching	16.67%	13.21%
Burning	9.26%	3.77%
Pain	7.41%	0%
Warmth/Heat	7.41%	0%
Other	5.56%	9.43%
Metallic/Iron taste	1.85%	1.89%

DISCUSSION

This is this first study using tDCS to explore the role of the right TPJ in self-other control in patients with schizophrenia in comparison to healthy control subjects. In healthy control subjects, there was a statistical significant difference between stimulation conditions on the control of imitation task, with anodal tDCS inducing superior imitative-control performance in comparison to both sham and cathodal tDCS. These findings of right TPJ stimulation in healthy subjects are similar to the results described by previous studies using tDCS.

Santiesteban et al. (2012) developed a stimulation trial where 49 healthy participants were randomly allocated to anodal, cathodal, or sham tDCS targeting the right TPJ. The authors found a higher imitative-control ability after anodal tDCS (M = 16.15 ms) in comparison to cathodal (M = 52.50 ms; p = 0.04) and sham tDCS (M = 52.30 ms; p = 0.051). The results regarding the control of imitation task in our trial were quite similar to this study, although our participants displayed a quite inferior imitative-control performance after the anodal tDCS condition (M = 32.97). More recently, another trial from the same research group also found that anodal tDCS targeting the right TPJ significantly improved control of imitation in comparison to a stimulation protocol targeting a brain region that had no previous relationship with social processing, namely the occipital cortex (Santiesteban et al., 2015). These findings allowed to understand that the observed effects on control of imitation were specifically associated with the rigth TPJ and not to active stimulation per se.

Another important topic when looking at the descriptive statistics of control of imitation performance in healthy subjects are the very close results between the sham and cathodal conditions. However, this is consistent with the findings from the meta-analyses of Jacobson et al. (2012) that suggests that while there are inhibition effects from cathodal tDCS in neurophysiological studies targeting motor areas, the same cannot be said regarding trials exploring stimulation effects on complex cognitive functions, which are supported by wider brain networks, possible leading to compensatory processes.

It is also very important to highlight that in our trial, although there was no significant condition by task interaction, there were also no effects of stimulation condition on the non-imitative control task. Hogeveen et al. (2015) also found similar task-dependent effects of tDCS on the right TPJ, as participants displayed improved inverse efficiency in the control of imitation

task in comparison to the sham condition, while there were no significant differences between conditions on the non-imitative control task. These findings are extremely important because, in spite of the task instructions and stimuli being similar to the control of imitation task, right TPJ stimulation only affected imitative-control performance. This clearly suggested that the right TPJ plays a specific role in the online control of representations of the self and others.

It is important to notice that previous studies assessing the effects of tDCS targeting the right TPJ used a between-group design, in contrast to our study where we selected a cross-over design. As our findings were reasonably similar to other trials, it suggests that the control of imitation and non-imitative control tasks can be used in cross-over studies, as learning effects did not seem to play a role on the reported findings. This could be extremely helpful when studying populations where participants' recruitment is difficult, as cross-over trials usually require smaller sample sizes.

Regarding patients with schizophrenia, there were no significant differences between stimulation conditions on both the control of imitation and non-imitative control tasks. It is important to notice that descriptive statistics showed no substantial differences between conditions on non-imitative control. However, imitative-control performance in anodal (M = 31.53; SD = 40.08) and cathodal (M = 35.56; SD = 64.84) tDCS was quite superior in comparison to sham stimulation (M = 50.59; SD = 42.67). Thereby, although there were no statistical significant differences between conditions, it seems that both anodal and cathodal tDCS had stimulation effects on imitative-control in the same direction. There are two main hypothesis to explain the reported findings.

Brain changes and right TPJ response to tDCS in schizophrenia

Our findings do not allow to conclude whether the right TPJ plays a role in self-other control in participants with schizophrenia. There is actually evidence suggesting that patients with schizophrenia recruit the same networks for social cognitive processes as healthy controls (Bosia, Riccaboni, & Poletti, 2012) in spite of displaying reduced temporoparietal junction activity when performing theory of mind tasks (Benedetti et al., 2009; Walter et al., 2009). However, it is possible to hypothesize that patients with schizophrenia present functional and biological abnormalities in this brain region that disturbs the excitability changes typically induced by tDCS. It is very well-

know that schizophrenia is associated with a wide-range of neurobiological, functional and electrophysiological changes that could play a role on the effects of tDCS on the right TPJ (Falkai & Moller, 2012; Glahn et al., 2005; Hill et al., 2004; Javitt, 2015; Javitt, Spencer, Thaker, Winterer, & Hajos, 2008; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006; Woo, 2014; Zakzanis, Poulin, Hansen, & Jolic, 2000).

Interestingly, Krause, Marquez-Ruiz, & Kadosh (2013) proposed that the behavioral improvements induced by tDCS could be related to the modulation of cortical excitation/inhibition balance. This hypothesis assumes that the optimal performance of any given brain region can only be achieved when there is an efficient interaction between excitation and inhibition. Only when this relative optimum is attained, it is possible to develop homeostatic control of activity-dependent plasticity and synaptic efficiency, ultimately leading to effective behavioral responses (Turrigiano & Nelson, 2000). Finally, excitation/inhibition balance is intrinsically associated with glutamate/GABA ratios, as GABA overexpression can lead to cortical over-inhibition and hyperactive glutamatergic activity to excessive network output and excitotoxicity (Krause et al., 2013).

There is a wide range of evidence implicating glutamatergic and GABAergic function in schizophrenia pathophysiology, suggesting their connection to illness course, cognitive and negative symptoms (Benes, 2015; de Jonge, Vinkers, Hulshoff Pol, & Marsman, 2017; Farber, 2003; Goff & Coyle, 2001; Gonzalez-Burgos & Lewis, 2008; Hu, MacDonald, Elswick, & Sweet, 2015; Kantrowitz & Javitt, 2010; Krystal et al., 2003; Lewis, 2014; Lewis, Hashimoto, & Volk, 2005).

Thereby, it is possible that these changes in glutamate and GABA expression could lead to an excitatory / inhibitory functional imbalance that is a crucial deficit in this disorder, in a least a subgroup of patients with schizophrenia (Keshavan, Nasrallah, & Tandon, 2011; Nasrallah, Tandon, & Keshavan, 2011). The direction of the excitatory/inhibitory imbalance may be closely related with the behavioral response to tDCS depending on several factors such as the particular brain region, the clinical population and inter-individual variability (Krause et al., 2013). Furthermore, evidence from animal studies actually suggest that elevated excitatory/inhibitory balance is associated with social and information-processing dysfunction, supporting its role in the symptomatology of several psychiatric disorders such as schizophrenia (Yizhar et al., 2011).

As some patients with schizophrenia may experience increased excitatory/inhibitory balance due to abnormal GABA/Glutamate ratios, it is possible that in some participants of our trial cathodal tDCS actually reduced over-activation, allowing for improved behavioral outcomes. This could explain why some participants reported improved imitation-control after anodal stimulation, while others enhanced their performance in the cathodal condition.

Medication interactions with tDCS in schizophrenia

The second hypothesis to explain the reported findings is the interaction between medication and tDCS. Antipsychotics are the gold standard pharmacological treatment for schizophrenia, with their main recognized mechanism of action being based on D_2 receptor blockade (Kapur & Mamo, 2003). However, antipsychotics are very heterogeneous, displaying a wide range of different actions with other neurotransmitters systems and diverse affinity profiles with D_2 receptors. Agarwal et al. (2016) were the first to directly assess the impact of antipsychotic drug type on tDCS effects in patients with schizophrenia. Participants with persistent auditory hallucinations were divided into three groups based on dopamine D_2 receptor affinity of their antipsychotics (low-affinity, high-affinity, and mixture of both) and completed 10 tDCS sessions with the anode targeting the left dorsolateral prefrontal cortex and the cathode targeting the left TPJ. Subjects taking high affinity antipsychotics displayed less improvement in hallucinations in comparison to the other groups, suggesting that the larger availability of dopamine receptors in patients taking low D_2 affinity medication is associated with better tDCS effects.

Evidence from pharmacological studies has also pinpointed the role of D_2 receptors on tDCS response. Nitsche et al. (2006) reported that blocking D_2 receptors using sulpiride hindered both cortical excitability enhancement and inhibition induced by anodal and cathodal stimulation, respectively. Conversely, applying a D2 agonist (bromocriptine) produced a non-linear dose-dependent interaction with tDCS effects (Fresnoza, Stiksrud, et al., 2014). Low and high doses eliminated the excitability changes in both anodal and cathodal tDCS. However, medium doses nearly reversed the effects of anodal tDCS, while in the cathodal condition the decrease in excitability was prolonged. Finally, there is also evidence suggesting that D_1/D_2 agonist pergolide prolonged the excitability decrease after cathodal stimulation, although it had no impact on anodal tDCS effects (Nitsche et al., 2006).

Although there is a significant amount of evidence suggesting other complex dopamine receptor-dependent interactions in tDCS (Fresnoza, Paulus, Nitsche, & Kuo, 2014; Kuo, Paulus, & Nitsche, 2008; Monte-Silva et al., 2009; Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010; Nitsche, Kuo, Grosch, et al., 2009), these findings taking together strongly support the crucial role of D2 receptor activity on NMDA receptor-dependent tDCS-induced excitability changes. Thereby, as D_2 receptors play a major role in the action of antipsychotics and the dopaminergic system is closely related with tDCS induced plasticity, is important to take into account that antipsychotics can interact with tDCS stimulation via dopamine changes (McLaren, Nissim, & Woods, 2017).

Besides antipsychotic medication, several participants in our trial also used other psychotropic drugs targeting other symptoms. Thereby, it is also possible that the drugs influenced tDCS response. For instance, a significant number of the included participants used some sort of benzodiazepine on a regular basis (n=5; 31.25%) or as an SOS medication for increased anxiety (n=4; 25%). Benzodiazepines pharmacodynamics are closely related to GABA receptors modulation and have been widely used in combination with antipsychotics in the pharmacological management of schizophrenia (Szarmach, Wlodarczyk, Cubala, & Wiglusz, 2017; Vinkers, Mirza, Olivier, & Kahn, 2010; Wlodarczyk, Szarmach, Cubala, & Wiglusz, 2017). There is evidence suggesting that a classical benzodiazepine (lorazepam) that acts as a GABA agonist delays the anodal effects of tDCS, but ultimately enhances and prolongs cortical excitability increases (Nitsche et al., 2004). More specifically, after a long-lasting excitability modulation protocol (11 minutes at 1 m.A.), increased cortical excitability was only enhanced 10 minutes after stimulation. In our stimulation protocol, participants completed the behavioral tasks immediately after stimulation, lasting up to 15 minutes. Thus, it is possible that participants taking benzodiazepines did not fully experience the cortical excitability increases and improved task performance after anodal tDCS. Furthermore, there is also evidence that tDCS efficacy is reduced in patients with major depressive disorder taking benzodiazepines (Brunoni, Ferrucci, et al., 2013).

There were also several participants taking anti-depressant medication (n=4; 25%), namely selective serotonin reuptake inhibitors (SSRI). Single dose intake or chronic administration of the SSRI citalopram have been shown to increase and prolong excitability enhancement after anodal tDCS (Kuo et al., 2016; Nitsche, Kuo, Karrasch, et al., 2009). There is actually evidence from a randomized controlled trial with patients with major depressive disorder suggesting that sertraline

increases the efficacy of tDCS (Brunoni, Valiengo, et al., 2013). However, it is also known that citalopram reverses cathodal stimulation effects, leading to increased plasticity instead of cortical inhibition (Kuo et al., 2016; Nitsche, Kuo, Karrasch, et al., 2009). Furthermore, this interaction seems to be related to NMDA-receptors as dextromethorphane intake combined with citalopram completely eliminated tDCS effects on both stimulation conditions (Kuo et al., 2016). Thereby, it is possible that the participants on SSRI's included our trials experienced behavioral improvements in both active stimulation conditions.

Besides benzodiazepines, some participants also used other psychotropic drug such as biperiden (n=3; 18.75%), carbamazepine, and levodopa (n=1; 6.25% each). Biperiden is a cholinergic antagonist typically used to target extra-pyramidal symptoms experienced by patients with schizophrenia while taking anti-psychotics and there is also evidence suggesting that cholinergic pathways play a role in tDCS induced excitability changes (Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007). Evidence suggests that carbamazepine probably blocks sodium channels and inhibits anodal tDCS effects (Nitsche, Fricke, et al., 2003). Previous evidence had also suggested that L-dopa had a dose-response effect on tDCS, as low and high dosages eliminated cortical excitability changes, but medium dosage turned anodal tDCS excitability enhancement into inhibition, and prolonged the decrease in cortical excitability in the cathodal condition (Kuo et al., 2008; Monte-Silva et al., 2010). Furthermore, there is evidence suggesting that the plasticity-abolishing effects induced by sulpuride on both anodal and cathodal stimulation are canceled by adding L-dopa, suggesting that D1 receptor activation under D2 receptor blockage reestablishes tDCS induced cortical excitability changes (Fresnoza, Paulus, et al., 2014; Nitsche, Kuo, Grosch, et al., 2009).

In conclusion, it is clear that pharmacological interventions that change ion or neurotransmitter concentrations may influence the complex mechanisms that lead to increased or reduced excitability after active tDCS. A recent review has highlighted that if medication interactions in tDCS studies are not addressed, findings reported by current literature will be very problematic to interpret (McLaren et al., 2017). Moreover, although it is possible to infer about single medication effects on tDCS based on previous studies, there is not enough evidence to predict how multiple medications can interact with stimulation effects, as it was the case in many of the included patients in our study.

Limitations and recommendations for future studies

There are also other limitations that could have played a role on the reported findings. For instance, stimulation procedures may have not been ideal to achieve behavioral changes in patients with schizophrenia. Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald (2014) found that 2 mA anodal tDCS targeting the left dorsolateral prefrontal cortex improved working memory performance in patients with schizophrenia, although the same protocol with current intensity set at 1 mA did not achieve the same results. It is possible that 1 mA is enough to produce cortical excitability changes and concurrent imitative-control improvement in healthy subjects, but a higher current intensity may be needed to produce similar changes in patients with schizophrenia. It is also feasible to postulate whether tDCS effectively targeted the right TPJ in patients with schizophrenia as there is evidence describing that this population displays smaller temporal lobes in comparison to healthy controls (Olabi et al., 2011). Future studies should use neuronavigation procedures in order to assure proper stimulation of the right TPJ in patients with schizophrenia. Finally, tDCS might stimulate the right TPJ while also producing effects on other brain regions. Besides increasing/decreasing the cortical excitability of the targeted brain region, it is known that tDCS also modulates multiple areas as well as connections between regions through diffuse current flow and synapse polarization (Rahman et al., 2013). Stimulation also targets deeper brain structures that are implicated in the pathophysiological mechanisms of schizophrenia and, although there is no evidence associating these regions with control of imitation, could have hindered the effectiveness of our tDCS protocol (Brunoni et al., 2014).

Although we did not found any significant effects of tDCS targeting the right TPJ on control of imitation in patients with schizophrenia, it is possible that the same protocol could produce behavioral improvements related to self-other control with other tasks. Several studies with healthy participants have found that right TPJ anodal tDCS can effectively improve performance on a perspective-taking task, where participants are asked to enhance other-representations and inhibit self-representations (Santiesteban et al., 2012, 2015). Thereby, future studies should explore the effects of right TPJ stimulation on alternative tasks associated with self-control in patients with schizophrenia. Furthermore, studies with healthy controls have also found that other brain regions play a clear role in self-other control, namely the inferior frontal cortex (Hogeveen et al., 2015) and the left TPJ (Santiesteban et al., 2015). Future trials could compare right TPJ stimulation with

montages targeting these regions in patients with schizophrenia in order to understand if the lack of stimulation effects in our trial is due to functional abnormalities in the right TPJ itself or it's rather a global brain dysfunction that impairs several components of the self-other processing network.

Small sample size can also explain our findings, impacting generalizability and providing a limited power to detect significant differences. Future studies can also explore different characteristics of the included sample in order to further understand the role of the right TPJ on self-other control in schizophrenia. As previously described, it is clear that psychotropic drugs typically used by patients with schizophrenia can interact with tDCS effects. Thereby, developing tDCS trials for first episode drug-naïve patients or individuals with ultrahigh risk for psychosis could help to eliminate this potential confounder. Setting more restrict age-related inclusion criteria, excluding longstanding chronic patients could also be a valuable strategy as there is evidence suggesting that TPJ activity changes throughout the course of the disease and is possible affected due to long-term antipsychotic usage.

CONCLUSION

This study is the first to use tDCS to explore the role of the right TPJ on self-other control in patients with schizophrenia in comparison to healthy objects. There were significant difference between stimulation conditions (anodal, cathodal, and sham) in the healthy control group, with anodal tDCS inducing improved control of imitation, as it was previous described by other authors. Furthermore, there were no behavioral changes in the non-imitative control task, reinforcing the specialized role of the right TPJ on control of the representations of the self and the other. However, there were no significant effects of stimulation in control of imitation performance in the schizophrenia group. It is feasible to postulate that the pathophysiology of schizophrenia leads to abnormal electrophysiological and neurobiological functioning of this brain region, which interferes with the cortical excitability modulation typically induced by tDCS. There is clear evidence that GABAergic and glutamatergic functioning is impaired in schizophrenia, leading to excitation / inhibition deviations that change the theoretically expected effects of tDCS.

There are also several factors that might confounded the previously reported findings. Psychotropic medication clear interferes with tDCS mechanisms to induce changes in cortical excitability and patients with schizophrenia typically use at least one antipsychotic medication. Antipsychotic drugs actions heavily relies on D_2 receptors and tDCS induced plasticity is intrinsically related to the dopaminergic system, allowing us to hypothesize that antipsychotics interact with tDCS effects via dopamine-related pathways. Patients with schizophrenia frequently use other psychotropic drugs for their treatment such as benzodiazepines, SSRI's, among other, which can also affect the expected effects of tDCS on cortical excitability. Future studies should explored the effects of tDCS on first episode drug-naïve patients or ultra-high risk participants in order to reduce medication as a potential confounder. Furthermore, there is a need to explore the effects of tDCS targeting the right TPJ in patients with schizophrenia while using other task related to self-other control (e.g. perspective-taking), different current intensities, and using neuronavigation tools to effectively stimulate this brain region.

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APPENDIX A. PUBLICATIONS DURING THE POSTGRADUATE PROGRAM

Campos, C., Rocha, N. B., Lattari, E., Paes, F., Nardi, A. E., & Machado, S. (2016). Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors. *Expert Rev Neurother, 16*(6), 723-734. doi:10.1080/14737175.2016.1179582

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Silva, V., Campos, C., Sa, A., Cavadas, M., Pinto, J., Simoes, P., . . . Barbosa-Rocha, N. (2017). Wii-based exercise program to improve physical fitness, motor proficiency and functional mobility in adults with Down syndrome. *J Intellect Disabil Res, 61*(8), 755-765. doi:10.1111/jir.12384

Telles-Correia, D., Barbosa, A., Cortez-Pinto, H., Campos, C., Rocha, N. B., & Machado, S. (2017). Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther, 8*(1), 26-38. doi:10.4292/wjgpt.v8.i1.26

APPENDIX B. WRITTTEN INFORMED CONSENT FORM

Instituto de Psiquiatria
Universidade Federal do Rio de Janeiro
CNPJ Nº 33.663.683/0025-93

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O Sr. (a) está sendo convidado (a) como voluntário (a) a participar da pesquisa **""Estimulação Transcraniana de Corrente Contínua e Esquizofrenia: Reabilitação Neurocognitiva e da Cognição Social"**. No decorrer desta pesquisa os participantes poderão participar em um ou mais dos experimentos planeados, completando os seguintes procedimentos:

- Avaliação clínica inicial através de entrevista realizada por psiquiatra ou psicólogo;
- Aplicação de testes para avaliação da sintomatologia (Escala de Avaliação da Sintomatologia Positiva e Negativa), funcionamento (Escala de Avaliação do Desempenho Pessoal e Social), cognição (subtestes da Escala de Inteligência Wechsler para Adultos) e cognição social (testes computorizados);
- Realização de sessões de treino cognitivo (exercícios de memória e concentração) utilizando o computador e jogos virtuais;
- Realização de sessões de estimulação transcraniana de corrente contínua (estimulação cerebral não invasiva de baixa intensidade).

A periodicidade e duração do tratamento pode variar consoante o número de experimentos em que o participante tem interesse em participar, com duração máxima de 3 meses. No final da pesquisa, os participantes poderão continuar a fazer o tratamento proposto nas instalações do Laboratório de Pânico e Respiração caso mantenham interesse. O risco da pesquisa está relacionado com alguns efeitos secundários ligeiros após a estimulação (coceira, ligeira sensação de ardor na zona estimulada).

Para participar deste estudo o Sr (a) não terá nenhum custo, nem receberá qualquer vantagem financeira. O Sr. (a) terá o esclarecimento sobre o estudo em qualquer aspeto que desejar e estará livre para participar ou recusar-se a participar. Poderá retirar seu consentimento ou interromper a participação a qualquer momento. A sua participação é voluntária e a recusa em participar não acarretará qualquer penalidade ou modificação na forma em que o Sr. (a) é atendido, que tratará a sua identidade com padrões profissionais de sigilo. Seu nome ou o material que indique sua participação não será liberado sem a sua permissão.

O (A) Sr (a) não será identificado (a) em nenhuma publicação que possa resultar.

Este termo de consentimento encontra-se impresso em duas vias originais, sendo que uma será arquivada pelo pesquisador responsável, no IPUB/ Universidade Federal do Rio de Janeiro e a outra será fornecida ao Sr. (a). Os dados e instrumentos utilizados na pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos, e após esse tempo serão destruídos. Os pesquisadores tratarão a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resolução Nº 466/12 do Conselho Nacional de Saúde), utilizando as informações somente para os fins acadêmicos e científicos.

Eu, _____, portador do documento de Identidade _____ fui informado (a) dos objetivos da pesquisa ""**Estimulação Transcraniana de Corrente Contínua e Esquizofrenia: Reabilitação Neurocognitiva e da Cognição Social**", de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim o desejar.

Declaro que concordo em participar. Recebi uma via original deste termo de consentimento livre e esclarecido e me foi dada à oportunidade de ler e esclarecer as minhas dúvidas.

Rio de Janeiro, _____ de _____ de 20 .

Nome: _____

Data: _____

Assinatura participante: _____

Nome: _____

Data: _____

Assinatura pesquisador:_____

Em caso de dúvidas, com respeito aos aspectos éticos desta pesquisa, você poderá consultar:

Pesquisadores do Projeto
Disponível por contacto telefónico de 2ª a 6ª feira, entre as 9h e as 16h
- Carlos Campos - Cel: (21) 99593–0052
- Sérgio Machado - Cel: (21) 99156-7006

Comissão de Ética em Pesquisa do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro
Endereço: Av. Venceslau Brás 71, fds – Prédio da Direção – 2º andar. 22.290-140 – Campus Praia Vermelha - Botafogo – Rio de Janeiro.
Telefone: 55 (21) 3938-5510

APPENDIX C. SOCIODEMOGRAPHIC AND SAFETY QUESTIONNAIRE

<table>
<tr><th colspan="2">1. Dados Sociodemográficos</th></tr>
<tr><td>Data da Avaliação:</td><td>Mão dominante: Direita Esquerda Ambas</td></tr>
<tr><td>Número de participante:</td><td>Ocupação:</td></tr>
<tr><td>Nome:</td><td rowspan="4">Situação profissional:
(1) Empregado
(2) Desempregado
(3) Licença médica
(4) Aposentado
(5) Dona de casa
(6) Estudante</td></tr>
<tr><td>Data de nascimento:</td></tr>
<tr><td>Idade:</td></tr>
<tr><td rowspan="2">Zona de residência (bairro):</td></tr>
<tr><td>Agregado familiar (com quem vive):</td><td>Estado civil:
(1) Casado ou união estável
(2) Solteira
(3) Viúva
(4) Separada ou divorciada</td></tr>
<tr><td>Escolaridade:
- Grau (primária, licenciado, etc) _____
- Número de anos _____</td><td>Contactos
Tel. Fixo:
Celular:
Email:</td></tr>
</table>

<table>
<tr><th colspan="2">2. Informação Clínica</th></tr>
<tr><td colspan="2">Dados a consultar no prontuário ou com o psiquiatra responsável</td></tr>
<tr><td>Psiquiatra responsável</td><td>Diagnóstico</td></tr>
<tr><td>Ano de diagnóstico</td><td>Ano do 1º internamento</td></tr>
<tr><td>Número de internamentos</td><td>Último internamento</td></tr>
<tr><td colspan="2">Alterações recentes na medicação (quais e quando):</td></tr>
</table>

3. Critérios de Exclusão e Contraindicações		
Em que ano foi internado(a) pela primeira vez num serviço de psiquiatria?		
Quando foi a última vez que teve internado(a)?		
Teve alguma alteração de medicação nas últimas 6 semanas (confirmar com psiquiatra)?	**SIM**	**NÃO**
Nos últimos 6 meses, tem algum historial de consumo, abuso ou dependência de álcool ou outro tipo de substâncias? _____	**SIM**	**NÃO**
É fumador(a)? Se sim, quantos cigarros costuma fumar por dia aproximadamente? ____	**SIM**	**NÃO**
Toma café? Se sim, quantos cafés costuma tomar por dia aproximadamente? _____	**SIM**	**NÃO**
Você tem algum historial de doença infetocontagiosa ou cardiorrespiratória?	**SIM**	**NÃO**
Você tem epilepsia ou já teve algum tipo de convulsão?	**SIM**	**NÃO**
Você já teve algum desmaio ou síncope? Se sim, descreva em que ocasiões	**SIM**	**NÃO**
Você tem algum historial de problemas ou doença neurológica (acidente vascular, doença neurodegenerativa, aneurisma)? _____	**SIM**	**NÃO**
Você já teve algum tipo de traumatismo craniano (seguido de perda de consciência)?	**SIM**	**NÃO**
Você tem algum tipo de problema de pele como dermatite, psoríase ou eczema?	**SIM**	**NÃO**
Você tem algum historial de problemas no couro cabeludo?	**SIM**	**NÃO**
Você tem algum tipo de implante eletrónico (implante coclear) ou algo semelhante?	**SIM**	**NÃO**
Você tem algum tipo de metal no cérebro ou crânio (e.g. fragmentos, implante de metal, parafuso, piercings)? Se sim, especifique o tipo de metal _____	**SIM**	**NÃO**
Você tem algum tipo de neuroestimulador, aparelho de infusão medicamentosa, dispositivo de drenagem cerebral ou algo semelhante no corpo?	**SIM**	**NÃO**
Você tem algum tipo de pace-maker (marca-passo) ou algum dispositivo que envolva metal no seu corpo?	**SIM**	**NÃO**
Já alguma vez fez algum procedimento de estimulação cerebral no passado? *Se sim, teve algum tipo de problema?* _____	**SIM**	**NÃO**
Já alguma vez fez algum tipo de ressonância magnética no passado? *Se sim, teve algum tipo de problema?* _____	**SIM**	**NÃO**
Você é gestante ou pensa em ser em breve?	**SIM**	**NÃO**

4. Tratamento Farmacológico

Medicação Psiquiátrica

Nome	*Princípio ativo*	*Quantidade (mg)*	*Frequência diária*	*Períodos do dia*

Outro tipo de medicação

Nome	*Princípio ativo*	*Quantidade (mg)*	*Frequência diária*	*Períodos do dia*

5. Outros tipos de tratamento

Faz algum tipo de tratamento além da medicação (psicoterapia, estimulação, meditação, grupo de apoio)?

Tipo de tratamento	*Há quanto tempo?*	*Frequência semanal*	*Tempo / Sessão*

6. Outras informações relevantes

APPENDIX D. ADVERSE EFFECTS OF TDCS QUESTIONNAIRE

ID:	**Nome:**

Você experienciou algum tipo de desconforto ou incómodo durante a estimulação elétrica? Por favor classifique o grau de intensidade do desconforto associado a cada uma das sensações em baixo, usando a seguinte escala:

Nenhum = Não senti a sensação descrita (0)
Ligeiro = Senti ligeiramente a sensação descrita (1)
Moderado = Senti a sensação descrita (2)
Considerável = Senti a sensação descrita num grau considerável (3)
Forte = Senti fortemente/claramente a sensação descrita (4)

Sessão: **Data:**	*Nenhum*	*Ligeiro*	*Moderado*	*Considerável*	*Forte*
Coceira					
Dor					
Queimação					
Calor					
Formigando Picaduras					
Sabor Metálico -Ferro					
Fadiga/Cansaço					
Outro _____					

Quando começou a sentir o desconforto?		
No início da estimulação	Aproximadamente a meio da estimulação	No final da estimulação

Quanto tempo durou o desconforto?		
Parou rapidamente	Parou a meio da estimulação	Parou no final da estimulação

Em que grau estas sensações afetaram o seu desempenho na tarefa?				
Nada	Ligeiramente	Consideravelmente	Muito	Muitíssimo

Descreva se estas sensações foram localizadas na zona da cabeça ou noutras zonas do corpo	
Na cabeça _____	Outras _____