S100 and Impact of ECT on Depression and Cognition

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Abstract

Objectives: The main side effects of electroconvulsive therapy (ECT) are in the realm of cognition. The S100-beta is a calcium-binding protein that is expressed by astrocytes in the central nervous system during depression and has been suggested to modulate the impact of ECT on cognition.

Methods: Serum samples of S100-beta were taken before and 1 and 2 hours after each ECT session in 12 depressed patients (mean age, 54 years), treated with bilateral ECT twice weekly (mean, 6 sessions). Measures of depression (Symptom Checklist-90 depression dimension) and neurocognitive test battery yielding 3 domains of general cognition, memory, and subjective cognitive impairment were administered 1 day before and 5 and 30 days post-ECT.

Results: Electroconvulsive therapy was associated with a reduction in depression and subjective cognitive impairment at 5 and 30 days post-ECT. Electroconvulsive therapy was associated with a small but significant rise in S100-beta 1 hour post-ECT (adjusted B = 0.013, P = 0.035), with a directionally similar but reduced effect size at 3 hours post-ECT (adjusted B = 0.010, P = 0.10). Higher level of S100-beta at baseline was associated with poorer memory function at 5 and 30 days of follow-up (adjusted B per tertile group increase, 0.38; P = 0.013) but also with less subjective cognitive impairment (B = -0.28; P = 0.001) and less depression at follow-up (B = -0.15, P = 0.099).

Conclusion: The S100-beta at baseline may be a marker predicting and possibly mediating the differential impact of ECT on cognition and depression.

Electroconvulsive therapy (ECT) is considered a safe and effective treatment for patients with major depressive disorder 1-3. The main side effects of ECT are in the realm of cognition, in particular memory impairment. 4 Anterograde amnesia after ECT rapidly resolves, but retrograde amnesia may persist, indicating possible frontal lobe involvement. 5 The effects of ECT on nonmemory cognitive functions, such as sustained attention and executive functioning, are much less pronounced and usually do not exceed the effects of depression 6. The question whether the cognitive impairments seen after ECT reflect structural brain damage has been addressed by neuroimaging studies. In a review of the neuroimaging literature, Devanand et al 7 concluded that despite continuing controversy with regard to ECT and its possible deleterious effect on the brain, there is no credible evidence for ECT causing structural brain damage. An alternative scenario, however, is the possibility of diffuse, small microstructural brain changes induced by ECT. Although there is no direct method to follow-up in vivo on this hypothesis, measurement of a protein called S100-beta may represent a sensitive method to unravel underlying mechanisms at the microstructural level in the brain. The S100-beta is a calcium-binding protein, expressed primarily by astrocytes in the central nervous system, which has a number of intracellular and extracellular functions.B-11 It may act as a neurotrophic protein, promoting neuritic outgrowth in response to nerve injury and may play a role in synaptic plasticity in memory and learning. 12 On the other hand, it may have deleterious effects in higher concentrations, leading to impaired spatial learning. 12 Increased aging, 14 and cell death. 15 There is evidence that S100-beta is a sensitive biochemical marker for brain damage associated with subacute cognitive dysfunction after general anesthesia, 16 abdominal surgery, 17 cardiac surgery, 18-22 stroke, 23,24 and head injury. 25-27 In patients with psychiatric disorders, the level of S100-beta autoantibodies is significantly higher than that in well controls, which may be related to behavioral alterations and learning and memory dysfunction. This highest level of S100-beta autoantibodies has been found in patients with dementia and bipolar disorder. 28, 29 Furthermore, elevated plasma levels of S100-beta have been described in patients with a diagnosis of schizophrenia 30, 31 and with major depression. 30, 32, 33 The hypothesis of an association between S100-beta and ECT, as an indicator of cerebral microstructural alterations, was investigated by Zachrison et al. 34 The authors reported that S100-beta levels were not significantly changed by ECT in patients with major depressive disorder, 34 nor did ECT influence neuron-specific enolase (NSE) levels, another sensitive marker for neuronal damage. 35 In agreement with these results, other research has demonstrated that tonic-clonic epileptic seizures do not elevate S100-beta levels in patients. 36, 37 Ageakiel et al 38 studied the effects of bilateral ECT on cognitive performance and levels of S100-beta and NSE in 14 patients with therapy-resistant major depression or "schizoaffective" psychosis. Electroconvulsive therapy produced no significant changes in NSE or S100-beta, and ECT-induced changes in cognitive performance were not associated with serum NSE or S100-beta concentrations. The authors concluded that ECT induces no detectable brain tissue damage. 38 Interestingly, however, the authors described a post hoc finding that patients with higher post-ECT S100-beta values showed the best cognitive test performances, leading to the hypothesis that ECT-induced release of NSE and S100-beta promotes neural plasticity and plays a part in mediating the antidepressant and cognitive effects of ECT. In this study, however, blood samples for S100-beta assessment were taken for the first time 6 hours after ECT which, given the very short half-life of S100-beta, 39 may likely have resulted in missing most of the S100-beta dynamics induced by ECT itself. In the current prospective study, the above-mentioned post hoc finding was examined in a priori, testing the effects of ECT on cognition and depression in relation to S100-beta levels in 12 depressed patients treated with bilateral ECT, carrying out multiple S100-beta assessments immediately after ECT, and using a broad range of neuropsychological tests administered in a longitudinal design to allow prospective assessment of change.
MATERIALS AND METHODS

Patients

The participants were 12 adult inpatients of the University Hospital Maastricht with clinical diagnoses of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition unipolar or bipolar depression. All participants provided written informed consent. The average age of 8 women and 4 men was 54 years (range, 41-80 years); all patients continued their antidepressant medication during ECT. The mean Hamilton Depression Rating Scale (17 items) score was 20 upon admission and 8 after treatment with ECT.

ECT Therapy

All patients were undergoing bilateral ECT twice a week with a mean of 6 sessions (range, 4-8 sessions). Etomidate was used as an anesthetic, and succinylcholine served as muscle relaxant.

Medications used by patients, including antidepressants, were continued during ECT, with the exception of benzodiazepines which were discontinued. Bifrontotemporal stimulation was performed using the Thymatron IV (0.5-ms brief pulse). Mean duration of seizure was 54 seconds (range, 22-124 seconds), and the average charge applied was 416 mC (range, 306-790 mC).

S100-beta

Serum samples (n = 204) were taken at different time points, immediately before ECT, after a few minutes of resting period to let patients adapt to the stress of being in the ECT suite and having a drip inserted, and 1 hour and 3 hours after ECT. After clotting, samples were centrifuged, and serum was stored at -20°C.

The S100-beta concentration was measured by a commercially available immunoluminometric assay (LiaMab Sangtec; 100; Sangtec Medical, Bromma, Sweden). As indicated by the manufacturer, the limit of detection of the assay (80 + 3 SD) was 0.02 µg/L, and the within- and between-assay imprecisions (coefficient of variation) were 5.5% and 10%, respectively, for concentrations of 0.28 to 4.17 µg/L; 0.3 µg/L was considered the clinical cutoff value.

Neuropsychological Measures

All tests and questionnaires were administered 3 times: the first, 1 day before administering ECT; the second, 5 days after the last ECT treatment; and the third, 30 days after the last ECT treatment. To investigate the possible effects of ECT treatment on cognition, a neurocognitive test battery was used measuring global cognitive functioning (Mini-Mental State Evaluation [MMSE]), verbal memory (immediate and delayed recall and recognition), 15-Word Learning Task, 41 short-term memory and sustained attention (Memory Comparison Task), 42 shifting between concepts (Concept Shifting Test), 43 speed of information processing (Letter-Digit Modalities Test), 44 attention processes/interference (Stroop Colour Word Test), 45 and verbal fluency for semantic categories (Fluency Task). In addition, the Cognitive Failure Questionnaire was administered (CFQ; 44) to assess subjective cognitive impairment, including the Symptoms Checklist 90 (SCL-90), a self-report inventory of current psychopathology which yields a validated dimension of depression (hereafter referred to as SCL-90 depression). The cognitive variables were subjected to a principal component factor analysis followed by oblique rotation of the loading matrix to obtain data reduction. Rotated factor analysis on the cognitive data revealed 3 factors. The first was a "general cognition" factor, with high loadings on MMSE, Word Learning Task, Concept Shifting Test, Letter-Digit Modalities Test, and Verbal Fluency. The second factor was "Working Memory," with high loadings of the Memory Comparison Task. Factor 3 was difficult to interpret, with high but contrasting loadings on CFQ, MMSE, and Stroop Colour Word Test. This factor was therefore not included in the analyses; instead, the CFQ, as a measure of subjective cognitive impairment, was included. General cognition, working memory, CFQ, and SCL-90 depression were all expressed as higher scores, indicating poorer performance.

Analyses

All statistical analyses were performed using Stata (version 8.0) (Stata Corp, College Station, TX).

ECT and S100-beta

Each individual had 3 S100-beta measurements within 1 ECT session (hereafter referred to as time), and each individual had between 4 and 8 ECT sessions (hereafter referred to as session), yielding a range of 11 to 23 S100-beta values for each person. As S100-beta observations were clustered within persons, violating assumptions of independence, a multilevel random regression analysis, which takes into account clustering within persons, was carried out using the Stata xtwreg routine to jointly examine the effects of time within session and of session on continuous S100-beta values, adjusted for age and sex. Effect sizes were expressed as the regression coefficient from the multilevel random regression equation; time and session were entered as dummy variables, with the first observation as the reference category. All analyses were adjusted for age and sex.

S100-beta and Cognition

As each individual had 3 measurement occasions for each cognitive test (one before ECT; one, 5 days after ECT; and one, 1 month after completion of ECT), multilevel random regression analysis, taking into account clustering within persons, was again carried out using the Stata xtwreg routine. To examine associations between S100-beta and cognitive measures, 2 measures summarizing S100-beta across time and session were constructed for each individual. The first was the mean S100-beta value before ECT across sessions (hereafter referred to as S100-baseline). The second was a measure reflecting the maximum S100-beta postbaseline difference (a peak-baseline measurement) across sessions (hereafter referred to as S100-max, calculated as the mean of the maximum difference at each session). The use of these 2 measures allowed testing for 2 plausible a priori hypotheses: (1) S100-beta values before ECT (ie, independent of ECT) are associated with cognition and (2) change in S100-beta values after ECT predict
RESULTS

ECT, Cognition, and Depression

At 5 and 30 days post-ECT, there was no change in either general cognition or memory (Table 1). Subjective cognitive impairment, as measured by CFQ, was reduced 5 days post-ECT (β = 2.0; 95% confidence interval (CI), −3.9 to 1.2; P = 0.34) with a similar but statistically not significant effect at 30 days (Table 1). Depression, as measured by SCL-90, was also reduced at 5 and 30 days post-ECT (5 days post-ECT [β = 2.7; 95% CI, −0.4 to 4.2; P = 0.06] and 30 days post-ECT [β = 1.8; 95% CI, −3.4 to 6.3; P = 0.63]; Table 1).

<table>
<thead>
<tr>
<th>Type of Outcome</th>
<th>5 Days Post-ECT</th>
<th>30 Days Post-ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cognition</td>
<td>−0.4</td>
<td>(−0.5 to 0.7)</td>
</tr>
<tr>
<td>Writing accuracy</td>
<td>−0.5</td>
<td>(−0.8 to 0.2)</td>
</tr>
<tr>
<td>Subjective CFQ</td>
<td>−0.5</td>
<td>(−0.9 to 0.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>−0.3</td>
<td>(−1.3 to 0.8)</td>
</tr>
</tbody>
</table>

TABLE 1. Changes in Cognition and Depression 5 and 30 Days Post-ECT

ECT and S100-beta

Descriptive, unadjusted results are depicted in Figures 1 and 2. All the S100-beta levels were well below the reference level of 0.3 µg/L. As shown in Table 2, ECT was associated with a small increase in S100-beta levels 1 hour after ECT (adjusted β = 0.012; 95% CI, 0.001–0.025; P = 0.039), with a directionally similar but reduced effect size at 3 hours (adjusted β = 0.010; 95% CI, −0.002 to 0.022; P = 0.10). There was no significant effect of session (Table 2).

FIGURE 1. Mean S100-beta within ECT session. T0 indicates before ECT; T1, 1 hour after ECT; T2, 3 hours after ECT.

FIGURE 2. Mean S100-beta between ECT sessions.
TABLE 2. Mean S100-beta Levels, Adjusted B, P values, and 95% CIs for Within-session and Between-session Order of ECT

Electroconvulsive therapy characteristics had no significant effect on S100-beta levels (duration of insult in seconds: adjusted B = 0.000; 95% CI, -0.0063 to 0.0005; P = 0.88; dose in milliampere: adjusted B = 0.000; 95% CI, -0.0001 to 0.0001; P = 0.95).

S100-beta and Cognition

Descriptive, unadjusted results are depicted in Figure 3. Higher S100-baseline was associated with poorer postbaseline memory at 5 and 30 days of follow-up (adjusted B per tertile group increase = 0.38; 95% CI, 0.09-0.66; P = 0.013) but also with less postbaseline subjective cognitive impairment (adjusted B = -0.32; 95% CI, -0.68 to -0.02; P = 0.036). There was no association with postbaseline general cognition (adjusted B = 0.06; 95% CI, -0.15 to 0.27; P = 0.56). S100-max was associated with neither memory at 5 and 30 days of follow-up (adjusted B per tertile group increase = 0.18; 95% CI, -0.18 to 0.54; P = 0.296), nor with postbaseline subjective cognitive impairment (adjusted B = -0.16; 95% CI, -0.36 to 0.05; P = 0.177), nor with postbaseline depression at follow-up (adjusted B = -1.2; 95% CI, -1.6 to 0.7; P = 0.268), nor with postbaseline general cognition (adjusted B = 0.12; 95% CI, -0.33 to 0.64; P = 0.225).

FIGURE 3. Postbaseline values of the cognitive and mood outcomes plotted against S100-beta values. Lines represent fitted values.

DISCUSSION

The finding reported by Agelink et al at 38 that patients with higher post-ECT S100-beta levels show the best cognitive test performance could not be replicated in this study. Our measure of dynamic change in S100-beta (S100-max) displayed neither large nor significant association with any of the measures of cognitive functioning. Interestingly, however, it was found out that patients with higher S100-beta levels pre-ECT were more likely to display poorer working memory post-ECT. The effect of pre-ECT S100-beta was directionally heterogeneous in a way that was analogous to the main effects of ECT, as it was also associated with less depression and less subjective cognitive impairment post-ECT. These latter findings do agree with the suggestion by Agelink et al at 38 that S100-beta may play a role in mediating the antidepressant and cognitive effects of ECT.
Methodological issues

A limitation of our study is the small number of patients—their unequal sex distribution and their large age range. Given the small number, we can thus not exclude the fact that nonsignificant positive, protective effects of S100-beta on general cognitive functioning may represent a type II error. The data in Figures 1 and 2 suggest the possibility of a significant sex difference. Post-hoc statistical analyses indeed revealed statistically significant interactions. This is unaccounted for in the literature and needs further a priori investigation.

The large age range may be of importance, given the fact that S100-beta levels may increase with advancing age.49

Another limitation of this study is the lack of data on healthy controls. In the literature, serum values of S100-beta in healthy controls vary between 0.018 and 0.098 μg/L, 29,31,33,50-53

In the current study, we found a small rise in S100-beta levels post-ECT; however, the mean values were below 0.08 μg/L in the range of healthy controls. Values of S100-beta in depressed patients, in the literature, vary between 0.056 and 0.41 μg/L, 33,50-53

The relatively low levels of S100-beta in our depressed sample may be partially because of the fact that all our patients used antidepressants during ECT. Schmeeter et al 53 found that antidepressant treatment reduced S100-beta levels in depressed patients from 0.41 to less than 0.1 μg/L (median).53

Another explanation for the low levels in our study may be deduced from the finding reported by Rothermundt et al 33 that only melancholic depressed patients showed significantly increased S100-beta levels compared with healthy controls; nonmelancholic patients had normal levels. In our sample, most patients have nonmelancholic depression.

Finally, there is the possibility that the small rise in S100-beta levels post-ECT is caused by the stress of being in the ECT suite and for the anesthesia and not to ECT. Stress can give rise to changes in S100-beta levels,54,55 but it seems unlikely that this impacted on the results, given the following: (1) patients were given a resting period of a few minutes to adapt to the situation of ECT before blood samples were collected, (2) the clinical observation that patients rapidly adapt to the stress of ECT after the first session, and (3) baseline S100 values in patients were within the reported range of normal controls, which seems to exclude large effects induced by stress.

Considering the possible effects of anesthesia, Liston et al 16 measured S100 levels in patients undergoing vascular, trauma, urological, or abdominal surgery. Preoperatively, median S100 serum concentration was 0.02 μg/L; postoperatively (after 30 minutes), S100 values varied between 0.1 and 0.65 μg/L, being the highest after vascular surgery.16 However, given the relatively brief anesthesia during ECT, the effects of anesthesia on S100-beta levels may be of no importance but cannot be ruled out.

Findings

In total, 17 statistical measurements/tests were performed, as described in Tables 1 and 2. Four of these correlated tests resulted in statistically significant P values, which is much more than the less than 1 significant result that would have been expected because of chance alone.

In the current study, we found a small rise in S100-beta levels post-ECT. This may be important given the heterogeneous effects of S100-beta described in the literature: low concentrations (<0.1 μg/L) may be neuroprotective and higher concentrations (>0.1 μg/L) may be neurotoxic.8,11 The current finding of a negative effect on working memory is not in accordance with this neuroprotective effect; however, the associations with reduction in depression and subjective cognitive impairment may be.

Neuroprotective effects of low concentrations of S100-beta are described in animal studies, resulting in improved learning and cognitive functioning through effects on neural plasticity and glial proliferation.9,12,56 In parallel with these findings is the observation that ECT can give rise to spraying and cell proliferation, particularly in serotonergic neurons in the hippocampal region.9,51 Interestingly, higher baseline S100-beta concentrations in the neuroprotective range have been associated with better treatment response 50 and better cognitive functioning 59 in depressed patients. This finding is (partly) replicated in our study, given the fact that baseline S100-beta predicted follow-up reduction in depression and improvement of subjective cognition. Baseline S100-beta, however, was associated with poorer working memory performance. This may be in accordance with the possible frontal lobe involvement in the cognitive effects of ECT as mentioned by Sachseim 5 The discrepancy between subjective and objective cognitive performance is described in the literature.60 The fact that the baseline value and not the change in S100-beta that makes the difference suggests that any associations between S100-beta and depression and cognition may reflect a cerebral trait rather than a state. The S100-baseline may be a substrate of the differential effects of ECT on depression and cognition and as such, may be used as a predictor of the impact of ECT. The correspondence between the main effects of ECT on cognition and depression with the associations between baseline S100-beta on the one hand and cognition and depression on the other suggests that S100-beta may in fact reflect underlying mediation of the effects of ECT. To conclude, baseline S100-beta may be a sensitive marker predicting and possibly mediating the differential effects of ECT on depression and cognition. If replicated, these findings may shed light on the therapeutic mechanism of ECT and the pathophysiology of depressive disorder.

REFERENCES


5. Sackeim HA. Memory and ECT: from polarization to reconciliation. J ECT. 2000;16(2):87-96. Ovid Full Text | Bibliographic Links | [Context Link]


12. Whitaker-Azmitia PM, Azmitia EC. Astroglial 5-HT1a receptors and 5-100 in development and plasticity. Perspect Dev Neurobiol. 1994;2(2):233-238. Serials Solutions 360 Link | Bibliographic Links | [Context Link]


48. StataCorp. Stata Statistical Software. College Station, 2002. [Context Link]


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