Psychiatry Research 235 (2016) 97–103

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients ☆

Sri Mahavir Agarwal [a,b], Anushree Bose [a,b], Venkataram Shivakumar [a,b,c], Janardhanan C. Narayanaswamy [a,b], Harleen Chhabra [a,b], Sunil V. Kalmady [a,b], Shivarama Varambally [a,b], Michael A. Nitsche [d,e,f], Ganesan Venkatasubramanian [a,b,*], Bangalore N. Gangadhar [a,b]

[a] The Schizophrenia Clinic, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India
[b] Translational Psychiatry Laboratory, Neurobiology Research Centre, National Institute of Mental Health and Neurosciences, Bangalore, India
[c] Department of Clinical Neurosciences, NIMHANS, Bangalore, India
[d] Department of Clinical Neurophysiology, University Medical Center, Georg-August-University, Göttingen, Germany
[e] Leibniz Research Centre for Working Environment and Human Resources, Dortmund, Germany
[f] Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
17 October 2015
Accepted 22 November 2015
Available online 2 December 2015

Keywords:
tDCS
Schizophrenia
Antipsychotic
Dopamine
Estrogen

ABSTRACT

Transcranial direct current stimulation (tDCS) has generated interest as a treatment modality for schizophrenia. Dopamine, a critical pathogenetic link in schizophrenia, is also known to influence tDCS effects. We evaluated the influence of antipsychotic drug type (as defined by dopamine D_2 receptor affinity) on the impact of tDCS in schizophrenia. DSM-IV-TR-diagnosed schizophrenia patients [$N=36$] with persistent auditory hallucinations despite adequate antipsychotic treatment were administered add-on tDCS. Patients were divided into three groups based on the antipsychotic's affinity to D_2 receptors. An auditory hallucinations score (AHS) was measured using the auditory hallucinations subscale of the Psychotic Symptom Rating Scales (PSYRATS). Add-on tDCS resulted in a significant reduction inAHS. Antipsychotic drug type had a significant effect on AHS reduction. Patients treated with high affinity antipsychotics showed significantly lesser improvement compared to patients on low affinity antipsychotics or a mixture of the two. Furthermore, a significant sex-by-group interaction occurred; type of medication had an impact on tDCS effects only in women. Improvement differences could be due to the larger availability of the dopamine receptor system in patients taking antipsychotics with low D_2 affinity. Sex-specific differences suggest potential estrogen-mediated effects. This study reports a first-time observation on the clinical utility of antipsychotic drug type in predicting tDCS effects in schizophrenia.

1. Introduction

Schizophrenia is a common and severe mental disorder (McGrath et al., 2008). Despite the best available treatment, many patients continue to experience severe symptoms such as auditory hallucinations. In 25–30% of the patients, these hallucinations are refractory to antipsychotic treatment (Kane et al., 1988; Meltzer, 1992), adding to distress and disability and creating a need for innovative treatment strategies.

In this context, transcranial direct current stimulation (tDCS), a neuroplasticity-modulating, non-invasive brain stimulation technique (Nitsche et al., 2008, 2003) has recently generated interest as an emerging add-on treatment modality especially for schizophrenia patients with persistent auditory hallucinations despite adequate treatment with antipsychotic medication (Agarwal et al., 2013). This technique involves the passage of a weak direct current that flows between electrodes placed over the scalp with resultant polarity-specific changes in neuronal excitability; anodal stimulation increasing and cathodal stimulation decreasing neuronal excitability possibly due to sub-threshold polarity-specific de- or hyperpolarisation of neuronal membranes. The after-effects of tDCS can persist for several hours, involve plasticity of the glutamatergic system, and are mediated by alterations of NMDA and GABA receptor activity. Reduction of tDCS-induced plasticity may serve as an endophenotype with deficits shared by schizophrenia

☆This study was awarded the Young Researcher Award at the International Conference on Schizophrenia (ICONS-VI) held at Chennai, India on August 21–23, 2014.

* Corresponding author at: Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India.
E-mail address: venkat.nimhans@yahoo.com (G. Venkatasubramanian).

http://dx.doi.org/10.1016/j.psychres.2015.11.042
0165-1781/

patients and their unaffected relatives (Hasan et al., 2013a, 2012, 2011, 2013b), and has also been proposed to underlie symptom pathophysiology (Mondino et al., 2015a). Furthermore, improvement in symptom severity may be due to adaptive modulation of cortical plasticity (Nawani et al., 2014a, 2014b).

tDCS has been demonstrated to be effective in reducing auditory hallucinations by presumably decreasing hyperactivity of the temporo-parietal junction (TPJ) in the first monocentric proof-of-principle trial (Brunelin et al., 2012). Indeed, pilot studies have demonstrated a significant clinical improvement with tDCS, with respect to auditory hallucinations (Brunelin et al., 2012; Mondino et al., 2015b; Rakesh et al., 2013; Shivakumar et al., 2013), negative symptoms (Brunelin et al., 2012; Kurimori et al., 2015; Mondino et al., 2015b) and insight into the origin and reality of psychotic experiences (Bose et al., 2014).

Several factors are known or presumed to affect the neuroplasticity-inducing potential of tDCS, such as subjects' age and sex, genetic profile, history of past response to tDCS or repetitive transcranial magnetic stimulation (rTMS) and medication (Ridding and Ziemann, 2010). Among these factors, the effect of central nervous system-acting medications on tDCS-induced plasticity has been the most extensively studied. Several animal model studies and studies in healthy volunteers have explored the impact of pharmacological agents on tDCS-induced plasticity (Fresnoza et al., 2014a; Monte-Silva et al., 2009; Nitsche et al., 2008', 2006', 2012; Nitsche and Paulus, 2000; Ridding and Ziemann, 2010). These studies have shown that enhancement/reduction of dopaminergic activity has a prominent, non-linear influence on the neuroplasticity-causing potential of tDCS. Moreover, dopamine receptor subtypes might have a differential impact on this interaction (Fresnoza et al., 2014a, 2014b; Monte-Silva et al., 2009; Nitsche et al., 2006). It is possible that an optimally functioning dopamine system might be critical for the induction of plasticity and medications that interfere with dopamine signaling are likely to have an impact on tDCS effects (Monte-Silva et al., 2009).

Antipsychotics, the mainstay of treatment in schizophrenia, are a heterogeneous group of drugs. Although several neurotransmitters have been implicated in schizophrenia pathogenesis, no drug has yet been identified with clinically effective antipsychotic action without significant affinity to the D_2 receptor (Kapur and Mamo, 2003). Most antipsychotics have widely varying actions on other neurotransmitter systems as well, which is thought to be critical for the efficacy and side effect profile of a specific drug. However, the most parsimonious explanation of the antipsychotic action of these drugs continues to be based on D_2 receptor blockade. Even though all antipsychotics bind to the D_2 receptor, they vary widely with respect to the pharmacodynamic profile of this drug-receptor interaction (Kapur and Seeman, 2000) The affinity to the D_2 receptor determines important drug characteristics, like the effective dosage, level of receptor block in vivo, and dopaminergic side effect profile (Kapur and Seeman, 2000). Hence, antipsychotics can be classified due to their affinity to D_2 receptors. Those with high affinity to the D_2 receptor (low dissociation constant [K_i],) and those that have either low affinity to D_2 receptors, or are partial agonists of these receptors (Supplementary Table 1 and Supplementary Fig. S1) (Kapur and Seeman, 2000; Richtand et al., 2007). All drugs of the first type cause hyperprolactinemia as a common side effect at clinically relevant doses, while the drugs of the second type do not. Prolactin elevation has been shown to be correlated positively with D_2 receptor occupancy (Tsuboi et al., 2013). Hence, the above-mentioned grouping enables one to classify antipsychotics according to their D_2 receptor occupancy, for which K_i values are the experimental indicator, and propensity for hyperprolactinemia a relevant clinical signature. The availability of D_2 receptors is vital for potentially adaptive neuroplastic effects of tDCS (Nitsche et al., 2006). It might therefore be speculated that the impact of tDCS on clinical symptoms in schizophrenia might vary according to the profile of antipsychotic medication the patient receives-antipsychotics with high affinity to D_2 receptors may block the effects of tDCS due to relatively lesser availability of these receptors in comparison with low affinity antipsychotics. In this study, we aimed to answer this question by exploring the role of psychotropic medications on clinical improvement accomplished by add-on tDCS in patients with schizophrenia. It was hypothesized that patients receiving antipsychotics with high affinity to D_2 receptors will show significantly lesser improvement compared to patients receiving antipsychotics with lower affinity to D_2 receptors.

2. Methods

2.1. Clinical characteristics

Thirty six patients attending the clinical services of the National Institute of Mental Health & Neurosciences (India), who fulfilled DSM-IV-TR criteria for schizophrenia, all right handed (assessed using the Edinburgh inventory) (Oldfield, 1971), with persistent auditory hallucinations despite antipsychotic medication at adequate dosage (400–600 mg chlorpromazine equivalents or more) (Barnes and McEvedy, 1996; Conley and Kelly, 2001) were examined in this study. Persistence was defined based on the Psychotic Symptom Rating Scales (PSYRATS) auditory hallucination sub-scale (Haddock et al., 1999) items of frequency, duration and disruption each having a score ≥ 2 despite treatment with adequate antipsychotic medication for at least 3-months (Brunelin et al., 2012). The diagnosis of schizophrenia was established by the Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998), and confirmed by at least one experienced psychiatrist via an independent clinical interview. None of the patients had (i) alcohol abuse/dependence, (ii) neurological/medical disorders, (iii) developmental delay/mental retardation. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Institute's ethics committee. Patients were recruited consecutively. This sample of 36 patients partially overlaps with the sample of a previously published study investigating the impact of tDCS on improvement in insight in patients with schizophrenia (Bose et al., 2014).

The severity of auditory hallucinations was measured by the auditory hallucinations subscale of PSYRATS, while insight was assessed using the Schedule for Assessment of Insight (SAI) (David, 1990) at baseline and after completion of tDCS. The study was performed using a naturalistic design. Hence, no changes to the patients' prescription were made during the course of the study. Patients continued to take medications as prescribed by their treating physician. Compliance was carefully ascertained via clinical interview and corroboration by at least one reliable adult relative.

2.2. Antipsychotic medication type

Based on the antipsychotic medication they received, patients were divided into three groups viz. group I: patients receiving antipsychotics with high affinity to D_2 receptors only (haloperidol, chlorpromazine, trifluperazine, risperidone and amisulpride) [$N=11$], group II: patients receiving antipsychotics with low affinity to D_2 receptors or partial agonists of D_2 receptors (clozapine, olanzapine, iloperidone, quetiapine and aripiprazole) [$N=12$], and group III: patients receiving both types of medication [$N=13$].