Research article

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Nerve growth factor serum levels in treatment-resistant schizophrenic patients following electroconvulsive therapy

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Abstract

Background Electroconvulsive Therapy (ECT) has been widely applied to treat schizophrenia (SCZ) in the presence of resistance to pharmacotherapy. The mechanism of action of ECT in schizophrenia has not been fully clarified, though its intrinsic mechanism presents analogies with some neurobiological processes mediated by nerve growth factor (NGF).

Objectives. The aim of this study was to investigate in patients with treatment-resistant schizophrenia (TRS) the effect of ECT on acute and long-term NGF serum levels and the association with the clinical outcomes.

Methods. Twelve male inpatients with TRS underwent eight sessions of ECT. Blood samples were collected during the first and the eighth ECT at the following time points: 5 minutes before the induction of seizure and then at 0, 5, 15 and 30 minutes after seizure.

Results. Following ECT treatment, a substantial clinical improvement in symptom severity was indicated by a significant reduction in the Positive and Negative Syndrome Scale (PANSS) total and subscales scores. Even though the baseline NGF levels showed an increase over time, there were no statistical differences in NGF at time 0 at the first and the eighth ECT session. Furthermore, no correlation was observed between the severity of schizophrenic symptoms and NGF levels.

Conclusions. This is the first study addressing peripheral NGF during ECT treatment in TRS, as well as the first study in which NGF has been evaluated in different ECT sessions at various time points. These findings may potentiate the knowledge about the neurotrophic effects of ECT and the role of NGF in synaptic plasticity related to possible mechanisms of schizophrenia treatment. ***Clin Ter 2021; 172 (1):e67-74. doi: 10.7417/CT.2021.2286***

Key words: *Neurotrophins (NTs), Nerve Growth Factor (NGF), Electroconvulsive Therapy (ECT), Seizure, Schizophrenia, Treatment-resistant schizophrenia (TRS)*

Introduction

The discovery of Electroconvulsive Therapy (ECT) is closely related to the treatment of schizophrenic patients. In 1938, Cerletti, Bini and Accornero were the first to use electricity in order to induce a seizure for therapeutic purposes in psychotic patients (1–3). After 80 years of use around the world and after a continuous improvement in technique and methodology, nowadays the ECT represents a well-established and safe method in the treatment of many severe psychiatric disorders, mostly mood disorders and some clinical forms of schizophrenia (SCZ), especially in pharmacoresistant patients (4). Ethical and legal implications arise from this practice as well (5). With specific regard to SCZ, the American Psychiatric Association (APA) recommends the use of ECT in schizophrenic patients in the following cases: treatment-resistant schizophrenia (TRS), catatonic state and psychotic symptoms in the current episode with an abrupt or recent onset (6). Similarly, in the UK, the Royal College of Psychiatrists (RCP) limits ECT in acute catatonic states, schizoaffective disorders, acute paranoid syndromes and in type I SCZ in which patients are intolerant or unresponsive to a dose of neuroleptic equivalent to 500 mg of chlorpromazine on a daily basis (7). On the contrary, the National Institute for Clinical Excellence (NICE), in London, recommends the use of ECT in catatonia (8).

Within the context of SCZ, TRS represents a critical clinical picture that regards approximately 30% of schizophrenic patients (9). Commonly, TRS patients are defined as unresponsive to at least two different antipsychotics at a dose of 600 mg chlorpromazine equivalent/day for at least six weeks (10). Neurocognitive performance impairment (11,12), poorer social adjustment and worst community functioning are more present in TRS compared to patients

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who respond to antipsychotics (13,14). All these findings are consistent with the possibility that, rather than representing a severe form of SCZ, the treatment-resistant subtype could have a fundamentally different cause than the treatment responsive one (15). This proposal is in line with the emerging view that TRS might be a non-dopaminergic subtype of SCZ, with symptoms which instead are driven by non-dopaminergic abnormalities, perhaps involving the glutamate system (16,17). A number of adjunctive treatments and antipsychotics augmentation, especially with clozapine, has been suggested in the management of TRS, however, only 60-70% of patients finally responded (18).

Neurotrophins (NTs), especially NGF (Nerve Growth Factor) and BDNF (Brain-Derived Neurotrophic Factor), have been involved in the vulnerability and resilience of various psychiatric and other disorders, among which SCZ (19–26). In the late 90s, we first observed changes in the brain and circulating NGF levels in animal models of SCZ as well as in schizophrenic patients (26–28). Through neurodevelopment animal models inducing -like behaviors, it was also found a reduction of brain mRNA and protein levels of NGF and BDNF along with structural brain abnormalities, resembling those observed in SCZ and SCZ-like psychoses (29–35). Different animal/human psychopharmacological studies, some of which pursued by our group, supported the potential role played by NGF and BDNF in the mechanisms of action of typical and atypical antipsychotics (36–41).

The mechanism of action of ECT has not been fully clarified. As for atypical antipsychotics, lithium, valproate, serotoninergic antidepressants, as well as agomelatine and low-dose ketamine, accumulating evidence from animal studies and few human studies have suggested a specific neurotrophic effect of ECT via phosphorylation/inactivation of GSK-3β and subsequent transcription/expression of different neurotrophic, angiogenic and neuroprotective proteins (26,30,42–44).

As for NGF, it is very important to underline that the intrinsic mechanism of ECT shows analogies with some neurobiological processes mediated by this NT. Indeed, if on one hand, NGF appears to be involved in neuronal plasticity, regulation of monoamine synthesis, neuroendocrine integration and maintenance of homeostasis (45), on the other hand, ECT would intervene in the promotion of synaptic exchanges, in the synthesis, turnover and uptake of brain monamines and in the normalization of neuroendocrine dysfunctions (46–49). Furthermore, animal studies have demonstrated that NGF may play an important role in seizure development (50,51).

A number of studies have been carried out on the neurotrophic effects of ECT in Treatment- Resistant Depression (TRD) (52–63) but only a few studies have been performed in SCZ (44) and only one in TRS (64). None of these studies explored the NGF blood levels during ECT in TRS. Therefore, the aim of the present study was both to investigate baseline serum NGF levels during the ECT treatment course as well as the acute NGF response to each ECT, and to look into the association of possible changes in NGF levels to clinical ECT-induced improvement.

Materials and methods

Subjects

The study sample was composed of twelve male inpatients meeting DSM-5 criteria for SCZ treated with ECT in the Department of Psychiatric Sciences and Psychological Medicine, Sapienza University of Rome, from 1992 to 1999, during the last period, when it was legally allowed to perform ECT in public hospitals in Italy. Patients' age ranged from 18 to 65 years (mean ± S.D. = 39.09 ± 18.44 years). The duration of illness ranged from 3 to 11 years (mean ± S.D. = 9.33 ± 3.61 years).

All patients fulfilled the conditions for TRS - based on at least two adequate prior drug trials of 4–6 weeks duration with no clinical improvement. All patients were kept free from psychotropic drugs for at least 1 week before entering the trial and during the ECT treatment in order to avoid changes in the seizure threshold (65) as well as to prevent confounding factors that might affect NGF levels.

Before undergoing ECT, each patient was screened for general medical conditions through an accurate clinical evaluation including the collection of a detailed medical history, a physical and neurological examination, blood and urine tests, electrocardiogram and a cerebral computed tomography scan. None of the patients reported alcohol and/or psychoactive substance use/abuse, a lifetime history of suicidal attempts, infections in the last month, immune, endocrine and/or neoplastic diseases, and/or showed mental retardation. None of the patients had previously been treated with ECT.

The psychopathological status was assessed by the same senior psychiatrist by the administration of the Positive and Negative Syndrome Scales (PANSS) (66). The patients were assessed at two different time-points: the day before the first ECT session and the day after the eighth session. For each patient, mean PANSS total and subscales scores were calculated.

A written informed release was obtained from all patients and their relatives, and all the study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983, for human experimentation.

Procedures

ECT was carried out by a team composed of an anaesthesiologist, three psychiatrists and a psychiatric nurse. In the morning, at 8.00, overnight fasting patients received ECT with the bilateral-bitemporal method using Mecta Spectrum 5000Q ECT device, with bifrontal EEG and ECG monitoring. An at least 25s EEG seizure was targeted by administering square wave-type pulses of 800 mA of current (stimulus width 1–2 ms, frequency 40–90 Hz, with a 0.5–2 s, 576 maximum mC charge).

Anesthesia was carried out by the same anesthesiologist (PO) by 0.5 mg of intravenous atropine, 0.5 mg/kg intravenous succinylcholine and propofol (1.2 mg/kg) in a rapid infusion. All patients were subjected to assisted ventilation with 100% O_2, administered through a mask and carried on until complete awakening. When the subjects had an initial

reduction in sleep depth, evidenced by the reappearance of eyelids' reflexes and the initial synchronization of the electroencephalographic pattern, the electrical pulse was administered. This method was used to mitigate the variability of convulsive response linked to the different stages of anesthesia at the moment of administration of the stimulus. The determination of the seizure threshold has been carried out according to the MECTA Manual in a session that took place two days before the beginning of the treatment.

The complete course of ECT consisted of 8 sessions (sessions 1-8) after the session for the identification of baseline ST, at a rate of 3 sessions per week. Hence, all patients received 8 ECT.

At 8.00 a.m., 5 ml blood samples were taken from the peripheral arm vein of the patients at the first and the eighth ECT sessions, at the following five-time points: 5 minutes before the induction of seizure, 0 minutes (baseline: immediately before the induction of seizure), 5, 15 and 30 minutes after the seizure. Blood samples, collected in heparin tubes, were immediately centrifuged at 3.000 rpm for 15 min and the serum was stored at -60 °C until NGF assay.

All samples were analyzed at one session by a researcher who was blinded to the group assignment of the patients. NGF serum levels were assessed using a commercial two-site immune-enzymatic assay (ELISA) Kit by Promega (Madison, WI - USA) following the manufacturer's instructions. The colorimetric reaction product was measured at 450nm using a microplate reader (DynatechMR5000, Germany). Neurotrophin concentrations were determined from the regression line for the NGF standard (ranging from7.8 to 500pg/ml) incubated under similar conditions in each assay. NGF concentration is expressed as pg/ml of plasma, and data are presented as mean ± sd.

Statistical Methods

NGF levels were analyzed by repeated-measures analysis of variance (ANOVA) (with NGF as within subject factor) followed by Greenhouse-Geisser correction according to methods previously described (67–69). When a significant difference was found, the *post-hoc* paired Student's *t*-test was used to compare the NGF concentrations at the various ECT sessions.

The PANSS total and subscales scores were also analyzed by a paired Student *t*-test. Possible correlations between the various clinical variables (age, duration of illness, and PANSS total and subscales scores) and NGF levels, between the maximum stimulus administrated and NGF levels, and between the changes in PANSS scores and ΔNGF (at each ECT session) were investigated using Pearson correlation test. Specifically, ΔNGF was computed by subtracting the pre-ECT baseline treatment values (5 minutes pre-ECT) from the 0, +5, +15, and +30 minutes baseline/post-ECT values.

All the statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA). Differences with $p < 0.05$ were considered statistically significant.

Results

The mean maximum stimulus administrated at the first and the eighth ECT was respectively 65.48 ± 33.68 and 85.56 ± 34.2 ms and the mean EEG-recorded seizure duration was 48.57 ± 21.39 s at the first and 38.14 ± 10.54 at the eighth ECT. No statistical correlation between the intensity of the stimulus and NGF levels response was found.

Even though NGF levels showed an increase over time, there were no statistical differences in baseline (T0) NGF levels before the first and the eighth ECT (Table 1).

Table 1. Mean NGF values during the first and the eighth ECT sessions compared with time points -5, 0, +5, +15, and +30 min.

	First ECT	Eighth ECT
NGF (pg/ml) [a]		
-5	76.98 (54.36)	111.69 (81.02)
0	41.59 (46.5)	84.23 (72.87)
+5	48.31 (49.67)	79.77 (67.7)
+15	105.53 (191.07)	155 (105.16)
+30	54.41 (31.27)	61.7 (49.15)

[a] mean (standard deviation)
-5 indicates 5 minutes before ECT; 0, ECT time; +5, +5 minutes after ECT; +15, 15 minutes after ECT +30, 30 minutes after ECT.

At the eighth ECT session, patients showed mean NGF levels that decreased significantly from time -5 to time 0 (t=3.6; p=.009), with even a trend toward a significant difference at the first ECT session (t=1.9; p=.08).

Clinical improvement throughout the treatment course was assessed by a significant reduction in the PANSS total and subscales scores from baseline to the end point (Table 2 and figure 1). No correlation was observed between the NGF levels and the considered clinical variables (age, duration of disease and PANSS total and subscales scores). No differences were found between ΔNGF and changes in PANSS values.

Table 2. Comparison of mean PANSS values at baseline and after the eighth ECT sessions

	Baseline	Eighth ECT	t	p
PANSS total score	121.88 (27.72)	77.86 (26.62)	4.272	0.005
PANSS positive scale	25 (11.36)	13.14 (5.43)	4.126	0.006
PANSS negative scale	37.38 (6.05)	24.86 (9.32)	3.552	0.012
PANSS general scale	62 (16.6)	39.86 (14.15)	3.668	0.01

t = Student's t test.

Discussion

To our knowledge, this is the first study aimed at evaluating NGF during ECT course in TRS as well as the first study in which this neurotrophin has been evaluated in the first and in the eighth ECT sessions at 5 different time points (-5 minutes pre-ECT, 0, 5, 15 and 30 minutes baseline/post-ECT), thus monitoring the changes of NGF in each session and not just between different sessions.

The main results of this study are: the absence of significant treatment-induced baseline NGF differences before and at the end of the treatment course, despite an increase of the final levels, in front of a positive clinical response and the absence of significant acute changes of NGF immediately following the ECT, despite the observed pattern of a curve response.

Notably, even though no significant differences were found between NGF levels at time 0 and the following time points, all patients showed mean NGF levels that decreased from time -5 minutes pre-ECT to time 0, significant at the eighth ECT session and with a trend at the first ECT session. This phenomenon might likely be related to the high level of anticipatory anxiety of the subject expecting the treatment. It has been speculated that anxiogenic stimuli are the most likely psychological/biochemical substrate(s) underpinning NGF synthesis and/or release into the blood (70). Consistent with this hypothesis are the findings of animal models of psychosocial stress (71–75) and studies performed on humans subjected to high levels of emotional/physical stress that demonstrate an increase in the circulating neurotrophins levels following and even before the exposure to specific challenging situations (40,45,76–80) and after a trauma. Furthermore, both animal models and studies on humans have (81) shown, in contrast to stressful situations, how sedation conditions can actually lower basal brain and blood NGF levels (37,82).

A condition of chronic stress, to which patients with a diagnosis of TRS are subjected, maybe at the basis of the higher NGF levels observed (from baseline onwards) compared to those reported in previous SCZ studies (83,84). Increased NGF levels have also been found in subjects with SCZ in the presence of cannabis and/or other substances abuse (85,86). These raised NGF levels have been hypothesized to correspond to attempted endogenous repair mechanisms both in the presence of significant cerebral alterations and/or damages as seen in SCZ and even more in the presence of a noxious stimulus such as cannabis, etc. (85–87). However, the pharmacological effects of previous antipsychotic medication on NGF concentration cannot be totally ruled out (88). Indeed, higher NGF levels have been reported in chronic schizophrenic patients treated with antipsychotics as compared to first episode SCZ patients and indeed the majority of previous studies reporting lower NGF levels in SCZ included drug-naïve SCZ patients (89).

As above mentioned, there are only a few studies that have investigated the effects of ECT on NGF and, to our knowledge, none of these studies have focused on SCZ. Confirming previous data in affective disorders (58,90), in this sample, NGF levels show an increase along the treatment course, even though with no significant differences of the

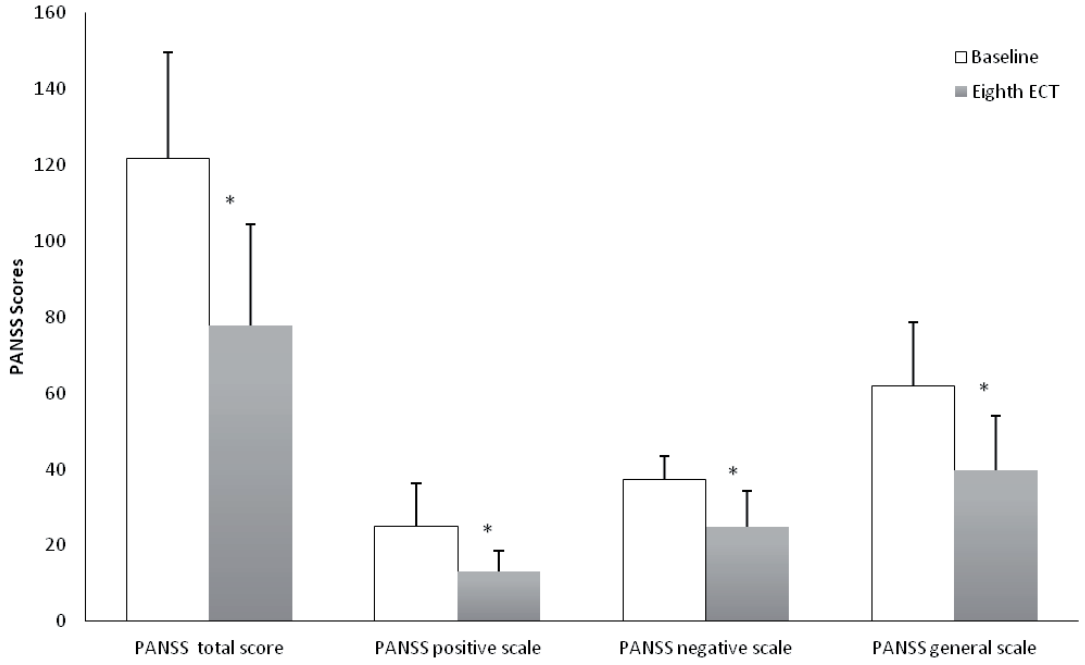

Fig. 1. Change in PANSS scores following eight ECT sessions. The error bars indicate pooled standard deviation means (SDM) derived from appropriate error mean square in the ANOVA. The asterisks indicate significant differences between time points (*, $p < 0.05$).

baseline NGF values between the first and the eighth ECT sessions. Interesting in this regard is that animal researches demonstrated how electroshock seizure is able to induce an upregulation of NGF in various brain regions - mostly in the hippocampus and frontal cortex (91–96).

As for a limit of this study, it can be assumed that a more significant NGF increase could have been observed in a wider group of patients. It can also be speculated that the patients were chronically treated as unresponsive patients with a brain somehow "aplastic", with a reduced capacity to change and rewire in response to ECT and that this might have affected the results. This could at least partially explain the lack of correlation between the absence of significant changes in NGF levels and the clinical improvement of the patients throughout the treatment period. This result is consistent with the findings of other similar studies in the literature (65,97) and supports the effectiveness of ECT in TRS (98).

In a recent review (99), we reported that treatment duration and stimulus parameters (intensity, frequency, pulse) appear to influence the vagus nerve stimulation effects on brain, behavior and clinical pictures through the progressive stimulation of different cerebral areas. It is possible that, in the study sample, the constancy of the electrical parameters in all sessions stimulated in an even way in the interested brain areas, obtaining the same NGF response. It would be interesting to evaluate, in animal models, the NGF response to electrical stimuli of different intensity, investigating the activation of different brain areas.

Future studies remain to be performed not only to deepen this research field and to increase the knowledge about the neurotrophic effects of ECT but also to better understand the role played by NGF in brain synaptic plasticity and hopefully for SCZ related disorders treatment.

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