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Research paper

Clinical predictors of acute response to transcranial direct current stimulation (tDCS) in major depression

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a promising neuromodulation intervention for poor-responding or refractory depressed patients. However, little is known about predictors of response to this therapy. The present study aimed to analyze clinical predictors of response to tDCS in depressed patients.

Methods: Clinical data from 3 independent tDCS trials on 171 depressed patients (including unipolar and bipolar depression), were pooled and analyzed to assess predictors of response. Depression severity and the underlying clinical dimensions were measured using the Hamilton Depression Rating Scale (HDRS) at baseline and after the tDCS treatment. Age, gender and diagnosis (bipolar/unipolar depression) were also investigated as predictors of response.

Linear mixed models were fitted in order to ascertain which HDRS factors were associated with response to tDCS.

Results: Age, gender and diagnosis did not show any association with response to treatment. The reduction in HDRS scores after tDCS was strongly associated with the baseline values of "Cognitive Disturbances" and "Retardation" factors, whilst the "Anxiety/Somatization" factor showed a mild association with the response.

Limitations: Open-label design, the lack of control group, and minor differences in stimulation protocols.

Conclusions: No differences in response to tDCS were found between unipolar and bipolar patients, suggesting that tDCS is effective for both conditions. "Cognitive disturbance", "Retardation", and "Anxiety/Somatization", were identified as potential clinical predictors of response to tDCS. These findings point to the pre-selection of the potential responders to tDCS, therefore optimizing the clinical use of this technique and the overall cost-effectiveness of the psychiatric intervention for depressed patients.

1. Introduction

Poor response to antidepressant treatment and treatment resistant depression are a major challenge in everyday clinical practice. Only one third of depressed patients achieve clinical remission after the first antidepressant trial, and up to four different treatment trials are needed to gain remission in about 70% of patients (Rush et al., 2006). Moreover, about 80% of patients requiring more than one treatment relapse within 1 year (Fekadu et al., 2009; Rush et al., 2006). Non-response to antidepressant treatment involves a higher risk of illness chronicity, suicidal behaviors (Rush et al., 2009), reduced quality of life and functional impairment (Culpepper, 2016). Tolerability is a major determinant of compliance to therapy: about 85% of patients under selective serotonin reuptake inhibitor (SSRI) medications experience at least one side effect during early stages of treatment (Hu et al., 2004), and side effects account for up to 20–35% of antidepressant disconti-

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Table 1
Descriptive statistics of the cohort.

Variable	Naples		Milan		Verona		Overall	
	N/Mean	%/[95%CI]	N/Mean	%/[95%CI]	N/Mean	%/[95%CI]	N/Mean	%/[95%CI]
Subjects enrolled	27	15.79	23	13.45	121	70.76	171	100
Gender								
Male	18	66.67	7	30.43	42	35.59	67	39.88
Female	9	33.33	16	69.57	76	64.41	101	60.12
Diagnosis								
Unipolar	19	70.37	16	69.57	91	77.78	126	75.45
Bipolar	8	29.63	7	30.43	26	22.22	41	24.55
Treatment								
10/bid/20 min/2 mA/bifrontal	–	–	23	100	99	81.82	122	71.35
10daily20min/1.5 mA/bifrontal	18	66.67	–	–	–	–	18	10.53
10daily20min/2 mA/bifrontal	3	11.11	–	–	–	–	3	1.75
10daily30min/2 mA/bifrontal	6	22.22	–	–	–	–	6	3.51
20/bid/20 min/2 mA/bifrontal			–	–	22	18.18	22	12.87
Age	52.44	[47.34, 57.54]	55.78	[49.95, 61.61]	52.03	[49.69, 54.37]	52.60	[50.64, 54.57]

Min: minutes; mA: milliampères; bid: bis in die (twice daily).

nuation (Demyttenaere et al., 2001; Hu et al., 2004).

In the last decade, there has been a growing interest in neuromodulation, including transcranial direct current stimulation (tDCS), as adjunctive or alternative treatment for psychiatric disorders. tDCS is a non-invasive and low-intensity electrical stimulation which can be selectively targeted to the neural networks involved in the pathophysiology of depression (Kunze et al., 2016).

Compared to other neurostimulation techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS), Vagus Nerve stimulation (VNS) or Deep Brain Stimulation (DBS), tDCS is more cost-effective and offers a better tolerability profile, being safer and less invasive. Moreover, tDCS might have a better tolerability profile compared to antidepressants as well (Bikson et al., 2016).

At the clinical level, the efficacy of tDCS is being tested in several psychiatric disorders, with published studies ranging from depression (Brunoni et al., 2016) to schizophrenia (Mondino et al., 2015), generalized anxiety disorder (Shiozawa et al., 2014b), obsessive-compulsive disorder (D'Urso et al., 2016) and Autism (D'Urso et al., 2015, 2014). Furthermore, different preclinical approaches are contributing to the study of tDCS. Animal studies are shedding light on the molecular and neurophysiological underpinnings of the tDCS effect (Pelletier and Cicchetti, 2014), while through computational studies it is possible to model the passage of current through the brain, so therefore optimizing the electrodes positioning as a function of the target regions, even when these are located in the deepest structures of the brain (Senco et al., 2015).

With regard to the treatment of depression, even if meta-analyses and treatment guidelines have recently become available (Milev et al., 2016; Shiozawa et al., 2014a), evidence on the clinical efficacy of tDCS is not definitive, since a number of methodological differences among clinical trials hinder a conclusive judgment (Kekic et al., 2016). According to the overall clinical evidence, tCDS in depression has been considered "probably effective" (Lefaucheur et al., 2017) and received a third line recommendation (Milev et al., 2016) by most recent guidelines.

Patient selection could be one factor affecting therapeutic efficacy of tDCS in depression. Therefore, an adequate exploration of the patients' predictors of response is crucial to maximize the clinical outcome (Stewart and Harkness, 2012).

Our hypothesis is that certain clinical features of depression may be associated with better response to tDCS. In the present study, we aim to isolate a set of clinical indicators of optimal response to tDCS in depression that may provide evidence-based selection criteria of potential responders, in order to maximize cost-effectiveness and resources allocation for tDCS treatment of depression. To the best of our knowledge, this is the first attempt to identify such prescriptive indicators of tDCS.

2. Materials and methods

In order to investigate the clinical predictors of response to tDCS, we performed a post-hoc pooled-cohort, longitudinal, within-subject, open-label interventional study. Data were collected independently by three centers in Italy. Clinical features at baseline were used as predictor variables, and Linear Mixed Models (LMM) were fitted with clinical response as outcome variable.

2.1. Cohorts

The study sample comprised 171 patients, recruited at three different centers between 2008 and 2013. 27 outpatients were enrolled at the Psychiatry Clinic of the University Hospital "Federico II" of Naples, 23 outpatients at the Psychiatry Clinic of the University Hospital of Milan, and 121 inpatients at the "Villa Santa Chiara" Psychiatry Clinic of Verona. All patients were suffering from a treatment-resistant depressive episode, with treatment-resistance being defined as the failure to reach symptomatic remission ($\leq$7 Hamilton Rating Scale for Depression, HDRS total score) after adequate treatment with either two different antidepressant drugs or one drug and cognitive-behavioral therapy (Nierenberg and DeCecco, 2001). Separate details for each center are given in Table 1.

Exclusion criteria were history of seizures, history of head injury, current physical health problems potentially interfering with the depressive episode and intellectual disability.

2.2. Treatment

Patients underwent one of the following tDCS protocols: 1) 10 daily 20-min sessions of 1.5 mA tDCS; 2) 10 daily 20-min sessions of 2 mA tDCS; 3) 10 twice daily 20-min sessions of 2 mA tDCS (i.e. 10 sessions in 5 days); 4) 10 daily 30-min sessions of 2 mA tDCS; 5) 20 twice daily 20-min sessions of 2 mA tDCS (i.e. 20 sessions in 10 days).

In all treatment protocols, the anode was placed on the scalp in correspondence of the left dorsolateral prefrontal cortex (DLPFC) and the cathode on the contralateral homologous region (F3 and F4 respectively, according the 10–20 international EEG system) (Ferrucci et al., 2009). Daily and twice daily sessions were performed throughout 5 or 10 consecutive weekdays, depending on the treatment protocol.