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Repetitive enhancement of serum BDNF subsequent to continuation ECT

Vanicek T, Kranz GS, Vyssoki B, Komorowski A, Fugger G, Höflich A, Micskei Z, Milovic S, Lanzenberger R, Eckert A, Kasper S, Frey R. Repetitive enhancement of serum BDNF subsequent to continuation ECT

Introduction: Continuation electroconvulsive therapy (c-ECT) is highly effective for the prevention of depressive symptom relapse. There is a lack of understanding, about how c-ECT works in humans, particularly with regard to its effects on brain derived neurotrophic factor (BDNF) concentrations. Here, we aimed to close a gap in the literature by evaluating BDNF levels in patients receiving c-ECT.
Methods: We included 13 patients with either unipolar or bipolar depression (mean age ± SD: 55.5 ± 17.1; f/m: 10/3; unipolar/bipolar: 10/3) who received between one and four c-ECT (average per patient: 2.8). Serum BDNF (sBDNF) levels were assessed before and after each c-ECT sessions. Clinical assessments were also administered both before and after treatment.
Results: Our analysis revealed a significant increase in sBDNF after each treatment (c-ECT 1-3: $P < 0.001$, c-ECT 4: $P = 0.018$). The application of multiple c-ECT treatments was not, however, associated with further sBDNF enhancements. Psychometric scores were not significantly altered following c-ECT.
Discussion: An increase in sBDNF concentrations subsequent to c-ECT parallel data from the animal literature, which has linked regularly applied electrical stimulation to neuroplastic processes. This finding suggests a relationship between ECT-induced sBDNF concentrations and (sustained) remission status, considering a stable clinical condition across c-ECT.

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Key words: depression; unipolar and bipolar affective disorder; continuation electroconvulsive therapy; brain-derived neurotrophic factor

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Significant outcomes

- Novel results show that increases in serum BDNF follow continuation ECT treatments in patients with unipolar and bipolar depression.
- Serum BDNF levels were similar before each continuation ECT treatment in repetitively treated patients.
- Covariates such as age, stimulation mode, concomitant medication, and seizure parameters did not influence serum BDNF changes.

Limitations

- Thirteen patients with unipolar or bipolar depression were included, leading to a total of 37 continuation ECT.
- Concomitant medication use was optimized during study participation for several patients in accordance with clinician judgement.
- Study findings do not reveal exact or exclusive mechanism(s) of action underlying the efficacy of continuation ECT.

Introduction

Worldwide, depression is a leading cause of disability and results in tremendous personal and societal challenges (1). Psychopharmacological treatment with antidepressant agents is first-line treatment for patients with depression (2, 3). Many patients with depression do not respond to psychopharmacological treatment (4). Thus, to develop better diagnostics and personalized treatment regimens and improve patient outcomes, there is a need to better understand the neurobiological processes and changes induced by successful antidepressive treatments.

Throughout life, neuroplastic processes persistently mold and rebuild the brain and its associated functions, in accordance with internal and external inputs. As an essential representative of the neurotrophin family, brain-derived neurotrophic factor (BDNF) mediates environmentally dependent influences on neurons in a bidirectional (trophic or atrophic) manner, depending on the type of cellular cascade stimulated (5). Depression and stress also alter central and peripheral BDNF levels and cause neuronal atrophy in brain areas of the limbic system that are partly facilitated via BDNF (6, 7). If the amount of stress exceeds a certain individual's threshold, the risk for developing depressive symptoms increases significantly (8). These changes may partly occur via BDNF-linked pathways or mechanisms.

Electroconvulsive therapy (ECT) is an especially effective treatment option for depression, with response rates between 60–80% in cases of otherwise treatment-resistant depression (9, 10). Patients suffering from different neuropsychiatric disorders benefit from ECT, which has been shown to be highly effective in treating depressive episodes psychotic symptoms, schizophrenia, and catatonic conditions (2, 11). When patients with recurrent severe depressive episodes definitely respond to an acute ECT series, a continuation ECT (c-ECT) is typically recommended thereafter. When c-ECT is delivered monthly for up to 6 months, it is highly effective at preventing relapse within the same episode in patients with unipolar and bipolar depression (12–15). Clinical trials have reported relapse rates higher than 80% when treatment is discontinued after a successful ECT series, whereas relapse rates were drastically lower when patients received psychopharmacological treatment (16). Another study demonstrated that combined psychopharmacological treatment and c-ECT following an ECT series achieved results superior to those observed following psychopharmacological treatment alone (14). However, a few clinical studies have systematically investigated the efficacy, tolerability, and appropriate frequency and duration of c-ECT (12), while there is a void of studies that have attempted to elucidate the underlying neuropathophysiological mechanisms. Nonetheless, previous studies have reported that both continuation electroconvulsive stimulation (ECS) (a c-ECT analog) and an ECS series of five stimulation sessions (an acute ECT series analog) can modulate neuroplastic processes in rodents (17).

Structural imaging studies have revealed limbic structure enlargements following ECT in depressive patients (18, 19). Some reports have described these ECT-induced increases in gray matter volume as transient, while returning to baseline within 3 or 6 months (20, 21). When evaluating the association between neural correlates and ECT efficacy, a recent mega-analysis found no association between brain structure and treatment response (22). Furthermore, monoaminergic

neurotransmission and neuroplastic processes, which are associated with changes in BDNF levels, may significantly contribute to the antidepressant action of ECT (23–25). Altered neurotrophic signaling pathways have been implicated in mood disorders, with attenuated peripheral BDNF levels in patients with unipolar and bipolar depression compared with healthy subjects (26, 27). Apart from studies linking stress and depression to decreased BDNF concentrations in the hippocampus (28–30), previous studies have reported that a single infusion of BDNF into the hippocampus leads to decreased depressive behaviour in rodents (31). Antidepressive drug interventions and ECT (or ECS) have been associated with increased peripheral BDNF levels following treatment (32–34). Polyakova and colleagues found that ECT treatment was associated with subsequent increases in peripheral BDNF levels (Hedges' g (95% CI): 0.37 (0.034–0.67))(27). Some studies have investigated ECT outcomes among patients with depression, although no randomized controlled trials have been conducted. However, studies investigating associations between peripheral BDNF levels and outcome examined inconclusive results (27, 32, 35, 36).

The exact neuronal mechanisms that are initiated via stimulus induced therapeutic seizures and subsequently account for symptom reduction and relief in depressive patients remain largely unclear. In particular, there is a lack of clinical studies that investigate the mechanisms underlying the efficacy of c-ECT in patients with depression. One line of animal model research indicates increased neurogenesis follows ECS. In this work, neurogenesis was also shown to be dependent on ECS quantity, with a protocol of five ECS sessions, resembling an index ECT in humans, followed by subsequent continuation ECS leading to the greatest level of neurogenesis (17).

Aims of the study

The goal of the present study was to test the BDNF hypothesis and its relevance to c-ECT. Patients with unipolar and bipolar depression received between one and four c-ECT treatments and their BDNF levels were examined twice before and twice after each ECT administration. Thus, we focused BDNF levels changes across multiple c-ECT sessions.

Methods

Study participants and clinical assessment

Altogether, we included 13 patients that had previously responded to treatment with an acute ECT series. Ten patients were diagnosed with unipolar depression without psychotic features, while three were diagnosed with bipolar depression according to ICD 10. Patients were assessed by experienced clinicians using the Structured Clinical Interview for the DSM-IV (SCID), the 17-item Hamilton Depression Rating Scale (HAMD), the Brief Psychiatric Rating Scale (BPRS), the Beck Depression Inventory (BDI), and the Mini-Mental State Examination (MMSE). In accordance with standard practices, c-ECT was initiated in patients who were regarded as acute ECT responders from both subjective and clinical perspectives. All included c-ECT patients experienced recurrent depressive episodes prior to treatment, without extensive periods of remission. These patients were motivated to be admitted on a monthly basis for inpatient ECT. Eight patients were included directly after an acute ECT series, with a 4-week interval between the acute course of ECT and the beginning of c-ECT. Five patients were recruited during an established course of treatment with monthly c-ECT. Inclusion criteria were as follows: clinical authorization for ECT and the absence of major somatic or neurological illnesses. Missing data were accounted for in statistical analyses using a linear mixed model. Included patients received psychopharmacological treatment during the course of c-ECT. The co-medication regimen was optimized in accordance with individual clinical needs, as is common during c-ECT. All patients provided written informed consent following a detailed explanation of the study procedure by an experienced psychiatrist. Patients were recruited at

Table 1. Mean Epidemiological and ECT-specific information

ID	ICD-10 diagnosis	Age	Sex	Number of continuation ECT	Stimulation modus	Mean seizure duration (EEG, sec)	± SD seizure duration (EEG, sec)
1	F33.2	49	f	1	BL	86	-
2	F31.4	71	f	3	UL	63	48.8
3	F33.2	49	m	4	BL	68	5.6
4	F33.2	74	f	4	UL	37	11.8
5	F33.2	22	m	4	UL	84	36.1
6	F33.2	70	f	3	UL	37	4.9
7	F33.2	72	f	4	UL	44	12.0
8	F31.4	49	f	3	UL	53	6.9
9	F33.2	67	f	3	UL	18	4.2
10	F33.2	51	f	2	UL	59	15.6
11	F33.2	53	m	2	UL	38	24.0
12	F33.2	69	f	3	UL	33	4.0
13	F31.5	26	f	1	BL	52	-

Diagnoses were provided during the preceding sufficient acute ECT series. UL/BL: unilateral or bilateral stimulation modus; mean seizure duration via EEG for each patient for each session assessed in seconds.

the Department of Psychiatry and Psychotherapy of the Medical University of Vienna. Data of five patients were also included in a previous report regarding changes in BDNF levels across acute and c-ECT (37). The study was approved by the Ethics Committee of the Medical University of Vienna and the General Hospital of Vienna (EC-number: 975/2010).

Serum BDNF (sBDNF) levels were assessed twice before and twice after each c-ECT session. Patients received between one and four c-ECT sessions. Blood draws and subsequent processing were performed (1) 1 day prior to ECT (morning hours until 12:00 pm); (2) the morning prior to ECT; (3) up to 2 h after ECT; (4) and the day after ECT (morning hours until noon). We then compared mean pre- to mean post-treatment sBDNF levels for each patient. Psychometric assessments including the HAMD, BPRS, BDI, and MMSE were performed before and after each c-ECT session.

Electroconvulsive therapy procedures

Continuation ECT was performed according to guidelines and consensus statements for ECT and Standard Operating Procedures (SOP) of the Department of Psychiatry and Psychotherapy based on an article by Frey and colleagues (38). Thymatrons® System IV device (Somatics, LLC, Lake Bluff, IL, USA) was used for ECT. Anesthesia was administered with methohexital (approximately 10 mg per 10 kg body weight) and muscle relaxation with succinylcholine (approximately 10 mg per 10 kg body weight). The stimulus intensity and the stimulation mode (unilateral or bifrontotemporal) were established at the last ECT of the acute ECT series or readjusted, if necessary, at monthly c-ECT. Seizure activity and duration was assessed by Thymatrons electroencephalography (EEG) and electromyogram (EMG). To assess seizure quality, we determined ictal concordance (39), which is defined by a ratio of seizure activity measured with EMG to seizure activity measured with EEG (EMG divided by EEG).

Evaluation of serum BDNF

Serum vacutainer tubes (Becton Dickinson) were used for blood withdrawal. Serum tubes were stored for 30 min at room temperature, then centrifuged at 1500 *g* for 15 min and further stored at −80°C. Serum BDNF levels were evaluated with an enzyme-linked immunosorbent assay (ELISA) kit (Biosensis® Mature BDNF RapidTM ELISA Kit: Human, Mouse, Rat; Thebarton, SA, Australia). Samples were diluted (1:100 for serum samples and 1:10 and 1:5), and measurement of BDNF was performed according to the manufacturer's protocol on a precoated mouse monoclonal antimature BDNF 96-well plate. Means of sBDNF levels were calculated from two-fold assessments. To measure intrinsic assay quality, we tested the intra-assay and the inter-assay coefficients of variation (CV), whereas intra-assay CV was ≤ 1% indicated very reproducible results. The inter-assay CV was 8.91% and in line with previously published study by Polacchini and colleagues (40). Serum BDNF is stated in ng/ml throughout the paper.

Statistical analysis

First, we calculated the impact of monthly c-ECT on HAMD, BPRS, and BID using c-ECT number (four levels) and measurement before and after each c-ECT (two levels) as fixed factors and subject as the random factor using linear mixed models analysis. A Wilcoxon signed-rank test was applied for results of the MMSE since values were not distributed normally. Then, we assessed the impact of monthly c-ECT on BDNF levels using c-ECT number (four levels), measurement before and after each c-ECT (two levels) and repeated blood sampling which presents test/retest in pre- as well post-ECT condition (two levels) as fixed factors and subject as the random factor using linear mixed models analysis. Pretreatment sBDNF levels were also compared across multiple treatments using linear mixed models. To test for potential confounders, separate interaction analyses were performed between visit measurement and the covariates age, sex, diagnosis (unipolar vs. bipolar depression), ECT stimulation mode (unilateral vs. bilateral), change in concomitant medication, mean seizure duration (per patients vs. per session), and ictal concordance (ratio between EMG and EEG separately). The significance level was set

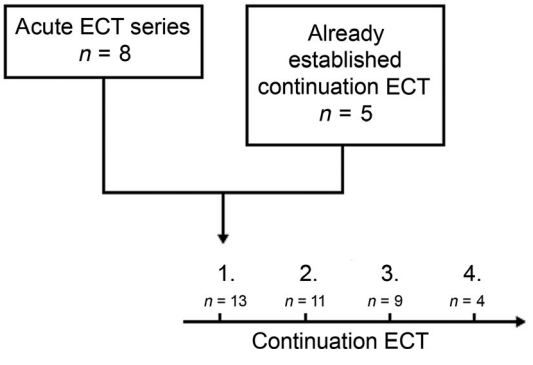

Fig. 1. Flow diagram illustrating patients' recruitment and the application of monthly continuation ECT.

Table 2. Mean values and standard deviations (SD) of sBDNF (in ng/ml) at the four continuation ECT sessions, before and after (i.e., pre and post) treatment

Continuation ECT		*N*	Mean	SD
1	pre c-ECT	13	31.0	10.1
	post c-ECT	13	51.2	15.6
2	pre c-ECT	11	25.4	11.6
	post c-ECT	11	47.4	21.6
3	pre c-ECT	9	31.2	8.4
	post c-ECT	9	44.9	13.2
4	pre c-ECT	4	36.7	6.2
	post c-ECT	4	55.0	14.6

For each patient, pre ECT was calculated by the mean of the BDNF assessments before continuation ECT (day before ECT; the morning before ECT); post ECT was calculated by the mean of the BDNF assessments after continuation ECT (up to two hours after ECT; day after ECT).

at $P < 0.05$ in all analyses. IBM® SPSS® Statistics (Version 24) was used for statistical analysis.

Results

Study sample characteristics and psychometric scores

Study design and patient characteristics are presented in Fig. 1 and Table 1. The sample includes 10 females and three males (mean age of 55.5 SD: ±17.1). Altogether, sBDNF data of 37 monthly c-ECT were available for evaluation. The number of assessments of sBDNF per individual patient varied between one and four c-ECT (mean: 2.8; see Table 1). Ten patients received unilateral, and three received bilateral stimulation. The mean seizure duration for each seizure was 51.7 s (SD: ±20.1) assessed with EEG and 31.4 s assessed with EMG (SD: ±8.9). Psychiatric symptoms, including HAMD, BPRS, and BDI, were stable across study participation, as indicated by an insignificant main effect of the time of measurement (pre/post c-ECT; all $P > 0.10$), ECT number (all $P > 0.10$) and interaction effect (all $P > 0.10$). Similarly, cognitive impairment did not significantly change, as indicated by an insignificant change of MMSE scores (all $P > 0.05$, Wilcoxon rank-sum test).

Effects of continuation ECT on serum BDNF levels

Linear mixed model analysis revealed a main effect of the time of measurement ($F = 52.55$, $P < 0.001$; see Fig. 2), but no main effect of c-ECT number ($F = 1.45$, $P > 0.10$). In addition, we found no main effect of repeated blood sampling (before, respectively after each ECT; $F =$ < 0.01, $P >$ 0.10). We observed no interaction between measurement and ECT number ($F < 0.66$, $P > 0.10$). Evaluating the effect of measurement separately for each c-ECT indicated a repeated increase of

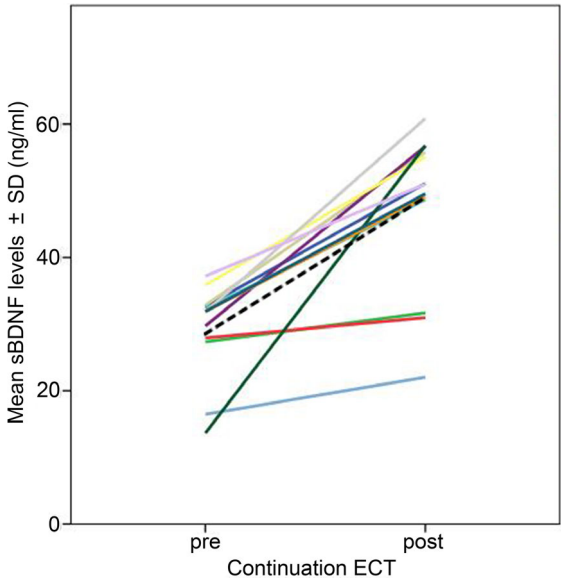

Fig. 2. Individual trajectories of serum BDNF concentrations from pre- to postmultiple continuation ECT. For each patient, represented with an individual color, we averaged sBDNF levels assessed before and after (i.e., pre and post) multiple continuation ECT separately, thus showing individual sBDNF changes across all pre- and all post-treatment levels. The dashed black line (bold) indicates mean sBDNF changes from pre (mean ±SD: 29.8 ± 10.3) to post (48.8 ± 17.1) continuation ECT for all patients.

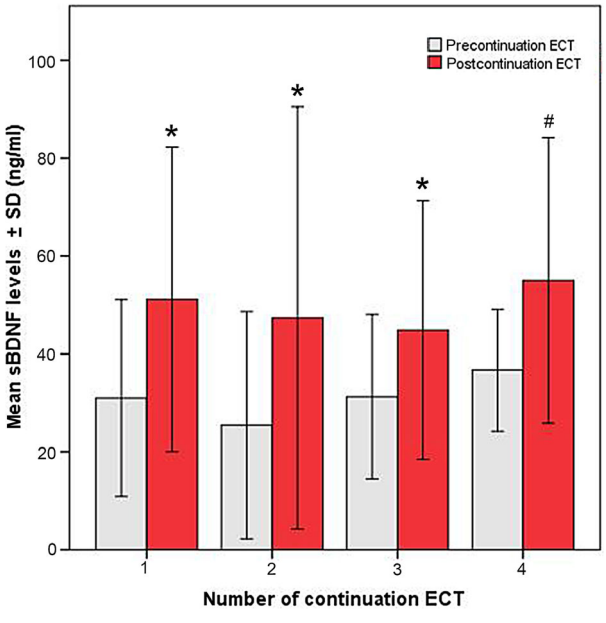

Fig. 3. Changes of serum BDNF levels from before to after multiple (time point 1–4) continuation ECT. Patients with uni- and bipolar depression received between one and four continuation ECT. Grey bars depict BDNF levels before and red bars after continuation ECT. Values are stated as mean ± standard deviation. The significance level was set at 5% in all analyses, highly significant differences ($P < 0.001$) were marked with a *, significant differences ($P < 0.05$) with #.

Table 3. Concomitant psychopharmacological treatment during the course of multiple c-ECT in 13 patients

Drug class	Specific drug
SSRI	Fluoxetin (1), Sertralin (2)
SNRI	Duloxetin (4), Venlafaxin (3)
SARI	Trazodone (3)
NaSSA	Mirtazapin (5)
MAOI	Moclobemid (1), Tranylcypromin (1)
NDRI	Bupropion (2)
TCA	Amitryptilin (2), Anafranil (1)
Other Antidepressants	Agomelatin (1)
Antipsychotics	Quetiapin (5), Prothipendyl (5), Olanzapin (4), Aripiprazol (1), Levomepromazin (1), Chlorprothixen (1)
Lithium/ Anticonvulsants	Gabapentin (1), Lamotrigine (3), Lithium (2), Pregabalin (3)
Stimulants	Modafinil (1)
Benzodiazepines	Lorazepam (4), Clonazepam (2)
Z-drugs	Zolpidem (2)

Numbers within brackets indicate how frequent a specific drug was prescribed.
SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitors, SARI, serotonin antagonist and reuptake inhibitors, NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine dopamine reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor.

sBDNF at each c-ECT (c-ECT 1-3: $P < 0.001$, c-ECT 4: $P = 0.018$, see Fig 3 and Table 2). Baseline sBDNF levels before each individual ECT were not significantly different across multiple treatments (no main effect of ECT number, $F = 2.31$, $P > 0.086$). Thus, multiple c-ECT treatments were not associated with further increases in sBDNF. Age, sex, stimulation mode, concomitant medication (listed in Table 3), diagnosis, mean seizure duration (measured with EEG and EMG), and ictal concordance had no effects on sBDNF increases (all $P \geq 0.09$; no significant interactions with measurement or main effect of covariate).

One patient (see Table 2, ID 3) received c-ECT with an interval of every 2 months since suffering from subjective memory deficits and an otherwise steady euthymic mental condition. This patients' BDNF levels increased repetitively from before to after c-ECT at each of the four time points (mean BDNF levels ±SD; before: 32.82 ± 10.20, after: 55.80 ± 16.00).

Discussion

In the present study, we tested whether c-ECT altered BDNF levels, as previously demonstrated in an animal model (17). We found that monthly c-ECT drove repetitive upsurges in BDNF concentrations, which were then followed by decreases to baseline levels within a month of each treatment, as indicated by comparable sBDNF baseline levels across multiple c-ECT. In analyzing BDNF values across multiple c-ECT treatment sessions, we did not find significant changes between the first and fourth sessions. No significant differences were observed between both pre- and both post-ECT sBDNF bloodsamplings. psychometric scores did not change from before to after or across c-ECT sessions.

In the absence of BDNF reports on patients who undergo c-ECT, data from patients undergoing an acute ECT series are of particular value. Meta-analyses found an increase in BDNF levels after an acute ECT series in patients with unipolar and bipolar depression (26, 27, 41). Previously published ECT trials have reported inconsistent results regarding the relationship between BDNF concentrations and patient outcomes (35–37, 42). Furthermore, meta-analyses have suggested that ECT-associated increases in BDNF levels are not related to clinical outcomes (26, 27). Thus, increases in peripheral BDNF levels following an acute ECT series may be unrelated to treatment responses. Thus, it remains unclear to what magnitude ECT-induced changes in BDNF levels contribute to a stable clinical condition.

Preclinical studies involving rodents have sought to exploit the neuroplastic processes associated with ECS for antidepressant treatment. Such studies have demonstrated that ECS increases BDNF levels in the hippocampus and prefrontal cortex in rodents (34, 43) and induces hippocampal neurogenesis, enduring for up to 12 months (44). Treatment regimens that differ in frequency have been investigated to disentangle the impacts of these parameters on hippocampal neurogenesis. For instance, a series of five ECS sessions led to comparable levels of neurogenesis as did low-frequency ECS, a protocol which resembles c-ECT in humans. Interestingly, highest bursts of cell proliferation were also found after a combination of serial and low-frequency continuation ECS sessions (17). These results agree with those of the present study given that we also found increases in sBDNF subsequent to each c-ECT session. Collectively, these findings suggest that monthly stimulation sessions following an acute ECT series may mediate BDNF levels, and therefore, neuroplastic processes, which may contribute to the stabilization of the patient's clinical condition.

Another matter of debate when interpreting findings on BDNF is to what extent peripheral BDNF concentrations mirror brain-derived BDNF. While BDNF has been found to cross the brain-blood-barrier (45), assessment of central and peripheral BDNF levels has revealed an association between blood and brain BDNF levels (46). This association has also been topologically

extended to the hippocampus (47). The link between hippocampal and peripheral BDNF has also been examined following ECS (43). A study found an upregulation of miR212, an endogenous non-coding microRNA that has a mutually regulatory relationship with BDNF, in the hippocampal dentate gyrus and in whole blood following acute and chronic ECS (48). Conversely, other studies have found that BDNF is generated and stored in megakaryocytes and then in platelets (49) and that BDNF does not cross the brain–blood barrier directly (50). Taken together, these conflicting findings do not yield reliable or definitive conclusions regarding the association between brain and peripheral levels of BDNF.

Despite its benefits, ECT can also cause cognitive side effects such as memory impairments, which are mostly attributable to a bilateral stimulation mode (51, 52). Critically, we did not observe a decline in MMSE scores across treatments in patients receiving either unilateral or bilateral treatment in the present study. In fact, given that c-ECT led to elevations in BDNF in our sample and that BDNF is critically involved in cognitive processes (53), cognitive performance, assessed via the MMSE, may have been bolstered by monthly, ECT-induced BDNF boosts. However, the MMSE is likely not sensitive enough to reveal these changes. Since seizure quality has been previously linked to peripheral BDNF concentrations (39), we also investigated the influence of stimulation mode and seizure-related parameters such as seizure duration and ictal concordance on ECT-induced changes in BDNF levels. This results suggests that this parameter might not be particularly relevant to BDNF levels in the context of continuous stimulation.

Of note, due to subjective impairments in memory but an otherwise steady mental status, one patient in the present study underwent c-ECT in a series of two rather than only once monthly. This patient's BDNF levels across four c-ECT sessions followed similar patterns as exhibited by the rest of the patients, who all underwent monthly stimulation. Previous studies found that ECT led to peripheral peak BDNF levels with latency of several days with up to a month (37, 39), while peak BDNF gene expression levels occurred and were sustained for eight hours after ECS in rats (54). We observed that sBDNF levels returned to initial levels within 4 weeks after a single c-ECT session. We observed sBDNF burst abruptly after each c-ECT, while returning to initial levels within 4 weeks after a single session. This sBDNF level upsurge subsequent to c-ECT might be caused by the aggregation of a BDNF pool throughout an index ECT (37). However, we were unable to predict the exact temporal pattern of decreases in sBDNF in the present study. Future c-ECT studies should aim to determine whether increases in sBDNF concentrations persist for hours, days, or weeks following treatment. Nonetheless, our findings indicate that psychometric scores are likely to remain stable following c-ECT. Increases in sBDNF may facilitate the release of BDNF in the brain, which may lead to improvements in the physiological equilibrium between the two across consecutive c-ECT sessions.

While the present study has some significant strengths, also the analysis has some limitations which warrant discussion. The first of these is its small sample size. In total, we included data from 13 depressed patients who underwent 37 c-ECT treatments. We also included patients with unipolar or bipolar depression given that previous assessments of BDNF in these subsets of patients with depression revealed no baseline differences in BDNF levels (26, 27). The design of the study was naturalistic, and blood withdrawal was carried out when feasible. This led to some missing data, which was, however, accounted for in our statistical analysis of each visit using a linear mixed model. We did not investigate BDNF or promotor and enhancer polymorphisms or methylation status and were thus unable to determine the genetical impact of neuroplastic processes on antidepressant treatment mechanisms. Various factors such as the time of blood withdrawal, differences in storage protocols, age, gender, smoking status, and physical activity are known to influence peripheral BDNF concentrations in rodents, healthy individuals, and patients with depression (28, 55–57). Such factors may have caused variations in serum levels of BDNF in our uncontrolled study. However, it is interesting that increases in sBDNF following c-ECT could be detected even using a relatively small sample size.

In conclusion, the findings of this study extend the existing literature on the influence of ECT on sBDNF levels and contribute to a broader understanding of the mechanisms underlying c-ECT, which was administered to prevent relapse in patients with depression. We found that repeated increases in BDNF levels after c-ECT were followed by decreases to baseline levels between monthly stimulation sessions. As expected, clinical measures remained predominantly unaffected in c-ECT recipients. In agreement with prior reports on the application of acute ECT in patients and animals to achieve changes in BDNF levels, we demonstrate here that c-ECT induces elevations of sBDNF, These findings implicate that BDNF may be

involved in depression-protective effects of ECT in patients with a history of severe depressive episodes.

Data availability statement

Data of the study will be shared on reasonable request.

Acknowledgements

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Conflict of interest

With relevance to this work, there is no conflict of interest to declare. Eckert A. has received grant/research support from Schwabe, Vifor, and Boiron. She has served as a consultant or on advisory boards for Vifor and Schwabe. Frey R. received speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and AOP Orphan. Kasper S. received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd. and Takeda. Kranz GS received travel grants from Roche, AOP Orphan Pharmaceuticals AG and Pfizer. Lanzenberger R. received conference speaker honorarium within the last three years from Shire and research support from Siemens Healthcare regarding PET/MR. Vanicek T. received travel grants and compensation for workshop participation from Pfizer and Eli Lilly and speaker honorary from Shire. Fugger G., Höflich A., Komorowski A., Milovic S., and Vyssoki B. declared no conflicts of interest.

References

1. Friedrich MJ. Depression is the leading cause of disability around the world. JAMA 2017;**317**:1517.
2. Bauer M, Pfennig A, Severus E et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatr 2013;**14**:334–385.
3. Bauer M, Severus E, Kohler S et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatr 2015;**16**:76–95.
4. Corey-Lisle PK, Nash R, Stang P, Swindle R. Response, partial response, and nonresponse in primary care treatment of depression. Arch Intern Med 2004;**164**:1197–1204.
5. Castren E, Antila H. Neuronal plasticity and neurotrophic factors in drug responses. Mol Psychiatry 2017;**22**:1085–1095.
6. Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev Neurobiol 2010;**70**:289–297.
7. Duman RS. Neural plasticity: consequences of stress and actions of antidepressant treatment. Dialogues Clin Neurosci 2004;**6**:157–169.
8. Colodro-Conde L, Couvy-Duchesne B, Zhu G et al. A direct test of the diathesis-stress model for depression. Mol Psychiatry 2018;**23**:1590–1596.
9. American Psychiatric Association. The practice of electroconvulsive therapy recommendations for treatment, training and privileging. A task force report of the American psychiatric association, 2nd edn. Washington, DC, 2001:355.
10. Husain SS, Kevan IM, Linnell R, Scott AI. Electroconvulsive therapy in depressive illness that has not responded to drug treatment. J Affect Disord 2004;**83**:121–126.
11. Baghai TC, Moller HJ. Electroconvulsive therapy and its different indications. Dialogues Clin Neurosci 2008;**10**:105–117.
12. Petrides G, Tobias KG, Kellner CH, Rudorfer MV. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology 2011;**64**:129–140.
13. Rabheru K. Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how? J ECT 2012;**28**:39–47.
14. Nordenskjold A, von Knorring L, Ljung T, Carlborg A, Brus O, Engstrom I. Continuation electroconvulsive therapy with pharmacotherapy versus pharmacotherapy alone for prevention of relapse of depression: a randomized controlled trial. J ECT 2013;**29**:86–92.
15. Odeberg H, Rodriguez-Silva B, Salander P, Martensson B. Individualized continuation electroconvulsive therapy and medication as a bridge to relapse prevention after an index course of electroconvulsive therapy in severe mood disorders: a naturalistic 3-year cohort study. J ECT 2008;**24**:183–190.
16. Sackeim HA, Haskett RF, Mulsant BH et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001;**285**:1299–1307.
17. Weber T, Baier V, Lentz K et al. Genetic fate mapping of type-1 stem cell-dependent increase in newborn hippocampal neurons after electroconvulsive seizures. Hippocampus 2013;**23**:1321–1330.
18. Gryglewski G, Baldinger-Melich P, Seiger R et al. Structural changes in amygdala nuclei, hippocampal subfields and cortical thickness following electroconvulsive therapy in treatment-resistant depression: longitudinal analysis. Br J Psychiatry 2019;**214**:159–167.
19. Cao B, Luo Q, Fu Y et al. Predicting individual responses to the electroconvulsive therapy with hippocampal subfield volumes in major depression disorder. Sci Rep 2018;**8**:5434.
20. Bouckaert F, Dols A, Emsell L et al. Relationship between hippocampal volume, serum BDNF, and depression severity following electroconvulsive therapy in late-life depression. Neuropsychopharmacology 2016;**41**:2741–2748.
21. Takamiya A, Plitman E, Chung JK et al. Acute and long-term effects of electroconvulsive therapy on human dentate gyrus. Neuropsychopharmacology 2019;**44**:1805–1811.
22. Oltedal L, Narr KL, Abbott C et al. Volume of the human hippocampus and clinical response following electroconvulsive therapy. Biol Psychiat 2018;**84**:574–581.
23. Nobler MS, Sackeim HA. Neurobiological correlates of the cognitive side effects of electroconvulsive therapy. J ECT 2008;**24**:40–45.
24. Baldinger P, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R. Neurotransmitters and electroconvulsive therapy. J ECT 2014;**30**:116–121.

25. Lanzenberger R, Baldinger P, Hahn A et al. Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression measured by PET. Mol Psychiatry 2013;**18**:93–100.
26. Brunoni AR, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt MA. BDNF blood levels after electroconvulsive therapy in patients with mood disorders: a systematic review and meta-analysis. World J Biol Psychiatr 2014;**15**:411–418.
27. Polyakova M, Schroeter ML, Elzinga BM et al. Brain-derived neurotrophic factor and antidepressive effect of electroconvulsive therapy: systematic review and meta-analyses of the preclinical and clinical literature. PLoS ONE 2015;**10**:e0141564.
28. Baj G, D'Alessandro V, Musazzi L et al. Physical exercise and antidepressants enhance BDNF targeting in hippocampal CA3 dendrites: further evidence of a spatial code for BDNF splice variants. Neuropsychopharmacology 2012;**37**:1600–1611.
29. Mikoteit T, Beck J, Eckert A et al. High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. Psychopharmacology 2014;**231**:2955–2965.
30. Schmitt K, Holsboer-Trachsler E, Eckert A. BDNF in sleep, insomnia, and sleep deprivation. Ann Med 2016;**48**:42–51.
31. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;**22**:3251–3261.
32. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M et al. Electroconvulsive therapy (ECT) increases serum brain derived neurotrophic factor (BDNF) in drug resistant depressed patients. Eur Neuropsychopharmacol 2006;**16**:620–624.
33. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiat 2008;**64**:527–532.
34. Segawa M, Morinobu S, Matsumoto T, Fuchikami M, Yamawaki S. Electroconvulsive seizure, but not imipramine, rapidly up-regulates pro-BDNF and t-PA, leading to mature BDNF production, in the rat hippocampus. Int J Neuropsychopharmacol 2013;**16**:339–350.
35. Freire TF, Fleck MP, da Rocha NS. Remission of depression following electroconvulsive therapy (ECT) is associated with higher levels of brain-derived neurotrophic factor (BDNF). Brain Res Bull 2016;**121**:263–269.
36. Ryan KM, Dunne R, McLoughlin DM. BDNF plasma levels and genotype in depression and the response to electroconvulsive therapy. Brain Stimulation 2018;**11**:1123–1131.
37. Vanicek T, Kranz GS, Vyssoki B et al. Acute and subsequent continuation electroconvulsive therapy elevates serum BDNF levels in patients with major depression. Brain Stimulation 2018;**12**:1041–1050.
38. Frey R, Schreinzer D, Heiden A, Kasper S. Use of electroconvulsive therapy in psychiatry. Nervenarzt 2001;**72**:661–676.
39. Bumb JM, Aksay SS, Janke C et al. Focus on ECT seizure quality: serum BDNF as a peripheral biomarker in depressed patients. Eur Arch Psychiatry Clin Neurosci 2015;**265**:227–232.
40. Polacchini A, Metelli G, Francavilla R et al. A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. Sci Rep 2015;**5**:17989.
41. Rocha RB, Dondossola ER, Grande AJ et al. Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: A meta-analysis study. J Psychiatr Res 2016;**83**:47–53.
42. Hu Y, Yu X, Yang F et al. The level of serum brain-derived neurotrophic factor is associated with the therapeutic efficacy of modified electroconvulsive therapy in Chinese patients with depression. J ECT 2010;**26**:121–125.
43. Sartorius A, Hellweg R, Litzke J et al. Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. Pharmacopsychiatry 2009;**42**:270–276.
44. Olesen MV, Wortwein G, Folke J, Pakkenberg B. Electroconvulsive stimulation results in long-term survival of newly generated hippocampal neurons in rats. Hippocampus 2017;**27**:52–60.
45. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 1998;**37**:1553–1561.
46. Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci Lett 2002;**328**:261–264.
47. Klein AB, Williamson R, Santini MA et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol 2011;**14**:347–353.
48. Ryan KM, O'Donovan SM, McLoughlin DM. Electroconvulsive stimulation alters levels of BDNF-associated microRNAs. Neurosci Lett 2013;**549**:125–129.
49. Chacon-Fernandez P, Sauberli K, Colzani M, Moreau T, Ghevaert C, Barde YA. Brain-derived neurotrophic factor in megakaryocytes. J Biol Chemist 2016;**291**:9872–9881.
50. Pardridge WM, Kang YS, Buciak JL. Transport of human recombinant brain-derived neurotrophic factor (BDNF) through the rat blood-brain barrier in vivo using vector-mediated peptide drug delivery. Pharm Res 1994;**11**:738–746.
51. Bansod A, Sonavane SS, Shah NB, De Sousa AA, Andrade C. A randomized, nonblind, naturalistic comparison of efficacy and cognitive outcomes with right unilateral, bifrontal, and bitemporal electroconvulsive therapy in schizophrenia. J ECT 2018;**34**:26–30.
52. Dunne RA, McLoughlin DM. Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. World J Biol Psychiatr 2012;**13**:248–258.
53. Hakansson K, Ledreux A, Daffner K et al. BDNF responses in healthy older persons to 35 minutes of physical exercise, cognitive training, and mindfulness: associations with working memory function. J Alzheimers Dis 2017;**55**:645–657.
54. Dyrvig M, Christiansen SH, Woldbye DP, Lichota J. Temporal gene expression profile after acute electroconvulsive stimulation in the rat. Gene 2014;**539**:8–14.
55. Bus BA, Molendijk ML, Penninx BJ et al. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 2011;**36**:228–239.
56. Rasmussen P, Brassard P, Adser H et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 2009;**94**:1062–1069.
57. Bus BA, Tendolkar I, Franke B et al. Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. World J Biol Psychiatr 2012;**13**:39–47.