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Electroconvulsive therapy improves clinical manifestations of treatment-resistant depression without changing serum BDNF levels

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ABSTRACT

Electroconvulsive therapy (ECT) is effective in treatment-resistant depression (TRD). It may act through intracellular process modulation, but its exact mechanism is still unknown. Animal research supports a neurotrophic effect for ECT. We aimed to investigate the association between changes in serum brain-derived neurotrophic factor (sBDNF) levels and clinical improvement following ECT in patients with TRD. Twenty-one patients with TRD (2 men, 19 women; mean age, 63.5 years; S.D., 11.9) were assessed through the Hamilton Depression Rating Scale (HDRS), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impressions scale, Severity (CGIs) before and after a complete ECT cycle. At the same time-points, patients underwent blood withdrawal for measuring sBDNF levels. ECT significantly reduced HDRS, BPRS, and CGIS scores, but not sBDNF levels. No significant correlation was found between sBDNF changes, and each of HDRS, BPRS, and CGIs score changes. sBDNF levels in TRD patients were low both at baseline and post-ECT. Our results do not support that improvements in TRD following ECT are mediated through increases in sBDNF levels.

1. Introduction

Treatment-resistant depression (TRD) is highly disabling, with about 50% of patients experiencing a chronic course and 20% showing insufficient response in spite of aggressive pharmacological and psychotherapeutic interventions (Fava et al., 2003; Hussain and Cochrane, 2004). Electroconvulsive therapy (ECT) is one of the most effective treatments for treatment-resistant depression, with a remission rate of 70–90%, which is higher than that of standard antidepressant treatment (Berton and Nestler, 2006). Despite clinical efficacy, its molecular mechanism of action remains unclear. Understanding the biological mechanisms underlying effective antidepressant treatments may contribute to the identification of therapeutic response biomarkers and to the improvement of current treatments. Different parameters such as cortisol, adrenocorticotropic hormone, corticotrophin-releasing factor, thyroid-releasing hormone, thyroid-stimulating hormone, prolactin, oxytocin, vasopressin, dehydroepiandrosterone sulfate, and tumor necrosis factor α, have been proposed as potential biomarkers of the effect of ECT (Wahlund and von Rosen, 2003; Hestad et al., 2003). However, animal and human data have been heretofore inconsistent, hence, no ECT biomarker is routinely used in clinical practice.

Accumulating evidence from animal studies supports a neurotrophic effect of ECT. Pre-clinical studies have shown that electroconvulsive seizures lead to increased hippocampal neurogenesis (Scott et al., 2000) and angiogenesis (Newton et al., 2006), and enhanced glial proliferation in frontal cortex (Ongür et al., 2007).

Over the past decades, different studies suggested that brain-derived neurotrophic factor (BDNF) might be involved in the pathophysiology of mood disorders. BDNF is a member of the nerve growth factor family, recognized to mediate cell growth, synaptic connectivity, and neuronal repair and survival (Laske and Eschweiler, 2006). BDNF abounds in the brain and peripheral tissues. It is mainly stored in human platelets; its serum levels are 100-fold higher than its plasma levels (Yamamoto and Gurney,

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1990). This difference is due to platelet degranulation during clotting (Fujimura et al., 2002). However, there are other potential cellular sources of plasma BDNF, including vascular endothelium, smooth muscle cells, activated macrophages, and lymphocytes, and since BDNF readily crosses the blood–brain barrier, it is likely that some of serum BDNF (sBDNF) may be of brain origin (Lommatzsch et al., 2005). BDNF has been hypothesized to play a role in depressive behavior and suicide (Brent et al., 2010; Taliaz et al., 2010, 2011). Studies have reported that blood (serum or plasma) BDNF levels are decreased in drug-free depressive patients (Karege et al., 2002; Shimizu et al., 2003; Fernandes et al., 2011), although higher levels were found in the most severely depressive subgroup of better antidepressant responders in one study (Mikoteit et al., 2014), witnessing the unpredictable nature of the association between BDNF changes and depressive psychopathology. sBDNF tends to increase with long-term antidepressant treatment (Shimizu et al., 2003; Aydemir et al., 2005; Huang et al., 2008; Molendijk et al., 2011). The mechanism by which increased BDNF expression could improve depression is unclear. Duman and colleagues have hypothesized that BDNF induces neuronal sprouting in brain regions like the hippocampus and cerebral cortex and improves synaptic connectivity and function of neural circuits involved in mood regulation (Duman et al., 1997; Duman and Vaidya, 1998). Electroconvulsive seizures increased BDNF gene expression and levels in various animal brain areas (Altar et al., 2003), but whether ECT affects blood BDNF levels in depressive patients remains controversial. Blood BDNF levels reflect brain concentrations across various species (Klein et al., 2011), hence it is appropriate to investigate sBDNF concentrations to infer about a treatment's effect on brain BDNF concentrations. Some studies have shown an increase in blood BDNF levels after ECT (Bocchio-Chiavetto et al., 2006; Marano et al., 2007; Okamoto et al., 2008; Hu et al., 2010; Haghighi et al., 2013), while others have reported no change after ECT (Fernandes et al., 2009; Grønli et al., 2009; Gedge et al., 2012). However, even if plasma (Haghighi et al., 2013) and serum (Salehi et al., 2014) levels were increased by ECT in two studies, the changes were unrelated to symptom improvement.

We aimed to investigate the association between changes in sBDNF levels and clinical improvement after ECT in patients with TRD.

2. Materials and methods

2.1. Patients

We conducted a prospective study of 21 patients with treatment-resistant depressive episode (2 men and 19 women, mean age 63.5 years ± 11.9 S.D.). Each patient was his/her own control. Patients were recruited at the Neuropsychiatry Department of Villa Rosa Hospital Viterbo, affiliated to Sapienza University, Rome, Italy, between September 2011 and December 2013. They met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) diagnostic criteria for major depressive episode (MDE) with or without psychotic features. Diagnosis, duration of illness, presence of psychiatric comorbidities, and number of ECT sessions are specified in Table 1, along with sociodemographic data. ECT sessions were scheduled three times in a week, on alternate days. ECT treatment cycles were completed on the basis of treating physicians' clinical judgment. Psychotropic medications, including antidepressants, antipsychotics and mood stabilizers (amitriptyline 100–150 mg/day in four cases, clomipramine 300 mg/day in three cases, sertraline 200 mg/day in three cases, fluoxetine 20–80 mg/day in five cases, fluvoxamine 300 mg/day in one case, citalopram 20–40 mg in two cases, venlafaxine 150–225 mg/day in three cases, olanzapine 5–10 mg/day in three cases, risperidone 3–4 mg/day in two cases, quetiapine 200–300 mg/day in two cases, lithium 900 mg/day in two cases, and valproate 1200 mg/day in four cases; more than one drug might refer to the same patient; all patients were receiving their medication regimen for at least 2 months), were discontinued before starting ECT and were suspended until the end of the ECT cycle. During the course of treatment, psychiatrists had the option of adding anxiolytic or sedative hypnotic medications for brief periods, based on clinical necessity. Blood samples for BDNF assays were obtained at baseline, prior to their first ECT session (T0), and after having completed their ECT cycle (T1). Patients were fully informed about all therapeutic procedures and gave free, written consent for each treatment, and specifically for ECT. The study has been approved by the local ethical committee (Villa Rosa Hospital).

Table 1
Sociodemographic and clinical and characteristics of our ECT TRD sample ($N=21$).

Age (mean ± S.D.)	63.5 ± 11.9
Gender (% Males)	9.5
Cigarette smoking (%)	31.8
Lifetime alcohol abuse (%)	19.0
Marital status (%)	
Single	19.0
Married	57.1
Separated/divorced	14.3
Widowed	9.5
Living Status (*n*, %)	
Home alone	28.6
Home with family	71.4
Education (*n*, %)	
Primary school	28.6
Secondary school	42.9
High school	19.0
Graduate school	9.5
Diagnosis (%)	
Major depressive disorder, without psychotic symptoms	23.8
Major depressive disorder, with psychotic symptoms	23.8
Bipolar disorder	28.6
Schizoaffective disorder	9.5
Psychosis not otherwise specified	14.3
Duration of illness (years) (mean ± S.D.)	2.24 ± 0.89
Psychiatric comorbidities (%)	23.8
ECT sessions *N* (%)	
Six	$N=14$ (66.67)
Nine	$N=5$ (23.81)
12	$N=2$ (9.52)

Abbreviations: ECT, electroconvulsive therapy; S.D., standard deviation; TRD, treatment-resistant depression.

2.2. Clinical assessment

We used the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) to rate depression, the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; Overall, 1974) to rate general psychopathology, and the Clinical Global Impressions Severity of Illness (CGIs) scale (Guy, 1976) to rate overall clinical severity at T0 and T1. All three are clinician-rated scales; the first consists in a thorough interview investigating somatic and psychological symptoms of depression, whereas the third is a one-item Likert scale ranging from 1 (not at all ill) to 7 (extremely ill). Each BPRS item is also rated on a similar 1–7 Likert scale, where 1 is not present and 7 extremely severe. Certified clinicians rated both HDRS and BPRS, showing a high interrater reliability (Cohen's $J=0.89$). Criteria for response and remission were an at least 50% drop of HDRS scores from T0 to T1, and a maximum score of 7 on the HDRS at T1.

2.3. ECT treatment

Before receiving ECT, they were taken full medical and psychiatric history and status, and underwent physical examination along with routine blood chemistry, cardiovascular, dental, and neurological assessments to exclude any clinical contraindications.

Electroconvulsive therapy was performed using a constant current Thymatron System IV brief-pulse ECT device (Somatics LLC, Lake Bluff, IL), delivering pulsed, bidirectional, brief, square-wave stimuli. Electrode placement was bilateral and bitemporal.

The initial stimulus dosage was adjusted with the age method for all patients (Swartz and Abrams, 1996). The mean charge for the short-term course was from 302.4 to 504.0 mC, and the mean seizure length was from 30 to 100 s. Anesthesia was induced through intravenous midazolam, 6 to 18 mg, and muscle relaxation through intravenous succinylcholine, 60–100 mg. We monitored seizure activity both clinically and through bifrontal electroencephalography; the latter was used to ascertain seizure length. The patients were ventilated with 100% oxygen until resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, blood pressure, electrocardiogram, and 1-channel electroencephalogram.

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