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Serum S100B protein after electroconvulsive therapy in patients with depression

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Original Article

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Abstract

Objective: S100B is a glial cell protein with bimodal function. In low concentrations, it exerts neurotrophic effects, but higher levels reflect neuronal distress. Recent research suggests that this molecule may be a biomarker of response to electroconvulsive therapy (ECT). We examined the effect of ECT on serum S100B and its utility as 1) a biomarker of a depressive state and 2) a predictor of ECT response. We also wanted to ensure that ECT does not cause a marked serum S100B elevation, indicating neural distress. *Methods:* We measured serum S100B in 22 in-patients treated with ECT due to depression. Depression severity was assessed using 17-item Hamilton Rating Scale for Depression (HAMD-17). The data were collected before an ECT series, within 1 week after the series (post-ECT), and at a 6-month follow-up. Changes in serum S100B and clinical outcomes were tested using a linear mixed model. A relationship between serum S100B and the clinical outcomes was examined using Spearman's and partial correlation. *Results:* Serum S100B did not change significantly immediately after an ECT series or 6 months later. The post-ECT serum S100B change was not associated with the clinical effect (rho = 0.14, $n = 22$, $p = 0.54$). The baseline serum S100B did not predict the clinical effect when controlling for age ($r = 0.02$, $n = 22$, df = 19, $p = 0.92$). *Conclusion:* The study neither supports serum S100B as a state marker of depression nor a predictor of ECT response. No evidence for ECT-related neural distress was found.

Significant outcomes

- Serum S100B does not seem to be a reliable biomarker of a depressive state.
- Baseline serum S100B could not predict the antidepressant effect of ECT.
- No evidence of ECT-related neural distress was found.

Limitations

- The small sample size increased the risk of overlooking the significant effects of ECT.
- The study investigated the subacute effects of ECT on serum S100B. Thus, any possible acute changes (occurring within a few hours after a single ECT session) were not assessed.

Introduction

Electroconvulsive therapy (ECT) is the most effective treatment for depression (Carney *et al.*, 2003) and is widely used in Denmark (Bjørnshauge *et al.*, 2019). Despite over 80 years of its application, clinicians do not have any reliable biomarkers informing an ECT practice. Thus, all treatment decisions are based solely on clinical information. Unfortunately, even the best clinical predictor of favourable ECT outcome (i.e. psychotic symptoms) has only a weak predictive value (Diermen *et al.*, 2018). A more precise prediction of ECT response would help identify ECT responders. Thus, potential non-responders can avoid ECT side effects and be offered other treatment options earlier. Another clinical challenge is a high risk of relapse in the depression after a successful ECT series (up to 50%) (Jelovac *et al.*, 2013), and the risk can be even higher if the depressive episode has not been treated sufficiently. Additionally, in the current practice, the duration of an ECT series is based only on clinical evaluation. A biomarker of a depressive state could thus help to treat a depressive episode sufficiently, increasing the chance for sustained remission.

S100 beta (S100B) is a Ca^{2+}-binding protein, primarily present in glial cells of the central nervous system, mainly astrocytes (Michetti *et al.*, 2019). Intracellularly, it stimulates cell proliferation and survival (Michetti *et al.*, 2019). Extracellularly, its role depends on the concentration.

Low (nanomolar) levels are thought to be neurotrophic and neuroprotective, whereas high (micromolar) concentrations are neurotoxic (Michetti *et al.*, 2019).

Furthermore, high serum S100B reflects neural distress and has been found in conditions such as acute traumatic brain injury (Ercole *et al.*, 2016), ischaemic stroke (Dassan *et al.*, 2009), and neurogenerative diseases (Michetti *et al.*, 2019). Moreover, the protein is used clinically in patients with possible traumatic brain injury, helping clinicians decide the indication for acute computerised tomography (CT) (Thelin *et al.*, 2017). A level higher than 100 ng/l thus strengthens suspicion of cerebral pathology, supporting the use of CT (Thelin *et al.*, 2017).

Previous studies examining the effect of ECT on serum S100B focused on whether the treatment leads to a marked elevation of this molecule, which could indicate neural distress. Most of them have not found any significant increases (Agelink *et al.*, 2001, Palmio *et al.*, 2010, Kranaster *et al.*, 2014). Only one research group detected a small transient increase 1 h after an ECT session (Arts *et al.*, 2006). Additionally, no evidence of ECT-related neural distress was corroborated by measurements of another protein – the neuron-specific enolase (NSE). This molecule is present in neurons, and its elevated serum level is associated with neuronal pathology (Anand and Stead, 2005, Cheng *et al.*, 2014). Three studies investigating serum NSE following ECT in depressed patients did not find any significant changes (Agelink *et al.*, 2001, Palmio *et al.*, 2010, Kranaster *et al.*, 2014).

Emerging evidence indicates that the role of serum S100B may go beyond being merely a biomarker of neural distress. A recent systematic review found that serum concentration of this protein was higher in patients with an acute depressive episode than healthy controls, suggesting the molecule may be a state marker of depression (Kroksmark and Vinberg, 2018). Moreover, another meta-analysis found a significant association between serum S100B and depression severity (Tural *et al.*, 2021). Patients with more severe depression had higher serum S100B. Consequently, longitudinal studies measuring serum S100B in different phases of the major depressive disorder (MDD) in the same individuals are essential.

ECT provides an excellent model for such studies. Two previous ECT studies did not find support for serum S100B as a state marker of depression (Kranaster *et al.*, 2014, Carlier *et al.*, 2019), but the results need to be corroborated.

More promising are studies assessing the value of the protein in predicting ECT response (Arts *et al.*, 2006, Kranaster *et al.*, 2014, Maier *et al.*, 2018, Carlier *et al.*, 2019). Three of them found some indications that patients with higher baseline levels were more likely to remit (Arts *et al.*, 2006, Maier *et al.*, 2018, Carlier *et al.*, 2019). However, two of the studies (Arts *et al.*, 2006, Maier *et al.*, 2018) were very small ($n = 12$ and $n = 11$), and the third examined exclusively elderly patients (Carlier *et al.*, 2019). Therefore, their findings also need to be replicated.

Aims of the study

The present study investigated short-term and long-term changes in serum S100B following ECT and the relationship with the clinical effect. There were two primary aims. First, we tested serum S100B as a state marker of a depressive episode, hypothesising that a decrease in serum S100B after ECT would correlate with a reduction in a depression score. Second, we assessed whether baseline serum S100B could predict the clinical effect as we assumed that patients with higher baseline concentrations would have a greater drop in depression score. The secondary aim was to ensure that ECT does not cause a marked elevation of serum S100B, indicating neural distress.

Material and methods

Study design and participants

We present a prospective naturalistic study examining in-patients treated with ECT due to depression. The study protocol was published on ClinicalTrial.gov before the recruitment (ID: NCT03040388). The same cohort was used in our recent articles reporting on the effect of ECT on hippocampal subfields (Gbyl *et al.*, 2020, 2021). Furthermore, the sample is an extension of the cohort used to determine the effect of ECT on cortical thickness (Gbyl *et al.*, 2019). The clinical data and serum S100B samples were collected at three time points: pre-ECT (within two days before an ECT series), post-ECT (within one week after the last ECT session in an ECT series), and at a six-month follow-up (six months after the end of an ECT series).

The cohort consisted of in-patients between 18 and 95 years diagnosed with a moderate to severe episode of MDD or bipolar depression according to ICD-10 and DSM-IV. All patients were admitted to one of the Mental Health Centres of the Capital Region of Denmark and treated with ECT. They were consecutively referred to the study by their treating clinicians and excluded if one of the following criteria was fulfilled: 1) contraindications for magnetic resonance scan, 2) ECT within the past 6 months, 3) severe psychotic symptoms or a high risk of suicide making transportation to our research centre hazardous, 4) the diagnosis of schizophrenia, 5) the dependency of psychoactive substances, 6) a severe neurological or physical conditions affecting the brain (e.g. a stroke), 7) head trauma resulting in more than 5 minutes of unconsciousness, and 8) a compulsory treatment.

The diagnosis of the current depressive episode was validated using the MINI (Mini-International Neuropsychiatric Interview) performed by an experienced psychiatrist (KG). To exclude any organic causes of depression, all participants underwent neurological and physical examination, electrocardiogram, and routine blood samples, including thyroid-stimulating hormone (TSH), cobalamin, and folic acid. To rule out any ongoing abuse of psychoactive substances, we conducted a dipstick urine screening for 12 drugs (the Rapid Response^{TM} Multi-Drug test). The patients continued their psychotropic medication as prescribed by the treating doctors during the study.

All patients signed informed consent after being thoroughly informed orally and in writing about the study. Before enrolment, the study was approved by the Regional Ethics Committee of the Capital Region of Denmark (ID: H-16042082).

Electroconvulsive treatment

ECT followed standard procedure applicable to Mental Health Services in the Capital Region of Denmark for all patients. They received a series of bitemporal ECT administered three times weekly. The ECT was continued until one of the following was observed by the treating clinician (independently of the research team): 1) remission, 2) no further improvement in combination with unacceptable side effects. Seizures were induced by a brief pulse stimulation (a width of 0.5–1.0 ms), delivered by the Thymatron system IV device (Somatics, LLC, USA). The initial charge was equal to half of a patient's age. Subsequent charges were based on the clinical effect and seizures evaluated on the

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electroencephalogram (EEG). Thiopental (2–4 mg/kg) was used for anaesthesia and suxamethonium (0.75 mg/kg) for muscle relaxation.

Severity of depression

The severity of depression was measured at three time points, specified in the 'Study design and participants' section. All assessments were performed by the same psychiatrist (KG). The 17-item Hamilton Rating Scale for Depression (HAMD-17) was used (Hamilton, 1960).

Clinical response was defined as more than 50% reduction of a baseline HAMD-17 score, while a HAMD-17 score of 7 or less was regarded as remission. Relapse was defined as fulfilling criteria of a depressive episode during the 6-month follow-up in remitters and was based on medical records and the patients' self-reports.

S100B

The glial cell protein S100B was measured in serum using the sandwich electrochemiluminescence immunoassay (ECLIA) Elecsys S100 on the automated Cobas e801 analyser (Roche Diagnostics, Switzerland) according to the manufacturer's instructions. Blood samples were collected at the same time points as the clinical data (see above). The sample aliquots were kept frozen at −80°C until the day of analysis for each assay. All analyses were performed immediately after thawing the samples, using one single batch of the assay. Assay performance was verified using the manufacturers' control specimens. The intermediary precision expressed as coefficient of variation (CV%) was 6% at the 0.09 and 3.3 µg/l concentrations. The measurement range for the assay was 0.02–30 µg/l.

A marked elevation of serum S100B was defined as a higher than 2-fold increase compared to the baseline level. Additionally, the value had to be greater than 100 ng/l, which is a cut-off level that strengthens the suspicion of cerebral pathology (Thelin *et al.*, 2017).

Statistical analyses

The results with a *p*-value less than 0.05 were considered statistically significant. The IBM SPSS Statistics (version 25.0, Armonk, NY, USA) was used in all analyses.

Changes in serum S100B

Changes in serum S100B were tested using *a linear mixed model* (LMM). The time was included in the model as the fixed effect and specified as a categorical variable with three categories (i.e. three visits). Residual and quantile–quantile plots were inspected to assure that the assumption of multivariate normal distribution was not violated. An unstructured covariance pattern was used to account for the correlation between repeated measurements and variation over time. The restricted likelihood estimation method was applied to estimate covariance parameters, as this method is appropriate for small samples. We assumed that missing values in our data set were missing at random. Under this assumption, an LMM handles missing data efficiently and provides valid estimates. The LMM was also used to test changes in depression severity. If there was a significant overall effect of time, we conducted post hoc pairwise comparisons between all three time points and corrected the results for multiple testing using the Bonferroni method.

Relationship between serum S100B and the clinical effect

Spearman's rank correlation coefficient rho was used to test whether a change in serum S100B immediately after an ECT series correlated with a change in depression severity (HAMD-17 score). This non-parametric correlation was chosen because the assumptions of parametric analyses were not met.

Baseline serum S100B as a predictor of the clinical effect

Partial correlation was used to test whether baseline serum S100B correlates with the post-ECT change in HAMD-17 score when controlling for age. Age was chosen as a covariate, as it may impact both serum S100B concentration (Schroeter *et al.*, 2013, Kroksmark and Vinberg, 2018) and the clinical effect (Diermen *et al.*, 2018).

Post hoc analyses

Spearman's correlation was also used to determine whether the post-ECT change in serum S100B correlated with 1) the number of ECT sessions, 2) the cumulative charge delivered during an ECT series, 3) the cumulative duration of EEG seizures in a series, and 4) the time between the last ECT session and S100B sample collection. Additionally, we tested whether remitters differed from non-remitters in 1) baseline S100B levels and 2) post-ECT S100B changes using *an independent-samples Mann–Whitney U-test.* Furthermore, using *Spearman's correlation,* we assessed whether baseline serum S100B correlated with the severity of the current depressive episode and the duration of the current depressive episode. Finally, we examined whether adding gender and the body mass index (BMI) as covariates changed the results of the partial correlation between baseline serum S100B and the clinical improvement.

Results

Sample

The cohort consisted of 22 patients, 21 diagnosed with MDD, and one with bipolar depression. Of the 21 MDD patients, 16 had recurrent depression (F33), and five had a single depressive episode (F32). The clinical characteristics of the sample and the series of ECT are presented in Table 1. All patients continued their psychotropic medication during the entire study. As reported in our previous publications, the medication did not change significantly during the study (Gbyl *et al.*, 2020, 2021). All 22 patients completed a pre-ECT and post-ECT assessment, whereas 21 attended a 6-month follow-up. Out of 66 planned measurements (22 individuals × three visits), there were five and one missing values regarding serum S100B and a HAMD-17 score, respectively. The time points and reasons for missingness are available in Supplementary materials (Table S1).

The antidepressant effect of ECT

ECT had a strong antidepressant effect in the sample. The response was achieved by 18 (82%) and remission 11 (50%) patients. Accordingly, the HAMD-17 decreased significantly after the series (mean change = −20 points; SD = 7; 95% CI: −23, −16; $t_{(21)} = -13$; $p < 0.001$). Although two individuals experienced a relapse during the 6-month follow-up, the sample's depression score remained low at the 6-month follow-up (mean change compared with the baseline HAMD-17 score = −21 points; SD = 9; 95% CI: −25, −17; $t_{(14)} = -11$; $p < 0.001$).

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Table 1. Clinical characteristics of the sample and the course of ECT

	Mean, median, or number
Subjects, *n*	22
Age in years, mean (SD)	45 (14)
Men/women, *n*	11/11
Age of onset in years, mean (SD)	34 (12)
Duration of affective illness in years, median (IQR)	7 (14)
Duration of current episode in months, median (IQR)	5 (7)
Baseline HAMD-17 score, mean (SD)	30 (5)
Patients with psychotic symptoms, *n*	6
Patients with melancholic syndrome according to MINI, *n*	18
Patients on psychotropic medication at study entry, *n*	22
Antidepressants, *n*	21
Lithium, *n*	2
Antipsychotics, *n*	9
Antiepileptics, *n*	3
Benzodiazepines, *n*	5
Patients treated with bilateral ECT, *n*	22
Number of ECT sessions in a series, mean (SD)	12 (5)
Cumulative charge, millicoulombs, median (IQR)	2910 (1714)
Cumulative duration of EEG seizures, s, median (IQR)	477 (240)

n, number; SD, standard deviation; IQR, interquartile range; MDD, major depressive disorder; MINI, mini-international neuropsychiatric interview; ECT, electroconvulsive therapy; HAMD-17, 17-item Hamilton depression rating scale; s, seconds.

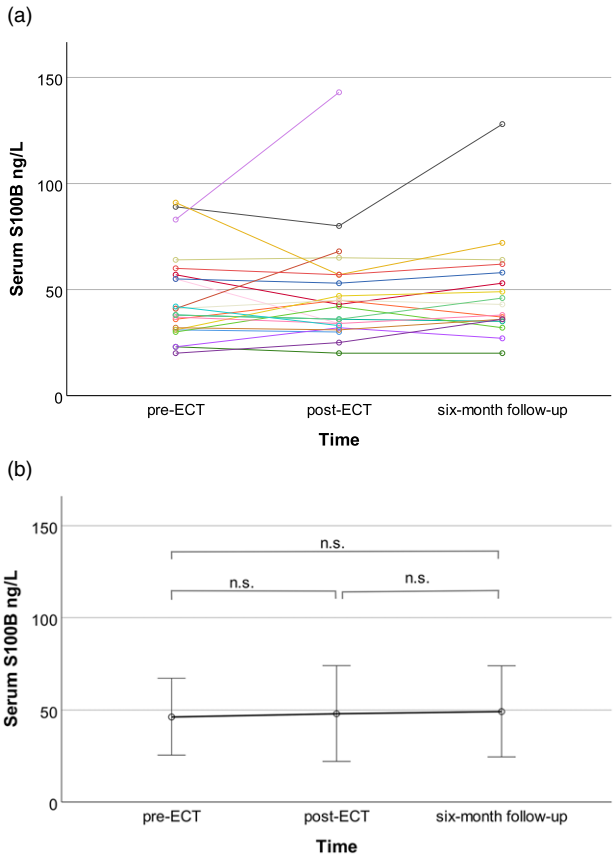

Fig. 1. Serum S100B changes following an ECT series in individual participants (a) and presented as the sample means (b). Error bars on Fig. 1b depict 1 standard deviation of the sample mean. ng/L, nanograms per litre; n.s., non-significant; pre-ECT, within 2 days before an ECT series; post-ECT, within 1 week after an ECT series; six-month follow-up, 6 months after an ECT series.

Serum S100B changes

Figure 1 A and B present serum S100B changes in individual participants and the sample, respectively. As shown in Table 2, serum S100B did not change significantly immediately after an ECT series, nor at the 6-month follow-up. The mean serum S100B was under a cut-off level of 100 ng/l at all time points.

In *post hoc* analyses, we explored whether the S100B changes correlated with 1) the number of ECT sessions, 2) the cumulative charge delivered during an ECT series, and 3) the cumulative duration of EEG seizures, without finding any significant associations. The Spearman rho with corresponding p-values were 1) rho = −0.10, $p = 0.66$, 2) rho = −0.13, $p = 0.58$, and 3) rho = 0.11, $p = 0.61$, respectively. Furthermore, the time between the last ECT session in a series and S100B blood sample collection (median = 39 hours, IQR = 69, range in hours = 5–144) was not significantly associated with the post-ECT S100B change (rho = 0.16, $p = 0.48$).

The relationship between change in serum S100B and clinical outcome

The change in serum S100B immediately after an ECT series did not correlate with the reduction of the depressive score (Spearman rho = 0.14, $n = 22$, $p = 0.54$).

In *post hoc* analyses, a Mann–Whitney U-test revealed no significant difference in the post-ECT serum S100B change between remitters (median change = −1 ng/l, $n = 11$) and non-remitters (median change = −2 ng/l, $n = 11$), $U = 54$, z score = −0.46, $p = 0.65$.

The baseline serum S100B as a predictor of clinical outcome

We did not find any significant associations between the baseline serum S100B and the antidepressant effect of ECT when controlling for age (the partial correlation coefficient $r = 0.02$, $n = 22$, df = 19, $p = 0.92$).

In *post hoc* analyses, we added the gender and the BMI to this partial correlation as covariates, but the results did not change markedly ($r = 0.01$, $n = 22$, df = 17, $p = 0.97$).

Furthermore, we did not detect any significant difference in the baseline serum S100B between remitters (median = 38 ng/l, $n = 11$) and non-remitters (median = 41 ng/l, $n = 11$). A Mann–Whitney U-test was 59 (z score = −0.13, $p = 0.90$). Finally, the baseline serum S100B did not correlate with the severity (rho = −0.08, $n = 22$, $p = 0.73$), nor duration of the current depressive episode (rho = −0.02, $n = 22$, $p = 0.94$).

Discussion

The current study investigated the clinical significance of serum S100B changes in depressed patients treated with ECT.

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Table 2. The change in serum S100B

	Mean, ng/l*	(SD)	95% CI
Pre-ECT ($n = 22$)	46	(21)	37, 55
Post-ECT ($n = 22$)	48	(26)	37, 59
Follow-up ($n = 17$)	53	(33)	38, 68

	Mean difference, ng/l†	(SD)	95% CI	*t*	df	*p*
Post- vs pre-ECT	2	(18)	−6, 10	0.5	21	0.65
Follow-up vs post-ECT	5	(14)	−1, 11	1.9	18	0.08
Follow-up vs pre-ECT	7	(21)	−3, 18	1.6	7	0.15

*Estimated marginal means in the linear mixed model.
†Pairwise comparisons based on the marginal means.
ng/l, nanogram per litre; *n*, the number of subjects; SD, standard deviation; 95% CI, 95% confidence interval; *t*, the *t*-statistic; df, the degrees of freedom; pre-ECT, within 2 days before an ECT series; post-ECT, within 1 week after an ECT series; follow-up, 6 months after the end of an ECT series.

As expected, a course of ECT improved mood substantially. Serum S100B did not change immediately after an ECT series or at a 6-month follow-up. Furthermore, the post-ECT changes in serum S100B did not correlate with the antidepressant effect, and the baseline serum level of this protein could not predict clinical improvement. Finally, no evidence for ECT-related neural distress was found as indicated by no marked S100B elevation after the treatment.

S100B as a state marker of depression

A systematic review found higher serum S100B concentrations in patients with an active depressive episode than healthy controls (Kroksmark and Vinberg, 2018), suggesting that serum S100B may be a marker of depression activity. An elevated level during a depressive episode could be a compensatory neurotrophic mechanism aiming at reversing glial cells loss related to the disease (O'Leary and Mechawar, 2021).

ECT provides an excellent model for investigating biomarkers of a depressive episode, as a substantial part of patients with severe depression achieve remission, usually within a short time. Our patients were severely depressed before ECT, and the ECT had a strong antidepressant effect in the sample. However, in contrast to our hypothesis, serum S100B did not change during the entire study and was not correlated with the clinical effect. Furthermore, we found no difference between the post-ECT change in serum S100B in remitters and non-remitters.

Our findings are in line with the results of three other research groups that investigated the effect of ECT on serum S100B in patients with depression (Kranaster *et al.*, 2014, Maier *et al.*, 2018, Carlier *et al.*, 2019). Neither have studies investigating the effect of antidepressants on serum S100B in depressed patients found any significant decreases in the protein level (Jang *et al.*, 2008, Ambrée *et al.*, 2016, Jiang *et al.*, 2021) apart from one small study (Schroeter *et al.*, 2002).

Of note, our study shows that S100B remained unchanged at the 6-month follow-up. This is an important observation, as a serum S100B reduction related to recovery from depression may be masked by an unspecific increase in the subacute phase after an ECT series. This subacute elevation may occur because of, for example, unspecific glial cell reaction or a transient breach of the blood–brain barrier (Andrade and Bolwig, 2014).

In our sample, baseline serum S100B was not correlated with depression severity, which agrees with the results of most other research groups investigating the association (Kroksmark and Vinberg, 2018). However, a recent meta-analysis of 11 studies comprising 267 depressed patients found that higher serum S100B correlated with greater depression severity (Tural *et al.*, 2021). Nevertheless, the effect size was small ($r = 0.2$), and the 95% confidence interval of this estimate was close to zero (0.03–0.36). Moreover, the correlation became weaker ($r = 0.13$) when serum S100B results were pooled with the cerebrospinal fluid and plasma studies.

To sum up, the current findings do not support serum S100B as a reliable marker that could be used for monitoring depression activity.

S100B as a predictor of clinical improvement

We have not found any significant correlation between baseline serum S100B and clinical improvement. Neither did the remitters' baseline serum S100B differ significantly from the non-remitters' level. Our results agree with another study with a similar design (Kranaster *et al.*, 2014), but they contrast with three studies suggesting that higher baseline S100B concentrations may predict a better clinical outcome (Arts *et al.*, 2006, Maier *et al.*, 2018, Carlier *et al.*, 2019).

Methodological differences between our and the three studies may explain this discrepancy. For example, the largest of these works ($n = 91$) divided patients into three groups based on their baseline serum S100B (Carlier *et al.*, 2019). Logistic regression revealed that patients in the intermediate tertile had higher remission odds than the lowest tertile; however, this was not found for the highest tertile. Moreover, the authors' post hoc analyses weakened the robustness of these findings. When the authors divided the sample into two groups based on an S100B threshold of 42 ng/l, no significant difference in the odds of remission was found. Furthermore, the sample comprised only elderly patients (mean age = 73 years), whereas our cohort was younger (mean age = 47 years). Small sample sizes (n = 12 and n = 11) were a limitation of the two remaining reports (Arts *et al.*, 2006, Maier *et al.*, 2018). Additionally, Arts and co-workers used a self-rapport inventory Symptoms Checklist 90 and only post-ECT scores (not a post- vs. pre-ECT change) to measure the clinical outcome.

Nevertheless, although methodological issues limit the three studies, their results are supported by investigations of serum S100B in depressed patients treated with antidepressants. The latter found that higher baseline serum protein levels were associated with a better clinical outcome (Jang *et al.*, 2008, Ambrée *et al.*, 2016).

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Serum S100B elevations are not specific to depression, as other psychiatric, neurological, and medical conditions are associated with an increase in the level of this protein (O'Leary and Mechawar, 2021). Furthermore, a range of factors modulates the S100B level, potentially confounding S100B analyses (Kroksmark and Vinberg, 2018). For example, higher age is associated with higher serum S100B (Schroeter *et al.*, 2013) and a better ECT response (Diermen *et al.*, 2018). Therefore, our analysis of the association between baseline serum S100B and the clinical effect was corrected for age. Other variables such as gender and BMI may also influence serum S100B, but the studies are inconsistent (Kroksmark and Vinberg, 2018). Adding these two variables as covariates to the partial correlation analysis in our sample did not change the results markedly. Finally, the psychotropic medication may impact serum S100B, but the findings are contradictory (Schroeter *et al.*, 2013, Kroksmark and Vinberg, 2018). This is discussed in the 'Strengths and Limitations' section.

At present, there is insufficient evidence for serum S100B as a reliable predictor of ECT response; however, a weak signal of a predictive value has been detected by some studies. This needs to be further investigated.

S100B as a marker of neural distress

An increase in serum S100B is considered a biomarker of neural distress. The half-life of this molecule is only 1–2 h (Ingebrigtsen and Romner, 2002). Thus, a very transient S100B release to the bloodstream is cleared after approx. 7–14 h (seven half-lives). However, several studies have found that different brain pathologies have different serum S100B trajectories. For example, following an acute ischaemic stroke, a peak S100B is achieved three days after the event (Dassan *et al.*, 2009), and after a traumatic brain injury, the peak has been detected 27 h after the incident (Ercole *et al.*, 2016).

Previous studies investigated the acute effects of ECT on serum S100B and performed serial measurements, typically before and a half, one, two, three, six, and 24 hours after a single ECT session (Agelink *et al.*, 2001, Arts *et al.*, 2006, Palmio *et al.*, 2010, Kranaster *et al.*, 2014). Overall, these works have not found any significant serum S100B changes except for one study that detected a marginal increase 1 hour after a single ECT session (Arts *et al.*, 2006). However, subacute measurements may also be relevant when studying ECT according to known studies of cerebral pathologies mentioned above.

We thus investigated whether an ECT series caused a marked serum S100B elevation subacutely, that is, within 1 week after an ECT series (median = 1.6 days). We did not detect any significant changes in the protein level, which is in line with a previous study with a partly similar design (Kranaster *et al.*, 2014). Our results also agree with a recent large study ($n = 91$) of elderly depressed patients treated with ECT (Carlier *et al.*, 2019). Our negative findings indicate no subacute S100B release, which could be triggered, for example, by unspecific glial cell activation. Additionally, our work provides evidence for no significant long-term serum S100B changes after ECT.

Notably, severe cerebral pathologies are associated with a large serum S100B increase. For example, this molecule rises 12-fold in an acute ischaemic stroke (Dassan *et al.*, 2009). We did not detect such high concentrations in any individual at any time point.

If ECT caused an increase in serum S100B, a dose-response association would be expected. Patients with a higher number of ECT sessions and a larger cumulative charge should have higher S100B increases. However, in line with other studies (Agelink *et al.*, 2001, Arts *et al.*, 2006, Palmio *et al.*, 2010, Kranaster *et al.*, 2014), we did not find any significant associations between these variables.

No evidence for ECT-related S100B increase is further supported by a study that measured the protein in the cerebrospinal fluid of depressed patients treated with ECT (Zachrisson *et al.*, 2000). No significant increase was detected; however, the study was small ($n = 9$).

To summarise, no evidence for neural distress following an ECT series as measured by serum S100B was found.

Strengths and Limitations

A strength of our study is a homogenous sample of severely depressed in-patients. Before study entry, all patients were thoroughly examined to rule out any organic causes of depression, including alcohol and drug abuse. Moreover, clinical outcomes were assessed by the same psychiatrist (KG) at all time points.

The study has several limitations. First, the sample size was small, increasing the risk of overlooking the significant effects of ECT on serum S100B. However, a recent markedly larger study ($n = 91$) did not find any significant serum S100B changes after ECT (Carlier *et al.*, 2019), supporting the validity of our results. Second, as we wanted to measure subacute changes in S100B, we cannot say anything about possible acute changes (i.e. within minutes to a few hours after a single ECT session). Third, all participants continued their psychotropic medication, which could influence serum S100B as several psychotropic drugs are neuroprotective (Hunsberger *et al.*, 2009). However, we have not found any significant changes in medication doses during the study, and concomitant use of such drugs reflects common clinical ECT practice. Fourth, the post-ECT S100B sampling time ranged from 5 to 144 h after the last ECT session, introducing additional variability. However, our post hoc analyses showed that blood sampling time was unrelated to the post-ECT S100B change. Finally, the number of ECT sessions and the cumulative charge delivered in series differed between the patients due to a naturalistic design. A more intensive treatment course could result in larger S100B increases, but no such association was found in our sample.

In conclusion, the current study does not support serum S100B as a state marker of depression. Our work neither indicates that S100B could be a reliable predictor of ECT response. Finally, we did not find any evidence for ECT-related neural distress. Due to the limitations motioned above, the results need to be interpreted with caution. Larger longitudinal studies measuring serum S100B in the same patients during depressive episodes and remissions are needed.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2022.8

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