Psychoneuroendocrinology 110 (2019) 104414

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

S100 calcium-binding protein B in older patients with depression treated with electroconvulsive therapy☆

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ARTICLE INFO

Keywords:
Depression
S100B
Electroconvulsive therapy
Biomarker
Remission

ABSTRACT

Background: Increasing evidence suggests that glial mediated disruption of neuroplasticity contributes to depression. S100 calcium-binding protein B (S100B) promotes neuronal protection in nanomolar concentrations. Studies on its possible role as a treatment outcome marker in affective disorders are limited. Recent evidence suggests a putative role for S100B as a state marker of illness activity as it is found elevated in episodes of major depression.

Aim: To investigate whether higher S100B is associated with favourable treatment outcome following electroconvulsive therapy (ECT) and to further explore whether S100B reflects a state marker of depression activity.

Methods: Serum S100B samples, at baseline and post-ECT and clinical assessments including Montgomery Åsberg Rating scales were collected in 91 older depressed patients (mean age: 73.0 years), referred for ECT. Change in pre- and post-ECT S100B was compared between remitters and nonremitters. Logistic and Cox regression analyses were used to determine whether S100B was associated with remission of depression.

Results: Patients with S100B levels in the intermediate tertile, that is, between 33 ng/L and 53 ng/L, had higher odds on remission, odds ratio: 5.5 (95%Confidence Interval (CI): 1.55–19.20, p = < 0.01), and were more likely to remit from depression over time, hazard ratio: 1.96 (95%CI: 1.04–3.72, p = 0.04), compared with patients in the lowest tertile. There was no significant decrease in levels of S100B after ECT in both remitters and nonremitters.

Conclusion: Our findings demonstrate that patients with higher S100B levels at baseline were more likely to remit from depression suggesting an association between higher S100B and responsiveness to ECT. Next, S100B levels do not decrease after remission, suggesting S100B is not a state marker of depression. S100B is not capable of predicting treatment outcome by itself, further research may combine outcome markers.

1. Introduction

Unipolar depression is a severe mental illness with impact on cognitive and social functioning as well as quality of life (Lépine and Briley, 2011). Despite various treatment options available, a significant number of patients remain symptomatic. Hence, over the past years research has focused on finding putative predictors of treatment outcome. Possible markers including Brain Derived Neurotrophic Factor (BDNF), c-reactive protein (CRP), inflammatory cytokines and cortisol have been examined in previous studies, both in antidepressant treatment and electroconvulsive therapy (ECT) (Lindqvist et al., 2017; Rocha et al., 2016; Strawbridge et al., 2015; Suijk et al., 2018).

☆ Research conducted at: Department of Old Age Psychiatry, GGZ inGeest, Amsterdam, the Netherlands and University Psychiatric Centre KU Leuven, Leuven, Belgium. Cytokine and CRP determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit Amsterdam.

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https://doi.org/10.1016/j.psyneuen.2019.104414
Received 6 May 2019; Received in revised form 19 August 2019; Accepted 19 August 2019

One protein of potential interest that seems to be involved in major depression is the S100 calcium-binding protein B (S100B) (Kroksmark and Vinberg, 2018; Schroeter et al., 2013, 2008). This glial protein is located in the cytoplasm and nucleus of astrocytes and adipocytes exerting several intra- and extracellular functions. Intracellular, it has a regulatory role where it can stimulate cell proliferation and inhibit apoptosis and cell differentiation (Donato et al., 2009). Extracellular effects of S100B are dose dependent. In the physiologic, nanomolar concentration range, S100B is thought to exert neurotrophic activity promoting neurite extension and protecting neuronal cells (Donato et al., 2013; Michetti et al., 2019), whereas in micromolar concentrations (≥ 500 nM/L) S100B contributes to cell injury and increases neuroinflammation by activating microglia (Donato et al., 2009; Michetti et al., 2019). In addition, S100B is sometimes regarded as a marker for blood-brain barrier (BBB) permeability as it is found elevated in studies regarding BBB disruption (Kanner et al., 2003; Thelin et al., 2017).

To date, the role of S100B in depression remains unclear. Previous studies examined S100B as a biomarker of treatment outcome. These studies suggest higher levels of serum S100B as a favourable feature in the course of disease. Higher baseline levels of S100B were associated with favourable ECT response in two studies (Arts et al., 2006; Maier et al., 2018) and in four other studies a better antidepressant treatment response in depressed patients with higher levels of S100B was reported (Ambrée et al., 2015; Arolt et al., 2003; Jang et al., 2008; Kranaster et al., 2014). In addition, a putative role for S100B as a state marker of illness activity has been suggested, based on elevated S100B levels that are consistently observed in major depression (Kroksmark and Vinberg, 2018; Rajewska-Rager and Pawlaczyk, 2016). Notwithstanding the limited number of studies and small sample sizes, these results are promising and challenge us to further elucidate the association between S100B and depression.

Because of the high remission rates following ECT compared with antidepressant medication (Heijnen et al., 2010; Rush et al., 2006), we aim to investigate whether higher S100B is associated with remission of depression after treatment with ECT. Next, we aim to further explore whether S100B reflects a state marker of depression activity by monitoring levels pre-ECT compared with post-ECT and investigating the association between S100B and severity of depression. Based on previous findings (Arts et al., 2006; Maier et al., 2018), we hypothesize that higher levels of S100B are associated with a favourable ECT outcome. Furthermore, if S100B is a state marker of depression, we expect a decline in S100B levels in remitted patients. The standardized procedures for the inclusion and treatment of patients in the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) multicentre study, as well as for the collection and storage of serum samples, give us the unique opportunity to study S100B and treatment outcome in a relatively large sample of depressed patients treated with ECT.

2. Methods

2.1. Subjects

The data for this study was derived from the multicentre study 'Mood Disorders in Elderly treated with Electroconvulsive Therapy' (MODECT) as described earlier (Dols et al., 2016). MODECT included 110 patients, aged > 55 years, who fulfilled the DSM-IV criteria for major depression (American Psychiatric Association, 2000), as assessed by the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1998), and who were referred for ECT. All patients were recruited from an inpatient population at the department of Old Age Psychiatry of GGZ inGeest, Amsterdam, the Netherlands and the University Psychiatric Center KU Leuven, Belgium. Patients with a DSM-IV diagnosis of bipolar disorder or schizoaffective disorder were excluded from the study. Moreover, patients with established dementia or a major neurological illness were excluded. Written consent was obtained from all patients. The study protocol was approved by the ethical review board of the Amsterdam UMC and UPC Leuven and adhered the declaration of Helsinki.

2.2. S100B

Serum samples were collected between 07h30 and 09h30 and were stored at −85 °C until assayed for S100B levels. Serum S100B values were determined using a chemiluminescence immunoassay (Elecsys® S100) run on the Cobas 6000 analyser system (Roche Diagnostics), at the Endocrinology laboratory of the Department of Clinical Chemistry of the University Medical Center, VUmc, in Amsterdam, the Netherlands. Baseline and follow up samples of a patient were always assayed in 1 run. The S100B test had a measurement range from 0.005 µg/L to 39 µg/L. To facilitate interpretation, we present S100B in ng/L. In every run and after each system calibration, control samples of different concentrations were included, and results plotted in the QC system. Intra-assay variation (CV) was 1.3% and the inter-assay CV 4.6%. As the relation between levels of S100B and remission of depression was not linear, serum S100B data was divided in categories. We additionally performed calculations to determine study size using Altman's nomogram (Altman, 1991; Whitley and Ball, 2002). We used an 80% probability of detecting differences in remission at a 5% significance level. The standardized difference was calculated using data from one earlier study investigating the relation between S100B and treatment outcome in depressed patients (Ambrée et al., 2015). The calculations showed that it was sufficient to have 30 patients. We used tertiles (lowest tertile: ≤ 32 ng/L, intermediate tertile: 33–53 ng/L, highest tertile: ≥ 54 ng/L) in order to minimalize loss of information and to maintain sufficient group size (n ≈ 30). To evaluate the robustness of these findings, we repeated the analyses for dichotomized values of S100B, cut-off median value (low S100B: < 42 ng/L, high S100B: ≥ 42 ng/L).

2.3. Measures

Data were available at baseline (T0) and one week post-ECT (T1). Patients with missing values in depression severity at T0 and T1 and patients with missing S100B values on T0 were excluded from analyses (n = 16). Attrition was differential with respect to inclusion site, with a higher number of persons with missing serum samples in Amsterdam, The Netherlands. Attrition was not associated with age, sex, and depression severity. Depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), assessed prior to ECT, weekly during ECT and one week after ECT was ended (post-ECT). A semi-structured interview was performed to retrieve socio-demographics and clinical characteristics and included age, sex, body mass index (BMI), the use of antidepressant medication during ECT, and presence of cardiovascular diseases and malignant neoplasms. Several depression characteristics were examined, including depression severity (total MADRS score), treatment resistance, presence of psychotic symptoms, age of onset, duration of index episode of depression and recurrence of depression. Treatment resistance was defined as at least one trial with a score on the Antidepressant Treatment History Form (ATHF) of ≥ 3, representing adequate dose and duration of the trial (Prudic et al., 1996). Considering differences in definitions, an elaboration on the definition of medication resistance is available in the supplemental material. The presence of psychotic symptoms was assessed by a psychiatrist according to DSM-IV criteria (American Psychiatric Association, 2000), and confirmed by the MINI (Lecrubier et al., 1998). Early onset is defined as first episode before 55 years of age. Self-report was used for duration of index episode (in months) and recurrence of depression (at least one previous episode of depression).

2.4. ECT procedures

Patients were treated twice weekly with ECT, in accordance with Dutch Guidelines (van den Broek et al., 2010v). Seizures were induced by brief-pulse ECT (1.0 ms), administered by the Thymatron System IV (Somatics, LLC, USA) with a maximum stimulus level of 1008 mC. Stimulus intensity was determined according to a dose titration protocol. A seizure of less than 20 s motor activity or less than 25 s EEG activity, was considered inadequate. Stimulation was changed to bilateral when clinical conditioned worsened or after six unilateral ECT sessions without improvement. Treatment was discontinued when patients reached remission, defined by a MADRS < 10 (Montgomery and Asberg, 1979), or when no further improvement was achieved. After discontinuing ECT, the majority of patients received antidepressants (n = 57/91) and add-on lithium (n = 30/91). A small portion of patients received maintenance ECT (n = 7).

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 23. Group differences for continuous variables were analysed using independent samples *t*-tests (for normally distributed samples) and Mann-Whitney U tests (for nonnormally distributed values). For categorical variables, $\chi 2$ tests were used. Normality was examined using visual exploration of the data. Outliers (above 3x interquartile range) for S100B at baseline (n = 3) were excluded from analysis. Spearman's test for correlations was used to examine correlations between depression severity and S100B. Change scores (delta, Δ) of pre- and post-ECT S100B levels and MADRS scores were calculated by subtracting T0 from T1. Change scores were accordingly evaluated using Mann-Whitney U test. The association of S100B with remission of depression was examined using logistic regression analysis. Hazard ratio (HR) was examined using Cox regression analysis, with total number of received ECT sessions as time indication. The assumption of proportionality of hazard was checked. All analyses were adjusted for age. To develop an optimal covariate model from several variables a stepwise procedure was chosen for logistic regression. The covariates used for backwards regression analyses were depression severity, presence of cardiovascular disease, presence of malignant neoplasm, the use of antidepressant medication during ECT, duration of index episode, pharmacotherapy resistance, and presence of psychotic symptoms as these are suggested in current literature as putative confounders (Donato et al., 2009; Manev et al., 2003; Michetti et al., 2019; Schroeter et al., 2013; Yang et al., 2008). To check for multicollinearity the variation inflation factors (VIF) were calculated, where a VIF of ≥ 2 was considered as an indicator of multicollinearity.

3. Results

3.1. Subject characteristics

Baseline characteristics of the study population and the distribution across tertiles of S100B serum levels are shown in Table 1. The sample consisted of 91 older depressed persons, of which 69.2% patients were female, with a mean age of 73.0 years. Patients received between 4 and 29 ECT sessions (mean of 11.6 ± 5.0 (Standard Deviation)). The majority of patients received unilateral ECT (64.8%). Mean depression severity at baseline was 33.7 on the MADRS indicating severe depression. Median S100B at baseline was 42 ng/L. There were no significant differences between patients with different levels of S100B with respect to age, gender, depression severity or duration of treatment.

3.2. S100B and remission

As shown in Table 2, there is an overall difference between S100B tertiles ($p = 0.03$) with respect to remission rates. Patients in the intermediate tertile (S100B: 33 ng/L - 53 ng/L) have higher odds on remission compared with patients in the lower tertile: odds ratio (OR) 5.46 (95%Confidence Interval (CI): 1.55–19.20). Confidence intervals are wide as expected with a small sample size. Also, patients in the highest tertile (S100B: > 54 ng/L) tended to have a higher odd on remission as compared with the lowest tertile, although this was not significant: OR 1.25 (95%CI: 0.42–3.74). Presence of psychotic symptoms was identified as putative confounder and was therefore included as covariate in multivariable analysis. Pharmacotherapy resistance and BMI were also identified as putative confounders ($p = 0.1$ and $p < 0.01$). However, considering the number of missing values (respectively, n = 8 and n = 30) of both covariates, we decided to include only presence of psychotic symptoms in multivariable analyses, in order to maintain sufficient power. There was no significant multicollinearity between covariates. In separate post hoc analysis including pharmacotherapy resistance and BMI as covariates (n = 56), a higher odd on remission for patients in the middle tertile compared with the lower tertile was found, although not significant: OR 3.76 (95%CI: 0.67–21.11). In addition, post hoc analysis showed an association between higher BMI and higher levels of S100B, *p* for trend = 0.01. Post hoc analyses with inclusion of baseline S100B outliers (n = 3) did not alter our findings. To test the robustness of our findings, analyses were repeated for dichotomized values of S100B, cut-off median value (≥ 42 ng/L), however results did not reach significance: OR 1.82 (95%CI: 0.73–4.56).

3.3. S100B and time to remission

In both univariate and multivariable Cox regression analyses, patients in the intermediate tertile were more likely to remit from depression over time, compared with the lowest tertile: HR 1.96 (95%CI: 1.04–3.72). For the dichotomized value of S100B, the HR for remission was 1.45 (95%CI: 0.86–2.44).

3.4. S100B as a biomarker

When measuring the predictive values of S100B as a biomarker of treatment outcome a sensitivity of 55.7% and specificity of 60.0% was found. The positive predictive value was 73.9% with a false positive rate of 40.0%. The negative predictive value was 40.0% with a false negative rate of 44.3%.

3.5. No change in S100B between pre- and post-ECT measurement

As shown in Fig. 1, there was no statistically significant difference in baseline and post-ECT S100B levels between remitters and nonremitters (respectively U = 813, $p = 0.4$ and U = 617.5, $p = 0.2$). In addition, there was no statistically significant difference in delta S100B from baseline to post-ECT between remitters and nonremitters (delta remitters = 1 ng/L, delta nonremitters = 2.5 ng/L, U = 723.5, $p = 0.9$). Median value for S100B in remitted patients was 44 ng/L at baseline and 45 ng/L post-ECT. Two patients were excluded from further analysis with a higher than three IQR increase in S100B, respectively a change of 618 ng/L and 457 ng/L.

3.6. No association with depression severity

There were no significant associations between baseline S100B and baseline MADRS (Spearman: −0.05, $p = 0.6$), recurrent depression (defined as at least one previous episode of depression, Spearman: 0.08, $p = 0.4$), presence of psychotic symptoms (Spearman: 0.122, $p = 0.3$) and duration of index episode of depression (Spearman: −0.09, $p = 0.4$).

Table 1
Sociodemographics, somatic morbidity and depression characteristics of the sample, across baseline S100B in older depressed patients treated with ECT (n = 91).

	Total n = 91	Lowest Tertile n = 30	Intermediate Tertile n = 31	Highest Tertile n = 30	*p*-value
Sociodemographics					
Age, years, mean (SD)	73.0 (8.0)	71.8 (7.3)	73.8 (8.7)	73.3 (8.2)	0.6
Women, No. (%)	63 (69.2)	20 (66.7)	22 (71.0)	21 (70.0)	0.9
Baseline MADRS, mean (SD)	33.7 (9.1)	34.5 (9.0)	33.4 (7.1)	33.4 (11.0)	0.7
Decline in MADRS, median (IQR)	26.0 (16.0)	26.0 (24.0)	28.0 (10.0)	24.5 (18.5)	0.5
Antidepressant use during ECT, No. (%)	13 (14.3)	4 (13.3)	7 (22.6)	2 (6.7)	0.2
Inclusion site, Amsterdam, No.(%)	52 (57.1)	21 (70.0)	17 (54.8)	14 (46.7)	0.2
number of ECT sessions, mean (SD)	11.6 (5.0)	12.9 (6.2)	11.2 (4.7)	10.6 (3.7)	0.2
Somatic morbidity					
Cardiovascular disease (CVD), No. (%)	22 (24.7)	7 (24.1)	7 (23.3)	8 (26.7)	1.0
Malignant neoplasm, No. (%)	15 (16.9)	5 (17.2)	4 (13.3)	6 (20.0)	0.8
BMI, mean (SD), n = 61	23.4 (3.9)	21.8 (3.6)	23.6 (3.6)	24.6 (4.2)	0.1[1]
Depression characteristic					
Psychotic, No. (%)	42 (46.2)	12 (40.0)	11 (35.5)	19 (63.3)	0.1
Medication resistant, No. (%),	56 (67.5)	14 (53.8)	21 (67.7)	21 (80.8)	0.1
Index episode, months, median (IQR),	6.0 (10.0)	6.0 (9.3)	6.0 (10.8)	6.0 (7.5)	0.9
Recurrence, No. (%)	70 (76.9)	23 (76.7)	25 (80.6)	22 (73.3)	0.8
Early onset, No. (%)	39 (42.9)	17 (56.7)	10 (32.3)	12 (40.0)	0.2
Serum					
S100B ng/L pre-ECT, median (IQR)	42.0 (27.0)	25.0 (7.3)	42.0 (10.0)	70.5 (33.0)	< 0.01
S100B ng/L post-ECT, median (IQR)	40.0 (30.0)	24.5 (14.3)	45.0 (14.5)	60.5 (35.3)	< 0.01

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg. Depression Rating Scale, BMI = body mass index.
[1] *p* for trend = 0.01.

Table 2
Association between S100B (ng/L) and remission of depression in logistic regression analyses shown for tertiles in older depressed patients treated with ECT. Overall difference between tertiles p-value 0.04 for univariate and p-value 0.03 for multivariable analysis.

	Univariate n = 91		Multivariable[1] n = 91	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Lowest Tertile	Reference		Reference	
Intermediate Tertile	4.55 (1.38; 15.05)	0.01	5.46 (1.55; 19.20)	< 0.01
Highest Tertile	1.51 (0.54; 4.24)	0.4	1.25 (0.42; 3.74)	0.7

OR = odds ratio, CI = confidence interval.
[1] Adjusted for age, gender and presence of psychotic symptoms.

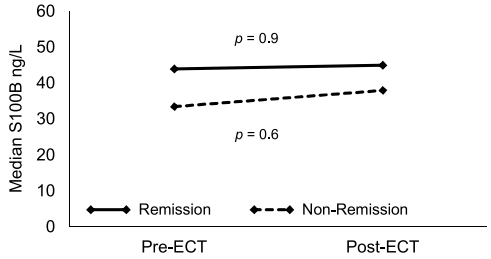

Fig. 1. S100B levels at baseline and one week post-ECT between groups of remitters and non-remitters in older depressed patients treated with ECT (n = 91).

4. Discussion

The aim of this study is twofold. First, we aim to determine whether higher S100B is associated with remission of depression after treatment with ECT. Second, we aim to investigate whether S100B reflects a state marker of depression activity, by monitoring change in levels pre- and post-ECT and investigating the association of S100B with severity of depression. We therefore assess the glial protein S100B in depression in a large cohort of patients treated with ECT. Our study provides evidence that higher serum S100B levels are associated with favourable treatment outcome and faster remission in response to ECT and demonstrates similarity in S100B levels post-ECT compared with pre-ECT in those remitted from depression. These findings are contrary to the idea that S100B reflects a state marker of major depression.

Our findings confirm the association between serum S100B levels and responsiveness to treatment. A favourable treatment response to antidepressant medication or ECT in depressed patients with higher levels of baseline S100B was demonstrated in multiple, albeit small studies, summarized in Table 3 (Ambrée et al., 2015; Arolt et al., 2003; Arts et al., 2006; Jang et al., 2008; Maier et al., 2018). All but one (Kranaster et al., 2014) study suggested increased responsiveness to treatment in patients with higher levels of S100B. These findings suggest the positive impact of S100B on plasticity processes. One hypothesis explaining these results might be that depressed patients suffer from a loss of neuroplasticity. The micro inflammation in the brain, initiated by neuronal impairment caused by depression (Maier et al., 2018) can result in a compensatory release of S100B, counteracting the neurodegenerative mechanisms of major depression. As suggested by Rajewska-Rager et al., S100B might have a positive impact on neuroplasticity processes (Rajewska-Rager and Pawlaczyk, 2016) because of its neuroprotective effect by inducing neuronal growth and differentiation. This theory is supported by increasing evidence showing a decreased density in glial cells in mood disorders suggesting a disruption in neuroplasticity as etiological factor (Innes et al., 2019; Manji et al., 2000; Pittenger and Duman, 2008). In our study, patients in the highest S100B tertile did not have a significantly better treatment response compared with the lowest tertile. Although patient samples were

Table 3
Overview of cohort studies examining baseline S100B and its relationship to depression treatment outcome or examining change in pre- and post-treatment levels of S100B.

	Treatment	n	Mean Age	Associated to treatment response	Mean baseline S100B Responders ng/L	Mean baseline S100B Nonresponders ng/L	Change in S100B in responders
Schroeter et al. (2002)	SSRI / TCA	9	44	n.d.	n.d.	n.d.	decrease[2]
Arolt et al. (2003)	SSRI / TCA	25	46	yes	151[1]	72[1]	n.d.
Jang et al. (2008)	SSRI / SNRI / TCA	59	60	yes	69	57	=
Ambrée et al. (2015)	SNRI / TCA	40	52	yes	63	41	=
Arts et al. (2006)	ECT	12	54	yes	n.a.	n.a.	n.d.
Kranaster et al. (2014)	ECT	19	66	no	52	59	n.d.
Maier et al. (2018)	ECT	11	47	yes	70	50	=
Carlier et al. (Current article)	ECT	91	73	yes	44	34	=

n.a. no data available.
n.d. not determined.
[1] measured in heparin-plasma, therefore values might deviate.
[2] all patients responded to treatment, therefore no comparison was made with nonresponders.

within the nanomolar range, this may be due to the wide distribution of S100B in the highest tertile, as a result of heterogeneity within this subsample of patients, and some patients having higher levels of S100B as a result of other factors than depression, such as an acute phase reaction (Michetti et al., 2019). The sensitivity and specificity of S100B were low suggesting this marker is not eligible as a sole predictor of treatment outcome. The additional benefit of combining biomarkers is subject for further research.

Second, there is an ongoing discussion whether higher levels of S100B in patients with depression represent a state marker of illness activity as S100B levels are consistently found elevated in depressed patients compared with healthy controls (Kroksmark and Vinberg, 2018; Rajewska-Rager and Pawlaczyk, 2016; Schroeter et al., 2013). If S100B were a state marker of depression, its levels would be expected to decrease after remission of depression and to be associated with severity of depression. However, our study, in line with one small ECT study (n = 11), shows there is no change in S100B over the course of ECT in both remitters and nonremitters, see also Table 3. In addition, in our study, with a larger study sample, S100B is not associated to depression severity. Two other studies describe no change in S100B after treatment with antidepressant medication (Ambrée et al., 2015; Jang et al., 2008) compared with one study showing reduced S100B levels after antidepressant treatment (Schroeter et al., 2002). Previous findings are inconsistent on whether S100B levels are influenced by severity of symptoms (Hetzel et al., 2005; Jang et al., 2008; Maier et al., 2018; Schroeter et al., 2002) or not (Ambrée et al., 2015; Kranaster et al., 2014). The majority of studies found no correlation between depressive symptoms and S100B (Kroksmark and Vinberg, 2018).

Our findings contradict the idea that S100B is a state marker of illness activity and fuel the idea that higher levels of S100B are a long-term adaptation of the brain to stress associated with depression or is innate contributing to the onset of depression. A positive correlation between levels of S100B and stressful activity has been shown in physicians on duty as well as in mother and new-born after prolonged labour (Gazzolo et al., 2010; Michetti et al., 2019; Scaccianoce et al., 2004) establishing the capacity of the brain to adapt, in this case to stressful circumstances. In addition, exposure to childhood trauma has been associated to higher levels of S100B in adolescents (Falcone et al., 2015). If this hypothesis is confirmed, this brain adaptation could on the one hand inflict susceptibility for psychiatric disease as is underlined by lower S100B in healthy compared with depressed patients (Kroksmark and Vinberg, 2018; Yang et al., 2008). On the other hand, this adaptation could imply an impact on neuroplasticity processes as mentioned above. Additional support for this hypothesis is the fact that an increase of S100B is not selectively found in depression but is also found in patients with schizophrenia (Aleksovska et al., 2014; Schroeter and Steiner, 2009). In addition, two studies found evidence that increased S100B levels help to restore normal cognitive functioning in depressed patients (Dietrich et al., 2004; Zhang et al., 2009), strengthening the idea that either S100B, or S100B releasing glial cells, have the ability to restore impaired processes. It would be interesting to look at cognition in relation to S100B in future studies.

Finally, it should be mentioned that S100B can exert a neurotoxic function as opposed to the neurotrophic function described above. Increased serum levels of S100B have been attributed to increased permeability through an impaired blood brain barrier (BBB) and is used as a biomarker of brain injury in Neurology (Michetti et al., 2019; Thelin et al., 2017). However, recent evidence suggests that higher serum S100B levels imply an active S100B release from glial cells reflecting neuroplasticity and glial activation rather than release from damaged astrocytes (Kleindienst et al., 2010) and should be interpreted as normal passage of S100B to the extracellular fluid (Kleindienst et al., 2010; Kleindienst and Bullock, 2006; Thelin et al., 2017). Studies in schizophrenia patients support this notion, as increased serum levels of S100B coincided with increased glial activation as detected by MR-spectroscopy (Rothermundt et al., 2007). Because the biologic effects of S100B are thought to be dose-dependent, the increased concentrations observed in our sample could indicate neuronal activation rather than neuronal damage or BBB damage.

4.1. Strengths and limitations

Notably, our findings should be interpreted in the context of the following strengths and limitations. To our knowledge, the current study has the largest sample of serum S100B in depressed patients referred for ECT. Nonetheless, confidence intervals are wide. Any conclusions drawn from these results need to be replicated in a larger sample size. Second, the substantial set of clinical data collected from patients allows us to adjust for putative confounders. An additional strength is that our study includes a well described, rather homogenous sample of severely depressed patients. On the other hand, a limitation of this study is that results might not be applicable to younger patients with mild or moderate depression. It is shown previously that age may have impact on S100B (Schroeter et al., 2013), therefore age is controlled for in our analyses. In addition, besides brain injury and glial activation, there are several other factors known to increase S100B, including heart ischemia, melanomas, BMI and the use of serotonergic medication (Donato et al., 2009; Manev et al., 2003; Michetti et al., 2019; Steiner et al., 2010). Adjustment for ischemic heart diseases, presence of malignancies and the use of antidepressant medication during ECT does not alter our results making it less likely to have influenced S100B levels in our sample. In addition, S100B levels were

determined one week after ECT, therefore it is unlikely that treatment received after discontinuing ECT (maintenance ECT or antidepressant medication) has influenced our results. Next, post hoc analysis shows a significant upward trend in BMI for higher S100B levels. This finding is explained by the well-known association between adipose tissue and levels of S100B (Holtkamp et al., 2008; Steiner et al., 2010). Despite the missing data on BMI, post hoc analysis with the available data (n = 56) showed similar results, which suggests a limited effect of BMI on the association between S100B and ECT outcome. In line with this, as S100B is viewed as a biomarker of brain injury (Thelin et al., 2017), one might suspect that ECT-induced seizures cause an increase in levels of S100B, limiting any statements on the change scores between pre- and post-ECT S100B. However, several studies have shown that there is no increase in S100B during the course of ECT and found no association between S100B and energy dose or seizure duration (Agelink et al., 2001; Kranaster et al., 2014; Palmio et al., 2010), suggesting ECT does not cause brain injury and thus does not cause an increase in levels of S100B. Finally, Yang et al. have shown a positive correlation between levels of S100B and number of episodes of depression which might suggest a form of kindling as the brain is going through recurrent depressive episodes (Yang et al., 2008). Therefore, one might expect to find higher S100B levels in patients with more previous episodes or a longer duration of index episode of depression. The absence of information on the number of previous episodes is considered a limitation in this respect. In addition, no correlation is found between S100B and index episode duration. However, the relative long index episode duration of the entire sample (mean: six months), might explain the absence of this correlation. Future studies should include the number of previous episodes and should include both short and long index episode duration.

4.2. Future implications

Higher levels of S100B are associated with favourable treatment outcome. Conversely, patients with low levels of S100B tend to benefit less from both ECT and antidepressant medication. Therefore, further research is needed to unravel treatment strategies for these patients. Although not yet studied in depression, a handful of studies regarding the effect of S100B on neurogenesis find positive neuroprotective effects of daily S100B administration in mice or human cell lines (Kleindienst et al., 2013, 2005; Reali et al., 2005). Given our findings, increasing the level of S100B may contribute to responsiveness to treatment.

4.3. Conclusion

This study provides evidence that higher levels of S100B in patients with severe depression, treated with ECT, are associated with higher and faster remission rates. Serum S100B levels do not decrease upon remission, which makes it less likely that S100B is a state marker for depression.

Our findings warrant replication. If future studies confirm our findings, higher levels of S100B could, in combination with other putative markers, potentially identify a subgroup of patients with favourable ECT outcome.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The data that has been used is confidential.

CRediT authorship contribution statement

Angela Carlier: Conceptualization, Methodology, Formal analysis, Methodology, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Kimberly Boers:** Formal analysis, Data curation, Writing - original draft. **Robert Veerhuis:** Methodology, Formal analysis, Resources, Data curation, Writing - review & editing. **Filip Bouckaert:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing. **Pascal Sienaert:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing. **Piet Eikelenboom:** Conceptualization, Methodology, Writing - review & editing. **Mathieu Vandenbulcke:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing. **Max L. Stek:** Conceptualization, Methodology, Resources, Writing - review & editing. **Eric van Exel:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Annemiek Dols:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration. **Didi Rhebergen:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision.

Acknowledgements

We thank our colleagues Anna Paauw, Gerard van Grootheest, Denise Wong and Lianneke Egberink for assistance with data collection and management.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.104414.

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