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Research paper

Predicting tDCS treatment outcomes of patients with major depressive disorder using automated EEG classification

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a promising treatment for major depressive disorder (MDD). Standard tDCS treatment involves numerous sessions running over a few weeks. However, not all participants respond to this type of treatment. This study aims to investigate the feasibility of identifying MDD patients that respond to tDCS treatment based on resting-state electroencephalography (EEG) recorded prior to treatment commencing.

Methods: We used machine learning to predict improvement in mood and cognition during tDCS treatment from baseline EEG power spectra. Ten participants with a current diagnosis of MDD were included. Power spectral density was assessed in five frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (30–100 Hz). Improvements in mood and cognition were assessed using the Montgomery-Åsberg Depression Rating Scale and Symbol Digit Modalities Test, respectively. We trained the classifiers using three algorithms (support vector machine, extreme learning machine and linear discriminant analysis) and a leave-one-out cross-validation approach.

Results: Mood labels were accurately predicted in 8 out of 10 participants using EEG channels FC4-AF8 (accuracy=76%, p=0.034). Cognition labels were accurately predicted in 10 out of 10 participants using channels pair CPz-CP2 (accuracy=92%, p=0.004).

Limitations: Due to the limited number of participants (n=10), the presented results mainly aim to serve as a proof of concept.

Conclusions: These finding demonstrate the feasibility of using machine learning to identify patients that will respond to tDCS treatment. These promising results warrant a larger study to determine the clinical utility of this approach.

1. Introduction

Recent years have witnessed the emergence of transcranial direct current stimulation (tDCS) as promising non-invasive and safe method for treating neuropsychiatric disorders and a tool for modulating cortical activity (Arul-Anandam and Loo, 2009; Keeser et al., 2011; Rae et al., 2013; Rosa and Lisanby, 2012; Stagg and Nitsche, 2011). tDCS involves applying a low current, typically 1–2 mA, across the brain through two or more electrodes placed on the scalp. Compared to other techniques of brain stimulation, tDCS has several practical advantages, such as cost effectiveness and minimal adverse effects (Martin et al., 2013; Nitsche et al., 2008), as well as being a clinically effective intervention (Boggio et al., 2008).

A number of studies have shown that tDCS can reduce depressive symptoms and improve cognitive functioning of depressed patients (Loo et al., 2012; Oliveira et al., 2013). However, up to 80% of patients do not respond to current forms of tDCS treatment, which deliver the same intensity of brain stimulation to all participants (Kalu et al., 2012). Of patient factors determining treatment response, a recent analysis based on individual patient data pooled from several randomized controlled trials only identified medication resistance as significant (Brunoni et al., 2016).

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The neurophysiological mechanisms involved in the antidepressant effects of tDCS remain incompletely understood.Different neuroimaging techniques have been used to identify changes in brain activity following tDCS treatment (Filmer et al., 2014; Shafi et al., 2012). Electroencephalography (EEG) plays a vital role in understanding the underlying neurophysiological states surrounding neuropsychiatric disorders such as MDD and for discovering biomarkers or diagnostic tools relating to these disorders (Peng et al., 2011). The neuromodulatory effects of tDCS on cortical activity for the treatment of mood disorders can be readily studied using EEG (Powell et al., 2014). In people with depression, EEG reveals an asymmetry in frontal alpha activity, i.e. lower alpha power in the right hemisphere compared to the left (Gotlib, 1998; Thibodeau et al., 2006). Alpha asymmetry is disorder specific (Kemp et al., 2010), and can be used to predict antidepressant treatment response (Bruder et al., 2008; Tenke et al., 2011). Powell et al. (2014) used EEG to study the modulatory effect of tDCS on changes in cortical activity in people with mood disorders. We recently showed that a multichannel deep belief network can be used to accurately classify EEG data that was recorded after active or sham tDCS (Al-kaysi et al., 2015). In addition, Wozniak-Kwasniewska et al. (2015) showed that EEG oscillatory activity was significantly different for depressed patients that responded to repetitive transcranial magnetic stimulation (rTMS) therapy compared to non-responders, suggesting that baseline EEG has predictive value for brain stimulation treatment outcomes.

In this study, we sought to identify features of resting-state EEG recorded at baseline that differentiate depressed participants who respond to a subsequent course of tDCS treatment from those who do not respond. Normally, treatment efficacy can only be evaluated after participants have completed all treatment sessions, which to some extent negatively impacts upon participants that do not respond, being an inefficient use of their time and exposing them to ineffective treatment. In this study we used machine learning to predict the improvement in mood and cognition following tDCS treatment based on spectral power of baseline EEG. We used three classification algorithms: Support Vector Machine (SVM), Extreme Learning Machine (ELM), and Linear Discriminant Analysis (LDA). Being able to predict the outcome of tDCS treatment from baseline measures may allow selection of patients most likely to respond to tDCS.

2. Methods

2.1. Participants

This research was conducted at the Black Dog Institute after obtaining approval from the Human Research Ethics Committee of the University of New South Wales. For the current study we used data sets from 10 participants meeting formal diagnostic criteria for major depressive disorder (MDD), who participated in a clinical trial at the Black Dog Institute investigating the efficacy of tDCS treatment for depression (Loo et al., 2012). Written informed consent was obtained from all participants prior to study enrolment in accordance with the National Health and Medical Research Council guidelines and the Human Research Ethics Committee of the University of New South Wales and all research conducted abided by the Australian Code of Responsible Conduct of Research. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) with the psychiatrist's confirmation was used to diagnose participants in a semi-structured interview. All participants had unipolar major depressive episode with a Montgomery-Åsberg Depression Rating Scale (MADRS; Asberg et al., 1978) of > =20 at study entry. Table 1 represents the demographic and clinical information of the participants.

2.2. Protocol

All data were originally acquired from participants entering a double-blind clinical trial to investigate the efficacy of tDCS treatment (Loo et al., 2012). These participants were formerly assessed for eligibility then randomised to receive either sham or active tDCS in 15 treatment sessions given over three weeks. All participants were then offered an additional 15 sessions of open-label active tDCS given over an additional three weeks. Psychiatric assessment of mood was assessed using the MADRS at baseline, session 8 and 15, 23 and 30, and at 1 week and 1 month after trial completion. Assessments at session 23 and 30 were part of the open-label phase. Neuropsychological assessment of acute cognitive effects was conducted using the Symbol Digit Modalities Test (SDMT; Smith, 1991) immediately before and after session 1. Each participant was assessed by the same blinded rater for mood evaluation using the MADRS.

Table 1
Demographic and clinical information.

	n	mean	SD
Gender: male/female	5/10		
Age		41.8	13.3
MADRS		28.7	5.1
CGI		4.3	0.5
Age of onset		24.8	10.4
Current episode (weeks)		23.0	29.5
All prior episodes (weeks)		59.0	66.8
QIDS-SR		14.7	3.6
Melancholia	5/10		
Dysthymia	3/10		
Concurrent use of antidepressants	7/10		
Failed antidepressant medication trials in current episode		1.7	1.4
Failed antidepressant medication trials in past episodes		0.9	2.4

SD: Standard Deviation, MADRS: Montgomery-Åsberg Depression Rating Scale, CGI: Clinical Global Impression, QIDS-SR: Quick Inventory of Depressive Symptomatology.

Participants were invited to participate in an EEG study prior to starting the clinical trial. Of the 64 participants that enrolled into the clinical trial, 18 also participated in the EEG study. EEG activity was acquired during rest and during a cognitive task at baseline, after a single session of active tDCS and after a single session of sham. We previously published EEG results from the cognitive task (Powell et al., 2014). For the current study on automated EEG classification, we used data from the ten patients enrolled in the active arm of the clinical trial. That is, we excluded two patients diagnosed with bipolar disorder and six patients that were randomized to the sham arm of the randomized control trial and for whom we could not determine their treatment response. For the current study we used resting-state EEG recorded at baseline. The duration between this baseline EEG and entry into the clinical trial was approximately 12 days.

We determined the labels for mood and cognition improvement used for machine learning classification based on data obtained during the clinical trial. Improvement in mood was determined based on MADRS obtained at baseline (S0) and after sessions 15 (S15) and 23 (S23). We did not use the MADRS after session 30, as not all participants completed this.

2.3. EEG acquisition

For the EEG acquisition participants were seated in a light and sound attenuated room. Continuous eyes-closed resting-state EEG was acquired for 10 min. EEG data was acquired using a 64-channel BrainAmp MR Plus amplifiers (Brain Products, Munich, Germany, hardware bandpass filter 0.1–250 Hz, resolution 0.1 μV, range +/23.3 mV) and custom electrode caps (Easy Cap, FalkMinow Services, Herrsching-Breitbrunn, Germany) with electrodes placed according to the international 10/20 system. All data were referenced against an electrode centred on the midline between Fz and Cz, and sampled at 5 kHz. Electrode impedance was kept below 5 kΩ. The electrooculogram (EOG) and two electrocardiogram (ECG) channels