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TOLERABILITY AND SAFETY OF 219 TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) 2.0 mA SESSIONS IN ADULT PATIENTS WITH SCHIZOPHRENIA

Adam Wysokiński

Medical University of Lodz, Department of Old Age Psychiatry and Psychotic Disorders, Łódź, Poland

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SUMMARY

Introduction: *The objective of the study was to evaluate safety and tolerability of tDCS treatment in schizophrenia patients. Our results confirm already established evidence that tDCS is a very safe and well tolerated method of non-invasive brain stimulation for patients with schizophrenia.*

Subjects and methods: *Database of 219 tDCS sessions in patients with paranoid schizophrenia has been analyzed.*

Results: *During 219 tDCS sessions there were no serious adverse effects. All adverse effects were mild to moderate and transitory and the most frequent were: itching/tingling (81%), burning (53%) or heat sensation (48%) and skin reddening (35%). Itching/tingling and burning sensation were also frequently reported as at least moderately severe. All major adverse events (itching/tingling, burning/heat sensation) were more often localized by patients under the anodal pad. Men were more prone to experience some adverse events (itching/tingling, burning/heat sensation, skin reddening, metallic taste and tiredness). Most of the adverse events had their onset at the beginning of tDCS session, resolved by the end of tDCS session (with the exception of skin reddening, which recovered within 30 minutes after stimulation) and were associated with mild or moderate distress.*

Conclusion: *Our results confirm already established evidence that tDCS is a very safe and well tolerated method of non-invasive brain stimulation for patients with schizophrenia.*

Key words: *transcranial direct current stimulation - tDCS – schizophrenia - safety*

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INTRODUCTION

Transcranial direct current stimulation (tDCS) is a modern, safe and effective method of non-invasive brain stimulation (NIBS) (Sudbrack-Oliveira et al. 2021). Preliminary studies showed tDCS efficacy in various neuropsychiatric disorders, including depression, schizophrenia, dementias, addictions, stroke and others (Lefaucheur et al. 2017).

Common tDCS-related side effects include: burning (skin sensation with no physical lesions), mild to moderate pain sensation, dizziness, erythema (skin redness), fatigue, headache, itching and tingling (Nikolin et al. 2018). Although tDCS treatment may lead to more serious adverse events, such as skin burns (Loo et al. 2011), even after a single tDCS session (Wang et al. 2015), which may result from excessive wear of the sponge pads into which electrodes are inserted (Wysokiński 2021). The vast body of evidence, however, supports safety of tDCS in human subjects (Bikson et al. 2016). These authors reported that across over 33,200 tDCS sessions and over 1000 subjects with repeated sessions, no serious adverse events have been reported. There are also some recent reports of tDCS safety in specific subpopulations of patients, e.g. with schizophrenia (Valiengo et al. 2019), depression (Huang et al. 2021) or obsessive-compulsive disorder (Silva et al. 2021). In children and adolescents tDCS is also safe and well tolerated (Buchanan et al. 2021), with the incidence of adverse events similar to that observed in adults (Krishnan et al. 2015). However, it must be emphasized that there is still a paucity of studies regarding the topic. Also, many studies are done with healthy volunteers and/or with low number of tDCS sessions. As a result, extrapolating these result to specific populations (e.g. elderly subjects with depression or patients with schizophrenia) should be made with caution.

As tDCS becomes more frequently studied in patients with schizophrenia, we wanted to analyze the safety and tolerability of tDCS treatment in this population. This is of particular interest as schizophrenic subjects present a specific experimental pain response profile, characterized by elevated sensitivity to acute pain but reduced sensitivity to prolonged pain (Lévesque et al. 2012). As a result schizophrenia patients may be more sensitive to tDCS induced itching, burning or heat sensations, which are experienced by approximately 50% of tDCS-treated schizophrenia patients (Valiengo et al. 2020).

SUBJECTS AND METHODS

This is a retrospective study. The computer database of all tDCS sessions performed until 31.12.2020 in our Department was analyzed. The study has been approved by a suitably constituted Ethics Committee of the Medical University of Lodz (RNN/244/19/KE).

The study conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All study subjects gave their informed consents for the tDCS treatment and for the use of acquired data for research purposes.

Safety data for two hundred nineteen (219) tDCS sessions were analyzed. One hundred twenty four sessions (124, 57%) were performed in men and 95 (43%) in women; all study subjects were Caucasian and right-handed. Mean age of the study subjects was 39.8±8.2 years (with women being significantly older 42.6±8.8 vs. 37.7±7.2, p<0.001). The majority of sessions (154, 70%) were performed in patients with paranoid schizophrenia, the remaining sixty five (65, 30%) sessions were performed in patients with catatonic schizophrenia. Among coexisting comorbidities there were allergies (16, 7%), asthma (44, 20%), epilepsy (29, 13%) and tachycardia (20, 9%). Average illness and treatment duration were both 14.9±8.0 years. For 125 (57%) sessions subjects were classified as treatment-refractory. All sessions were performed in antipsychotic-medicated patients.

All tDCS sessions were performed by the author of this report, using the same stimulator (DC-Stimulator PLUS; neuroCare, Germany). All stimulations were performed using 5×7 cm rubber electrodes placed in saline-soaked sponge pads (average volume of 0.9% saline was 10.8±6.0 mL per two electrodes); for all sessions the same set of electrodes and sponge pads was used. For all sessions a current of 2.0 mA was applied, thus resulting in the current density of 0.57 A/m^2. The locations (according to the 10-20 International System of Electrode Placement) of the anodal electrode were: F3 (211, 96%), C3 (7, 3%) or C4 (1, 0.4%) sessions, while the location of cathode were: above the right orbit (111, 51%), F4 (65, 30%) or T3 (43, 20%). Stimulation duration was 1200 seconds (20 minutes) for all sessions, while average ramp-in and ramp-out were both 17.8±4.2 seconds.

For safety data we used the tDCS adverse event questionnaire proposed by Brunoni et al. (2011), which was modified to add a few more parameters. The safety protocol was filled in by all study subjects after each tDCS session. The following data were collected: itching/tingling, pain, burning sensation, heat sensation, cold sensation, skin reddening, metallic taste, tiredness and headache. Also, subjects were asked about any other condition not listed in the protocol. If there were any adverse effects observed by the doctor performing tDCS sessions, there were also reported. For each condition the following features were evaluated: severity (on the scale from 1 to 5, where 1 indicates very mild and 5 indicates very severe), onset (from the beginning of the current session, during the session or at its end), duration (only at the beginning, resolving completely by the end of the session or lasting at least by the end of stimulation), subjective level of distress (mild, moderate or significant) and location (both anode and cathode, only anode, only cathode or generalized).

Statistical analysis of the safety data was performed with R 4.0.4 (R Core Team). Simple descriptive statistics (mean ± standard deviation) were generated for continuous variables, discrete scores are reported as mode, while for other discrete variables absolute and relative numbers are presented. Comparisons between men and women subgroups was performed using Chi-Squared or Fisher's Exact tests. Correlations were measured using the Pearson's product-moment correlation. The level of significance was set at p<0.05 (two-sided).

RESULTS

The frequency and severity of reported adverse events is reported in Table 1 and Figure 1. There were some significant differences between men and women in terms of frequency and severity for itching/tingling (p<0.001), burning sensation (p<0.001), heat sensation (p=0.006), skin reddening (p<0.001), metallic taste (p<0.001) and tiredness (p<0.001). Other adverse events did not differ between men and women. No serious adverse events (such as skin burn, worsening of schizophrenia symptoms or cognitive deterioration) were reported. No subjects discontinued tDCS treatment due to adverse events or intolerability. All reported side effects resolved within 30 minutes after the tDCS session, with the skin reddening being the slowest resolving event. Numbers of session after which patients reported at least high severity (score 4 or 5 out of 5) were as follows: itching/tingling: 17 (8%), pain: 0, burning sensation: 18 (8%), heat sensation: 3 (1%), cold sensation: 0, skin reddening: 0, metallic taste: 0, tiredness: 4 (2%), headache: 0. Table 2 shows a detailed characteristic of reported adverse events in terms of their onset, recovery, subjective distress and position in relation to tDCS electrodes. Age was correlated with severity of burning sensation (R=0.34, p<0.001), skin reddening (R=-0.53, p<0.001) and metallic taste (R=0.95, p<0.001), other correlations were not significant.

Table 1. Frequency and severity of reported tDCS-related adverse events

Event	Frequency	Most frequent severity*
Itching/tingling	178 (81%)	3 (moderate)
Pain	5 (2%)	1 or 2 (v. mild or mild)
Burning sensation	115 (53%)	3 (moderate)
Heat sensation	105 (48%)	2 (mild)
Cold sensation	6 (3%)	2 (mild)
Skin reddening	76 (35%)	2 (mild)
Metallic taste	30 (14%)	3 (moderate)
Tiredness	36 (16%)	2 (mild)
Headache	3 (1%)	2 (mild)

* Reported as mode of score 1 to 5 (very mild to very severe)

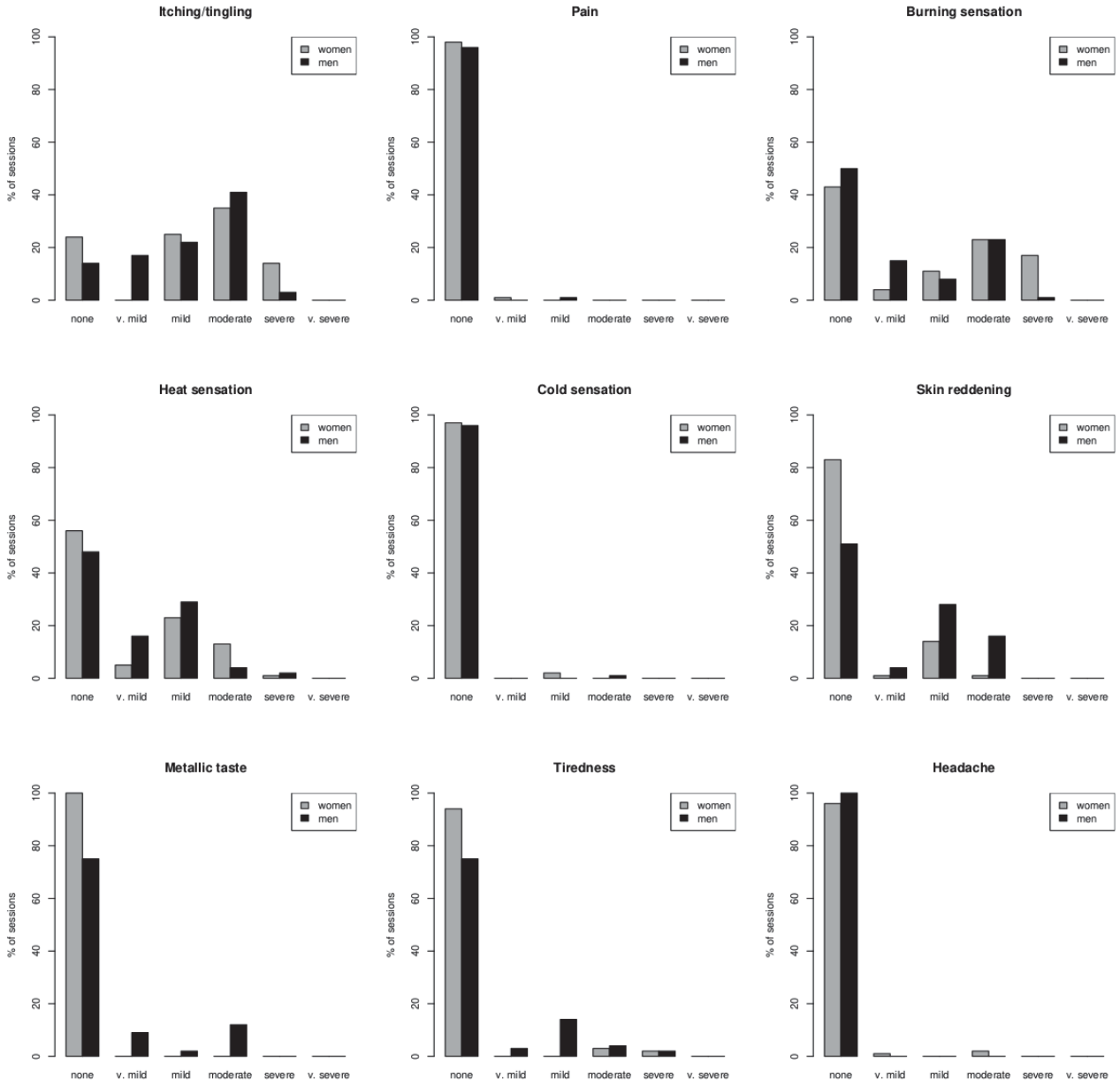

Figure 1. Frequency and severity of reported tDCS-related adverse events

DISCUSSION

The objective of the study was to evaluate safety and tolerability of tDCS treatment in schizophrenia subjects. Our results confirm already established evidence that tDCS is a very safe and well tolerated method of non-invasive brain stimulation for patients with schizophrenia, as it was reported in the largest systematic review so far (Bikson et al. 2016), although this report was reasonably criticized (Godinho et al. 2017). Godinho et al. pointed several important issues here. First of all, reporting bias is a serious and common problem. That systematic review of Bikson et al. is only based on published data, while up to 95% of the information regarding adverse events remains unpublished (Golder et al. 2016). They also criticize limitations in searching methods and emphasize that many studies lack of proper and rigorous measurement methods to detect adverse events.

During 219 tDCS sessions there were no serious adverse effects. No patients withdrawn their consent for tDCS due to adverse events. This suggests that side effects experienced by these patients did not affected their willingness in adhering to tDCS treatment. All adverse effects were mild to moderate and transitory and the most frequent were: itching/tingling (81%), burning (53%) or heat sensation (48%) and skin reddening (35%). Itching/tingling and burning sensetion were also among the events most frequently reported as at least moderately severe. The vast majority of adverse events (unless they are dispersed of their nature, e.g. tiredness headache or metallic taste) were bilateral and located withing both anode and cathode. Most of the adverse events had their onset at the beginning of tDCS session, resolved by the end of tDCS session (with the exception of skin reddening, which recovered within 30 minutes after stimulation) and were associated with mild or moderate distress.

Table 2. Detailed characteristic of reported tDCS-related adverse events

Event	Itching/ tingling	Pain	Burning sensation	Heat sensation	Cold sensation	Metallic taste	Tiredness	Headache
Onset during tDCS session								
beginning	166 (76%)	4 (1%)	112 (51%)	84 (38%)	6 (3%)	16 (7%)	23 (10%)	3 (1%)
middle	11 (5%)	1 (<1%)	5 (2%)	20 (9%)	0	14 (6%)	13 (6%)	0
end	0	0	0	0	0	0	0	0
Recovery during tDCS session								
beginning	18 (8%)	2 (<1%)	11 (5%)	2 (<1%)	0	0	0	1 (<1%)
middle	27 (12%)	1 (<1%)	29 (13%)	5 (2%)	0	0	1 (<1%)	0
end	133 (61%)	2 (<1%)	77 (35%)	97 (44%)	6 (3%)	30 (14%)	35 (16%)	2 (<1%)
Level of distress								
mild	121 (55%)	4 (2%)	82 (37%)	78 (36%)	3 (1%)	14 (6%)	13 (6%)	2 (<1%)
moderate	56 (26%)	1 (<1%)	35 (16%)	26 (12%)	2 (<1%)	16 (7%)	23 (10%)	1 (<1%)
severe	1 (<1%)	0	0	0	1 (<1%)	0	0	0
Location								
anode and cathode	145 (66%)	3 (1%)	95 (43%)	96 (44%)	4 (1%)	0	0	0
anode	28 (13%)	0	18 (8%)	7 (3%)	0	0	0	0
cathode	5 (2%)	2 (<1%)	4 (2%)	1 (<1%)	2 (<1%)	0	0	0
generalized	0	0	0	0	0	30 (14%)	36 (16%)	3 (1%)

The percentages are calculated for the total number of tDCS sessions (n=219), thus columns within one feature may not sum to 100%

In a large (2000+ sessions) study of Beaulieu et al. the commonly reported adverse events during tDCS included burning sensations (16.2%), skin redness (12.3%), scalp pain (10.1%), itching (6.7%), and tingling (6.3%), while most of the adverse events were noted to be mild, transient and well-tolerated (Chhabra et al. 2020). Higher percentages of patients experiencing side effects in our study may result from the fact that the Chhabra et al. study included patients not only with schizophrenia, but also with many other psychiatric conditions, while schizophrenia patients may be particularly sensitive to tDCS induced itching, burning or heat sensations (Valiengo et al. 2020).

All major adverse events (itching/tingling, burning/heat sensation) were more often localized by patients under the anodal pad (see Table 2). This should be taken into consideration particularly for protocols requiring blinding the position of the anodal electrode. The results also indicate that men were more prone to experience some adverse events (itching/tingling, burning/heat sensation, skin reddening, metallic taste and tiredness), see Figure 1. Workman et al. have found that women reported higher sensation severities than men both from 2 mA (as used in our study) and 4 mA tDCS (Workman et al. 2021). These observations highlight differences in adverse events reported by men and women. Consequently, future studies should consider for potential differences between women and men to improve sensation tolerability and blinding.

There is an ongoing debate upon safety limits of tDCS stimulation. Initial report of McCreery has shown that current densities below 25 mA/cm^2 do not induce brain damages even when applied for several hours (McCreery et al. 1990). However, this was an animal study and human neuronal tissue might have different sensitivity. Our study protocol was based on parameters typically used in other tDCS treatment regimens (2.0 mA applied using two electrodes, each of 35 cm^2) (Thair et al. 2017). This corresponds to the current density of 0.057 mA/cm^2, which is approximately 440-times lower than that threshold. Human studies indicate that tDCS using current up to 4.0 mA is safe and well tolerated (Workman et al. 2019). Another parameter that also should be included in safety parameters is the duration of stimulation (20 minutes in our study, again a typical value for tDCS studies).

As it was stated by Chhatbar et al. safety criteria should apply charge density instead of current density, as it is a more comprehensive safety measure of tDCS (Chhatbar et al. 2017). Charge density is the amount of electric charge (current multiplied by time, expressed in coulombs) per unit of brain volume (ideally, but practically difficult to adopt) or electrodes surface area (which is practically much more feasible). For our protocol the surface charge density was 686 C/m^2. Again, this value is several orders of magnitude lower than the lesion threshold for rats established by Liebetanz et al. (52400 C/m^2) (Liebetanz et al. 2009). These comparisons demonstrates that typical tDCS protocols are well within limits, with a large safety margin.

CONCLUSION

In conclusion, this study indicates that tDCS treatment is safe. Also, tDCS seems to be well tolerated by patients with schizophrenia. This is particularly important considering the fact that compared with the general population, schizophrenia patients may be more sensitive to common tDCS-related side effects. The most frequent side effect is itching or tingling sensation, which severity was mild or moderate. The presence of typical side effects may have a significant impact on treatment blinding and should be considered while planing a study protocol. Good safety and tolerability profile of tDCS

may help schizophrenia patients to have a positive attitude towards this therapeutic method and support good adherence. As stated above, standardized methods of measuring and reporting tDCS-related adverse events are required to confirm safety of this method.

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Conflict of interest: None to declare.

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Correspondence:
Prof. Adam Wysokiński, MD PhD
Medical University of Lodz, Department of Old Age Psychiatry and Psychotic Disorders
Czechosłowacka 8/10, 92-216 Łódź, Poland
E-mail: adam.wysokinski@umed.lodz.pl